



## 2020 ASPHO Conference Paper and Poster Index

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## **REDUCED FREQUENCY OF MAINTENANCE PULSES IN STANDARD-RISK B ACUTE LYMPHOBLASTIC LEUKEMIA AALL0932**

**Anne Angiolillo, Reuven Schore, John Kairalla, Meenakshi Devidas, Karen Rabin, Patrick Zweidler-McKay, Michael Borowitz, Brent Wood, Andrew Carroll, Nyla Heerema, Mary Relling, Ashley Lane, Kelly Maloney, Cindy Wang, William Carroll, Naomi Winick, Raetz Raetz, Mignon Loh, Stephen Hunger**

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### **Background:**

A key component of COG maintenance chemotherapy for B-ALL has been vincristine/steroid pulses administered every 4 weeks. In contrast, Conter et. al. showed that pulses of vincristine and dexamethasone during the continuation phase of BFM treatment do not affect overall survival in children with intermediate-risk ALL. There was thus uncertainty regarding the optimal frequency of pulses in COG ALL therapy.

### **Objectives:**

AALL0932 was designed to optimize maintenance therapy by asking: (1) whether giving vincristine/dexamethasone (VCR/DEX) pulses every 12 weeks was non-inferior to every 4 weeks; and (2) whether a starting weekly oral methotrexate (MTX dose) of 40 mg/m<sup>2</sup>/dose would be superior to the standard 20 mg/m<sup>2</sup>/dose.

### **Design/Method:**

Average risk (AR) patients participating in the randomization included NCI SR B-ALL without CNS3 or testicular leukemia, unfavorable genetic characteristics or Down syndrome, AND either favorable genetics (trisomies of chromosomes 4 & 10 or ETV6/RUNX1 fusion) with Day 8 peripheral blood (PB) minimal residual disease (MRD)  $\geq 0.01\%$  or CNS2 status, Day 29 bone marrow (BM) MRD  $< 0.01\%$ , OR if neutral cytogenetics, had Day 8 PB MRD  $< 1\%$  and Day 29 BM MRD  $< 0.01\%$ . AR patients were randomized to 1 of 4 Maintenance regimens using a 2 x 2 factorial design: (A): VCR/DEX pulses every 4 weeks and oral MTX 20 mg/m<sup>2</sup>/week; (B): VCR/DEX pulses every 4 weeks and oral MTX 40 mg/m<sup>2</sup>/week; (C): VCR/DEX pulses every 12 weeks and oral MTX 20 mg/m<sup>2</sup>/week; and (D): VCR/DEX pulses every 12 weeks and oral MTX 40 mg/m<sup>2</sup>/week. Between 2010 and 2016, 2364 patients were randomized at the start of maintenance to VCR/DEX pulses every 4 weeks [Arms A and B (n=1186)] or VCR/DEX pulses every 12 weeks [Arms C & D (n=1178)].

### **Results:**

The 5-year disease-free survival (DFS) ( $\pm$ SE) measured from the time of randomization for AR patients randomized to receive VCR/DEX pulse every 4 weeks vs. every 12 weeks was 94.1%  $\pm$ 1.0% vs. 95.1%  $\pm$ 0.9%, respectively (p=0.86) indicating no evidence of DFS inferiority for 12 week frequency). The 5-year overall survival (OS) ( $\pm$ SE) for AR patients randomized to receive VCR/DEX pulse every 4 weeks vs. every 12 weeks was 98.3%  $\pm$ 0.5%, vs. 98.6%  $\pm$ 0.5%, respectively (p=0.69).

**Conclusion:**

The AR SR B-ALL patients who received reduced VCR/DEX pulses maintained outstanding outcomes. VCR/DEX pulses every 12 weeks will thus be incorporated into frontline COG B-ALL trials thereby reducing the burden of maintenance therapy.

Conter, Lancet, 2007

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Plenary Paper # 2002

**INCREASED EXPRESSION OF CXCR4 LEADS TO ENHANCED CELL MIGRATION IN CALM-AF10 DRIVEN LEUKEMIA**

**Shelby Fertal, Sayyed Zaidi, Gabriel Cohn, Gary Stein, Jessica Heath**

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**Background:**

The bidirectional nature of interactions between leukemic cells and the bone marrow stromal components is increasingly recognized as important in controlling cell proliferation, quiescence, and chemoresistance in aggressive leukemias. Adhesion of leukemic blasts to the bone marrow stroma through cell surface and secreted proteins, including the G-protein coupled receptor CXCR4, is proposed as a mechanism by which leukemia evades chemotherapy, resulting in disease relapse. CALM-AF10 is a leukemogenic chromosomal translocation found in 15% of T-ALL, and is associated with bulky mediastinal disease and a propensity for CNS relapse, both phenomenon related to leukemia cell adhesion. We identify an increase in the adhesive nature of CALM-AF10+ leukemia cells and examine mechanisms responsible for this phenotype.

**Objectives:**

We hypothesize that CALM-AF10 modulates the leukemic cell interactions with the bone marrow stroma via CXCR4, and that this can be targeted to therapeutic effect.

**Design/Method:**

We utilized two independent systems to study CXCR4, including murine and human leukemia cell lines characterized by the presence or absence of CALM-AF10 (CALM-AF10+ or CALM-AF10-). We compared expression of CXCR4 in CALM-AF10+/- leukemia cells. We then evaluated whether CXCR4 expression correlated with a phenotypic or functional change. We assessed whether differences in cell adhesion, migration, or proliferation are altered by activating CXCR4 with its ligand CXCL12, or inhibiting it with the small molecule inhibitor, AMD3465.

**Results:**

We identified increased CXCR4 expression in CALM-AF10+ leukemias, in comparison to CALM-AF10- leukemias. This is evident at the mRNA transcript level, as well as at the protein level. We specifically identified an increased expression of CXCR4 at the plasma membrane. Importantly, we found that CALM-AF10+ cells expressing high levels of cell surface CXCR4 demonstrated a two-fold increase in cell migration towards a CXCL12 stimulus; the control

CALM-AF10- cells did not exhibit this change in migration. Mechanistically, we identified that inhibition of CXCR4 signaling is accompanied by a decrease in pERK/ERK, and are currently investigating the functional consequences of this perturbation.

**Conclusion:**

We conclude that CALM-AF10+ leukemia is characterized by increased expression of CXCR4, and that this is associated with an increase in cell migration, enhanced by stimulation of the CXCR4 axis. Future studies will dissect the mechanisms of overexpression, and will continue to assess possible synergy between targeted CXCR4 inhibitors and traditional chemotherapy.

The Children's Leukemia Research Association, Pediatric Cancer Research Foundation, Northern New England Clinical and Translational Research Network, Emily M. Lyman Pediatric Leukemia Fund, and Keegan Bradley Charity Golf Classic supported this work.

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Paper Session/Young Investigator Award Recipient # 2003

**LEUKEMIA PREDISPOSITION OR CLONAL HEMATOPOIESIS IN SHWACHMAN DIAMOND SYNDROME: DIFFERENT PATHWAYS**

**Alyssa Kennedy, Elissa Furutani, Kasiani Meyers, Gwen Muscato, Kaitlyn Ballotti, Christopher Gibson, Chad Harris, Shanshan Liu, Edie Weller, Scott Carter, Nicholas Camarda, Ashley Galvin, Steffen Boettcher, Maggie Malsch, Mark Fleming, Stella Davies, Akiko Shimamura, Coleman Lindsley**

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**Background:**

Shwachman Diamond syndrome (SDS) is a bone marrow failure disorder with a high risk of myeloid malignancies. SDS is caused by impaired removal of EIF6 from the nascent 60S ribosome subunit, resulting in defective ribosome assembly. Prognosis of patients with SDS-associated MDS and leukemia is poor. A rational surveillance strategy could identify incipient transformation and improve patient outcomes.

**Objectives:**

We investigated the prognostic significance and mechanistic basis of somatic clonal progression in SDS.

**Design/Method:**

Samples were prospectively collected from 110 patients in the SDS Registry. To define the somatic mutational landscape in SDS, we initially performed whole exome sequencing (WES) of 43 bone marrow samples from 29 patients with paired fibroblasts. Targeted error-corrected sequencing was then conducted for 316 samples from 110 patients.

**Results:**

Somatic clonal hematopoiesis (CH) was detected in a majority of SDS patients. In contrast to canonical CH, 91% of mutations involved only two genes: EIF6 and TP53. Single cell DNA

(scDNA) sequencing demonstrated that TP53 and EIF6 mutations arose within separate clones.

To define the mechanism by which EIF6 mutations cause clonal expansion, we tested the functional consequences of 7 mutations. The majority of EIF6 mutations resulted in decreased levels of EIF6 protein, which improves the aberrant ribosome profiles in SDS. A common N106S mutation affected a conserved residue within the contact interface between EIF6 and the 60S subunit. Polysome profiling showed that N106S impaired the association of EIF6 with the 60S subunit. EIF6 missense mutations are thus unified by their ability to improve ribosome maturation in SDS cells through functional haploinsufficiency.

A majority of patients with MDS/AML had acquired TP53 mutations. WES and scDNA sequencing demonstrated a majority (9 of 11) of TP53 mutated MDS/AML clones had inactivation of the second TP53 allele whereas a minority (3 of 26) non-transformed TP53 clones had alteration of both alleles. scDNA sequencing of serial samples demonstrated stable monoallelic TP53 mutations followed by development of a clone with TP53 CN-LOH which expanded just prior to leukemic transformation.

**Conclusion:**

In SDS, impairment of ribosome maturation drives CH with somatic EIF6 or TP53 mutations. EIF6 mutations promote competitive fitness by rescuing the SDS ribosome defect with limited leukemic potential. TP53 mutations do not correct the ribosomal defect and have high leukemic potential particularly upon biallelic inactivation. Our results define adaptive and maladaptive pathways of clonal expansion driven by a germline mutation and provide a mechanistic rationale for clinical surveillance.

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Paper Session/Young Investigator Award Recipient Poster # 2004

**MECOM DYSREGULATION VIA ENHANCER HIJACKING IN PEDIATRIC THERAPY-RELATED MYELOID NEOPLASMS**

**Jason Schwartz, Jing Ma, Jennifer Kamens, Tamara Lamprecht, Michael Walsh, Xiaolong Chen, Guangchun Song, Gang Wu, Stanley Pounds, Huiyun Wu, Cristyn Branstetter, Michael Walsh, Yanling Liu, Priya Kumar, John Easton, Scott Newman, Charles Mullighan, Jinghui Zhang, Tanja Gruber, Xiaotu Ma, Jeffery Klco**

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**Background:**

Therapy-related myeloid neoplasms (tMN) occur in children secondary to cytotoxic therapies for primary malignancies, are resistant to chemotherapy, require hematopoietic cell transplantation, and have a dismal prognosis. The genomic alterations that drive tMN in children have not been comprehensively described.

**Objectives:**

To define the somatic and germline genomic profiles of pediatric tMN.

**Design/Method:**

Samples from 62 pediatric patients diagnosed with tMN (tMDS: n=23, tAML: n=39) were obtained from the St. Jude Children's Research Hospital Tissue Bank and analyzed using WES, WGS, and RNA sequencing. WES was completed for 58 tumor/normal pairs using Nextera Rapid Capture Expanded Exome (Illumina). Fifteen cases were analyzed by WGS (11 also had WES). Normal comparator genomic DNA was obtained from flow-sorted lymphocytes or non-tumor peripheral blood or bone marrow. Primary tumors were varied (hematological (74%), bone and soft tissue (23%), and brain (3%)).

**Results:**

The mutation burden of pediatric tMN (28 mutations/patient) is significantly higher ( $p < 0.001$ ) than both pediatric primary MDS (5 mutations/patient) and de novo AML (6 mutations/patient). KRAS was the most frequently mutated gene (18 somatic mutations in 14 cases). Germline variant analysis revealed 4 cases (6%) with pathogenic/likely pathogenic TP53 mutations. Other notable germline variants included ETV6 (n=2), PMS2 (n=1), and NF1 (n=1).

RNA-Seq completed on 56 cases identified 28 (50%) cases with KMT2A rearrangement (KMT2Ar). In addition to KMT2Ar, we identified a RUNX1-MECOM fusion. Alterations involving the MECOM locus have been described in myeloid neoplasms like tMN, and its overexpression is associated with a poor prognosis. MECOM expression levels varied in this cohort (FPKM range: 0.004 – 38.4) with 24 cases (43%) having an FPKM > 5 (MECOM-High). In addition to the RUNX1-MECOM event, these 24 MECOM-High cases included 18 with KMT2Ar (64% of KMT2Ar group) and 1 with a NUP98 fusion (NUP98-HHEX). The remaining 4 MECOM-High cases demonstrated allele-specific MECOM expression, suggesting a cis-regulatory element is driving this expression. Three of these 4 cases were found to contain rearrangements involving MECOM (chromosome 3) and noncoding regions of chromosome 2 (n=2, ZFP36L2@-MECOM) or chromosome 17 (n=1, MSI2@-MECOM). Both ZFP36L2 and MSI2 are transcription factors expressed in hematopoietic cells.

**Conclusion:**

Ras/MAPK pathway mutations and KMT2A rearrangements are frequent in pediatric tMN as are high levels of MECOM expression, a portion of which is driven by enhancer hijacking.

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Paper Session # 2005

**ENHANCEMENT OF ANTI-TUMOR IMMUNITY BY T CELLS ENGINEERED TO RESTORE HLA EXPRESSION IN NEUROBLASTOMA**

**Fiorella Iglesias, Siani Weston, Djordje Atanackovic, Tim Luetkens**

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**Background:**

T cells can target cancer cells by recognizing tumor-specific peptides presented by HLA proteins. HLA downregulation is one of the most common neuroblastoma (NB) immune escape mechanisms, and it is associated with an adverse prognosis. Interferon-gamma (IFN $\gamma$ ) has been

shown to rescue HLA expression on NB cells; however, no strategies exist for the targeted delivery of IFN $\gamma$  to upregulate HLA on tumor cells.

**Objectives:**

To present a novel approach to induce HLA expression in NB cells using targeted cellular therapy.

**Design/Method:**

We genetically engineered GD2-specific T cells expressing synthetic-Notch (synNotch) receptors. In our receptors, an internal Notch domain is cleaved upon binding of the target antigen GD2, which releases a transcription factor driving expression of IFN $\gamma$  (IFN $\gamma$ -synNotch). We analyzed co-cultures of IFN $\gamma$ -synNotch T cells and human NB cell lines by flow cytometry, enzyme-linked immunosorbent assay, enzyme-linked immunospot assay, and luminescence-based cytotoxicity assays.

**Results:**

Treatment with recombinant IFN $\gamma$  led to a strong induction of HLA expression in 6/6 NB cell lines. Next, we generated 13 synNotch receptors targeting NB-specific antigen GD2, and one CD19-specific synNotch receptor. One of the 13 GD2-targeting synNotch receptors showed strong surface expression and no basal IFN $\gamma$  expression. T cells expressing this construct (GD2-IFN $\gamma$ -synNotch T cells) produced IFN $\gamma$  in the presence of GD2-positive NB cells and not GD2-negative cells. In vitro, GD2-IFN $\gamma$ -synNotch T cells efficiently upregulated HLA on NB cell lines SK-N-DZ and NB-1643. HLA upregulation was maintained for seven days after removing GD2-IFN $\gamma$ -synNotch T cells from the co-culture. In contrast, treatment with GD2-IFN $\gamma$ -synNotch T cells did not increase PD-L1 on NB cells or PD-1 on T cells. In vivo, NOD.Cg-PrkdcscidIl2rgtm1Wjl/SzJ (NSG) mice were engrafted with the human NB cell line Kelly. Once tumors reached a diameter of 5 mm, GD2-IFN $\gamma$ -synNotch T cells were injected intratumorally. Three days after treatment, mice were euthanized, and their tumors were harvested and analyzed by immunohistochemistry for HLA induction. Mice treated with GD2-IFN $\gamma$ -synNotch T cells, but not CD19-IFN $\gamma$ -synNotch T cells, showed HLA upregulation in their tumors. Finally, GD2-IFN $\gamma$ -synNotch T cells significantly enhanced the killing of HLA-A\*02+ NB cell lines by T cell receptor (TCR) transgenic T cells targeting the tumor antigens NY-ESO-1 and PRAME.

**Conclusion:**

Induction of HLA on tumor cells using engineered IFN $\gamma$ -synNotch T cells is feasible and increases T cell-mediated tumor cell killing. Treatment with GD2-IFN $\gamma$ -synNotch T cells alone or in combination with TCR-transgenic T cells represents a promising approach to improve anti-tumor immunity in solid tumors.

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Paper Session # 2006

**HIF EXPRESSION IN ANTIGEN-SPECIFIC AND CAR-T CELLS IMPROVES ANTITUMOR RESPONSE TO SOLID TUMORS**

**Colette Lauhan, Deborah Witherden, Ananda Goldrath**

**Background:**

Adoptive cellular therapy (ACT) with antigen-specific and chimeric antigen receptor (CAR) T cells is a valuable tool for treatment of malignancy. However, in solid tumors, T cells are limited by a hostile hypoxic environment. In hypoxia T cells accumulate hypoxia inducible factors (HIFs), transcription factors which promote advantageous adaptations. In normoxic conditions, HIF degradation is facilitated by the Von Hippel Lindau complex (VHL). T cells lacking VHL have constitutive HIF activity and superior antiviral responses coincident with increased differentiation to the tissue resident memory T cell (TRM) phenotype. This phenotype is antigen-specific and long-lived; intratumoral accumulation of TRM like cells is associated with improved survival in human tumor studies. Manipulation of the HIF pathway and subsequent TRM differentiation of adoptive T cells may improve efficacy and durability of their antitumor response.

**Objectives:**

To determine if unrestrained hypoxia inducible factor activity in antigen-specific and CAR T cells improves anti-tumor response in murine melanoma and rhabdomyosarcoma (RMS) models.

**Design/Method:**

Tumor antigen-specific CD8 T cells were isolated from Von Hippel Lindau (VHL)-deficient (VHL KO) mice and wild type (WT) mice. Following in vitro activation, T cells were transferred to tumor-bearing mice and monitored for tumor progression. Alternatively, activated VHL KO and WT CD8 cells were mixed and transferred to tumor-bearing mice; donor T cells were analyzed from tumors, spleens, and draining lymph nodes (LNs) after 7-8 days. In similar studies, activated VHL KO and WT CD8 T cells were transduced to express anti-human CD19 CAR and transferred to mice bearing tumors expressing human-CD19 surface antigen; donor T cells were later analyzed from tumors, spleens, and LNs.

**Results:**

Adoptive transfer of antigen-specific VHL KO cells reduces tumor burden and increases recipient survival compared to WT recipients. Antigen-specific VHL KO cells demonstrate increased intratumoral accumulation over WT cells in both melanoma and RMS models. Further, transfer of a mix of VHL KO and WT CAR T cells to tumor-bearing mice results in increased VHL KO accumulation over WT CARs. Increased intratumoral accumulation is associated with increased expression of TRM phenotypic markers (CD69+CD103+) and effector molecules.

**Conclusion:**

Constitutive HIF expression in ACT results in improved tumor control and intratumoral accumulation in T cells expressing antigen-specific receptors and in CAR T cells. These advantaged cells resemble classic antiviral TRM cells and their phenotype allows for sustained and effective antitumor response. This effect is notable in multiple solid tumor models, indicating potential applicability to a variety of solid tumors.

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## **OBESITY IMPAIRS T-CELL FUNCTION WHICH MAY IMPACT THE EFFICACY OF CAR T-CELLS IN PEDIATRIC LEUKEMIA**

**Anthony Ross, Miyoung Lee, Jamie Hamilton, Ganesh Talekar, Curtis Henry, Sunil Raikar, Jamie Story**

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### **Background:**

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood. Despite vast improvements in treatment, recent studies have shown that children who are obese at diagnosis have poorer survival. The mechanisms of decreased therapeutic responses in obese individuals are not well understood. Changes in pharmacokinetics are partially responsible; however, there is growing interest in understanding how obesity-associated changes to the leukemia micro-environment impact leukemia progression and therapeutic responses. Compromised immune responses have also been observed in obese patients, which is of particular interest given the increasing use of immunotherapy in hematologic malignancies. An immunotherapy that has shown success in refractory/relapsed B-ALL is chimeric antigen receptor T-cell therapy (CAR-T) which requires functional T-cells to target and effectively eliminate leukemia cells. The impact of obesity on the efficacy of CAR-T cell based immunotherapies is currently unknown.

### **Objectives:**

- 1) Determine the effect of obesity on non-engineered T-cell and CAR T-cell function
- 2) Determine if ameliorating obesity-induced chronic inflammation improves the efficacy of CAR T-cells in obese micro-environments

### **Design/Method:**

We have developed an in vitro model of obesity utilizing a protocol that differentiates murine bone marrow stromal cells (OP-9 cells) into adipocytes. Primary mouse T-cells were stimulated for 72 hours in the presence of either unconditioned media or conditioned media (stromal cell-conditioned media or adipocyte-conditioned media) followed by flow cytometry to determine the expression of activating (CD44) and inhibitory (PD-1) surface proteins, intracellular cytokine production (IFN- $\gamma$  and TNF- $\alpha$ ), and levels of cytolytic machinery (Perforin and Granzyme B). Similar experiments were conducted on ex vivo T-cells isolated from leukemia patient samples from the Emory Biorepository. We are currently examining the impact of adipocyte secreted factors on CAR-T function in vitro and in vivo.

### **Results:**

Compared to murine T-cells activated in control media, CD4+ and CD8+ T-cells activated in the presence of adipocyte-secreted factors exhibited an exhausted phenotype highlighted by the failure to produce the effector mediators IFN- $\gamma$ , TNF- $\alpha$ , Perforin, and Granzyme B. Similar compromised responses were seen when T-cells were isolated from obese children with leukemia. In preliminary studies we also found that engineered CD19 directed CAR T-cells

stimulated in vitro in the presence of adipocyte-secreted factors exhibited increased PD-1 surface expression and reduced TNF- $\alpha$  production.

**Conclusion:**

T-cells activated in the presence of adipocyte-secreted factors have reduced functional potential which may compromise immune clearance of leukemia cells and the efficacy of CAR-T cell based therapies moving forward in obese children with leukemia.

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Paper Session # 2008

**TARGETING ADENOSINE IN THE MARROW MICROENVIRONMENT AFFECTS STROMAL AND LEUKEMIA CELL SURVIVAL**

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**Background:**

Nonmalignant bone marrow stromal cells support acute lymphoblastic leukemia cell survival. NT5E (5'-ectonucleotidase), also known as CD73, is a defining molecule for stromal cells. However, its function in supporting hematopoietic cells is unknown. The protein encoded by this gene is a plasma membrane protein that catalyzes the conversion of extracellular nucleotides to nucleosides, including the conversion of extracellular adenosine monophosphate (AMP) to adenosine. Adenosine signaling plays a role in lymphocyte regulation and also plays a role in regulating differentiation of mesenchymal stem cells. NT5E is highly expressed by stromal cells, but not by ALL cells. Adenosine receptors are present on both stromal and leukemia cells.

**Objectives:**

The pathways for adenosine generation through NT5E and adenosine receptors on leukemia and stromal cells are drug-able. Our hypothesis was that manipulation of adenosine metabolism in the marrow microenvironment would alter the survival of leukemia and/or stromal cells.

**Design/Method:**

We have developed a simple but powerful experimental system of human marrow derived stromal cells co-cultured with patient derived xenograft expanded primary human high risk ALL cells (not established cell lines) that allows us to study the molecular mechanisms of stromal interactions with leukemia. We manipulated adenosine metabolism by genetic means. NT5E expression in stromal cells was knocked down by lentivirus shRNA vectors or overexpressed with lentivirus NT5E vectors. Adenosine receptors A2A, A2B and A3 were knocked down with shRNA lentivirus vectors in leukemia or stromal cells. Survival of leukemia and stromal cells was measured by flow cytometry.

**Results:**

Interference with NT5E function severely impaired stromal cell viability. Lentivirus knockdown of NT5E in stromal cells led to stromal cell death while control vector cultures were unaffected. Overexpression of NT5E had no effect on stromal cells. Knockdown of adenosine receptor 2A in

stromal cells also led to widespread stromal cell apoptosis. In contrast, lentivirus mediated knockdown of adenosine receptors in leukemia cells had much more modest effects; leukemia cell survival of knockdowns was approximately 70% that of control treated leukemia cells.

**Conclusion:**

Generation and activity of adenosine in the stromal cell-leukemia cell microenvironment is important in promoting survival of both stromal cells and leukemia cells. The direct effects on stromal cells are much greater compared to the direct effects on leukemia cells. These results suggest that pharmacologic manipulation of adenosine signaling could have antileukemia effects. We are currently testing this hypothesis in our in vitro system with a panel of adenosine agonists and antagonists.

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Paper Session # 2009

**FOLLOW-UP OF HYDROXYUREA (HU) IN INFANTS WITH SICKLE CELL ANEMIA(SCA):FINDINGS FROM BABY HUG STUDIES**

**Zora Rogers, Susan Assmann, Jeffrey Lebensburger, R Clark Brown, Suvankar Majumdar, James Casella, Jennifer Rothman, Sharada Sarnaik, Ofelia Alvarez, Naomi Luban, Sohail Rana, Sherron Jackson, Tave Hamza, Myron Waclawiw, Ellen Werner, Scott Miller, Winfred Wang**

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**Background:**

BABY HUG, a 2-year randomized clinical trial (RCT) in 193 infants with SCA, 9–18 months at entry, found that HU increased total/fetal hemoglobin and decreased painful events. After the RCT, all children were offered HU per local management in an observational follow-up study (FUS).

**Objectives:**

To identify long-term toxicities and benefits of treatment with HU.

**Design/Method:**

Data were collected during 6-month intervals. Outcome measures for the RCT+FUS were compared (1) by RCT randomization (HU vs placebo), (2) between periods on vs not on HU, and (3) among patient-year (pt-y) quartiles of HU exposure. Analysis of all available timepoints, adjusted for baseline values assuming some children are intrinsically prone to certain events, were used to calculate incidence rate ratios (IRR), 95% confidence intervals (CI), and p-values.

**Results:**

Of the 193 participants, 143 were followed through 2016, and 164 (85%) received some HU. There were 1727 pt-y of follow-up (median 10.2 years/patient), including 1200 pt-y (69%) on HU. Patient HU exposure ranged from 0-12.39 years (median 7.44). Cumulative exposure was 0-337.35 mg/kg-years (median 181.51).

Repeated measures analysis demonstrated lower pitted cell counts (preserved spleen function), higher mean cell volume, and total/fetal hemoglobin in children randomized to HU, effects that continued throughout FUS when on HU ( $p < 0.0001$ ). Fetal hemoglobin increased with increasing pt-y of HU. There were no significant differences in DNA-based genotoxicity. Hydroxyurea maintained already increased glomerular filtration rates (attenuated hyperfiltration), and improved QOL and Vineland performance.

Periods on HU had lower reported major event (ME) rates [0.088 vs 0.172; IRR 0.51; CI (0.37,0.72);  $p < 0.001$ ], acute splenic sequestration (ASSC) [0.011 vs 0.045; IRR 0.24; CI (0.11,0.49);  $p < 0.001$ ], and hospitalization [0.969 vs 1.789; IRR 0.54; CI (0.44,0.66);  $p < 0.001$ ]. There was a downward trend in acute chest syndrome (ACS) [0.48 vs 0.78; IRR 0.61; CI (0.39,0.95);  $p = 0.03$ ], but no decrease in pain events [1.965 vs 1.891; IRR 1.04; CI (0.73,1.48);  $p = 0.83$ ]. Early initiation of HU, during the RCT, was associated with a significant decrease in MEs, ACS, hospitalization, and pain [ $p < 0.001$ ], but not in ASSC [ $p = 0.052$ ].

### **Conclusion:**

During 1200 patient-years of HU exposure starting at a young age, no unforeseen toxicity events occurred, and MEs were decreased. The trend toward less ACS on HU in the RCT was confirmed with 10 years of follow-up. ASSC was less common on HU, and occurrence was not influenced by early initiation. BABY HUG FUS results support offering HU to all children with SCA starting at 9 months of age.

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Paper Session # 2010

## **TCD VELOCITIES CONVERSION RATE BASED ON INCREASING HB CONCENTRATION: ANALYSIS FROM THE SCCRIP COHORT**

**Jeremie Esteppe, Ze Cong, Irene Agodoa, Guolian Kang, Juan Ding, M. Beth McCarville, Jane Hankins, Winfred Wang**

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### **Background:**

Sickle cell anemia is marked by hemolytic anemia, vaso-occlusion, and end-organ damage. The most devastating complications in children are overt stroke and silent cerebral infarcts (SCIs), which result in physical and neurocognitive deficits. Transcranial Doppler ultrasonography (TCD) measures cerebral artery blood flow velocity, and children with conditional TCD ( $\geq 170$  to  $< 200$  cm/sec) are at increased risk of stroke compared to those with normal velocities ( $< 170$  cm/sec). Anemia is associated with an increased risk of stroke, SCI, and abnormal TCD ( $\geq 200$  cm/sec), but the extent to which hemoglobin (Hb) influences TCD elevation is unknown.

### **Objectives:**

Using longitudinal, real-world data, this study sought to quantify the impact of the rise in Hb during hydroxyurea (HU) therapy on TCD.

### **Design/Method:**

Children (<16 years) with HbSS/HbS $\beta$ 0-thalassemia in the Sickle Cell Clinical Research and Intervention Program (SCCRIP) who initiated HU before 12/31/2017 were included. Patients on chronic RBC transfusions were excluded. Cross-sectional correlations between TCD velocities and Hb at 1, 2, and 4 years after HU initiation were assessed. Mixed-model repeated measures (MMRM) were employed to estimate the impact of Hb on TCD.

**Results:**

In total, 202 children (mean age: 7.5 years) were evaluated. At baseline, 33 had conditional and 162 had normal TCD velocities. Mean (SD) baseline Hb was 8.4 (0.97) g/dL; reticulocyte count was 10.01 (3.81)%; WBC count was 13.24 (3.68) x 10<sup>9</sup> cells/L. In cross-sectional analysis, Hb was negatively associated with TCD at 1, 2, and 4 years post HU (all comparisons P<0.05). The rate of normalization from conditional to normal TCD velocities was assessed. Following 1 year of HU, conditional velocities normalized in: 66.7% of patients with Hb increases <0.5 g/dL, 75.0% for Hb increases 0.5-1.0 g/dL, 87.5% for Hb increases 1.0-2.0 g/dL, and 100% for Hb increases >2.0 g/dL. The same analysis after 2 years of HU yielded similar results. No patient with a conditional TCD at baseline converted to abnormal TCD. MMRM showed a 1 g/dL increase in Hb was associated with a 14 cm/sec reduction in TCD (P<0.0001). Hb remained negatively associated with TCD velocities when the same MMRM models were repeated for all patients regardless of baseline TCD (P<0.05).

**Conclusion:**

In children with conditional TCD velocities, an increase in Hb was significantly associated with a reduction in TCD velocity. The increase in Hb was associated with normalization of the TCD, which likely conveys a reduction in risk of stroke.  
Study supported by Global Blood Therapeutics.

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Paper Session # 2011

**HOSPITALIZATION FOR IRON DEFICIENCY ANEMIA IN YOUNG CHILDREN: A MULTICENTER ANALYSIS.**

**Julia Segal, Meghan McCormick, James Zullo, Ram Kalpatthi**

*UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, United States*

**Background:**

Iron deficiency anemia (IDA) can be detrimental to growth and neurodevelopmental outcomes in young children. Approximately 3–7% of preschool children will experience IDA, typically due to dietary habits. IDA is primarily managed in the outpatient setting, though some children with severe anemia may require admission for evaluation or management. No prior studies exist looking at children with severe IDA admitted to US children’s hospitals.

**Objectives:**

The primary objective is to describe characteristics of children requiring inpatient admission for a primary diagnosis of IDA. We further aimed to describe the management of these patients and factors associated with readmission.

**Design/Method:**

Using the Pediatric Health Information system (PHIS) database, an administrative database collecting inpatient data from 52 US Children's Hospitals, we identified children age 0-5 years admitted from 2004-2018 with a primary diagnosis of IDA. Information abstracted included demographics, laboratory studies, blood product transfusion, medication administration and hospital resource utilization. We compared the characteristics of patients who did or did not require ICU admission and patients who did or did not require readmission by chi-square test or t-test of means, respectively. Univariate logistic regression was used to identify factors associated with readmission.

**Results:**

A total of 4963 unique patients were identified who accounted for 5202 hospitalizations during the study period. The mean age at admission was 1.6 years with no gender difference. The population was predominantly white (52.2%) and 21.3% Hispanic. A trend towards an increasing number of admissions was noted in recent years (18% in 2004-2006 vs 23% in 2016-2018). The majority of the patients received blood transfusions (86.8%) and oral iron (59.1%), whereas only 5.1% of patients received intravenous iron. Overall, 13% of patients required ICU admission, which was more common in female patients and children of Black or Asian race. Readmission within 7 days was seen in 67 children (1.3%) and 180 children (3.6%) were readmitted with IDA at any time point. Blood transfusion and oral iron during the hospitalization were associated with decreased odds of readmission. Multiple admissions were more common in older children. Patients who were readmitted were significantly more likely to receive IV iron and less likely to receive a transfusion.

**Conclusion:**

The recent uptrend in admissions and substantial requirement of hospital resources is concerning as IDA is preventable with the potential for detrimental long term outcomes. Further study is essential to understand the etiology of the increase in admissions and for prevention of severe IDA.

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Paper Session # 2012

**THE SHWACHMAN-DIAMOND SYNDROME REGISTRY: 10 YEAR UPDATE**

**Kasiani Myers, Elissa Furutani, Sara Loveless, Maggie Malsch, Ashley Galvin, Leann Mount, Stella Davies, Akiko Shimamura**

*Cincinnati Children's Hospital Medical Center and Boston Children's Hospital, Cincinnati and Boston, Ohio and Massachusetts, United States*

**Background:**

The Shwachman-Diamond Syndrome Registry (SDSR) opened in December 2008 with the goal of understanding the natural history of Shwachman-Diamond Syndrome (SDS) to improve medical management and treatment.

**Objectives:**

The SDSR enrolls patients with a genetic diagnosis or clinical features of SDS including exocrine pancreatic dysfunction in the presence of bone marrow failure.

**Design/Method:**

Two hundred sixty-one patients have been enrolled.

**Results:**

Study subject ages span 0.3-69 years with a median age of 14 years. One hundred forty-eight individuals are genetically defined with biallelic SBDS mutations, 8 carry one SBDS mutation, 2 have an SRP54 mutation, and biallelic EFL1 and DNAJC21 mutations are carried by one subject each. Documentation of genetic diagnosis is pending in 50 individuals. Twenty-two patients are deceased at a median age of 22 years, all with biallelic SBDS mutations, predominantly due to myelodysplasia/acute myeloid leukemia (AML) (n=13), but also aplastic anemia, thoracic dystrophy and cirrhosis. Ongoing characterization of SBDS mutation-negative individuals (n=52) has identified subgroups of clinically defined SDS individuals, as well as a more heterogeneous subgroup with features of SDS but in whom a clinical diagnosis cannot be confirmed by classic diagnostic criteria. Cytopenias were nearly universal, with intermittent neutropenia the most frequent. Sixty SBDS mutation-positive patients have required use of G-CSF. Ten individuals developed AML, 16 myelodysplasia, and one B-cell lymphoma. Twenty-five SBDS mutation-positive patients underwent hematopoietic stem cell transplant (HSCT). No mutation-negative patients have undergone HSCT to date. Data from the SDSR continues to identify clinical features associated with SDS including congenital anomalies, cardiac, liver, skeletal, endocrine and neuro-cognitive abnormalities. Elevated liver enzymes early in childhood are common seen in 58% (46/79) of those with SBDS mutations as well as abnormalities by imaging in 28% (17/60). Pathologic findings were seen on liver biopsy in 20 of 26 including fibrosis, steatosis and inflammation at a median age of 1.8 years (0.4-20). Eighty-four individuals have survived into adulthood with persistence of clinical symptomatology including both pancreatic, neuropsychological, skeletal dysfunction, and hematologic disease and progression of cytopenias or dysplasia in a subset.

**Conclusion:**

These data have expanded our understanding of the disease phenotype, and identified a broader range of clinical presentations for SDS altering the clinical approach to diagnosis and management. The SDSR continues to grow and mature as a resource for clinical and biological studies in the study of this rare disorder stimulating further progress in our understanding of genetic etiology, mechanism, and disease pathophysiology and treatment.

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Paper Session # 2013

**RETROSPECTIVE REVIEW OF NEUROLOGICAL MANIFESTATIONS IN 189 PATIENTS DIAGNOSED WITH CLOVES SYNDROME**

**Ian Erkkila, Richard Greiwe, Meghan O'Hare, Steven Fishman, Ahmad Alomari, Cameron Trenor, Denise Adams**

**Background:**

Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevis, Spinal/Skeletal Anomalies/Scoliosis (CLOVES) syndrome is a very rare condition characterized by vascular malformations, fatty overgrowth and musculoskeletal deformities. CLOVES clinical features are typically defined by spinal arteriovenous malformations (AVM), tethered cord, macro/microcephaly and fatty collections on the trunk. While disease severity varies, CLOVES patients are at risk for serious neurological manifestations and complications.

**Objectives:**

Our goal was to characterize neurologic complications in CLOVES patients to improve standard of practice, better understand how to monitor patient's long term. Our results may identify precursors to neurological complications or clinical symptoms relating to CLOVES.

**Design/Method:**

An IRB-approved retrospective review of the clinical and radiological findings of 189 patients diagnosed with CLOVES syndrome was performed. Data was compiled using the Lymphatic Anomalies Registry, PowerChart, and Vascular Anomalies Center databases to analyze prevalence of neurologic involvement, age of presentation, complication type, functional impairment and any predictive trends. Patients were excluded for an inconclusive diagnosis or incomplete records.

**Results:**

Of the 189 patients reviewed, 50% (n=95) had neurological findings. Fifty-two percent (n=49) were male. Sixty-four percent (n=61) exhibited only spinal involvement, 15% (n=14) exhibited only brain involvement, and 21% (n=20) exhibited involvement of both the spine and brain. The most common type of spinal manifestation was the presence of infiltrative paraspinal lesions (n=61) associated with fatty, lymphatic malformation (n=25), venous (n=13), or arteriovenous malformation (n=21). In addition, cord tethering, compression of the cord or theca (n=48), and canal stenosis (n=8) were noted. Chiari malformation (n=16), megalencephaly (n=15), polymicrogyria (n=11), and heterotropia (n=4) were the most common cerebral findings. Fifty-six percent (n=53) had at least one of the following symptoms: neurological impairment in extremities (n=36), neurogenic bladder (n=21), seizure (n=17), and/or stroke (n=7). Forty-four percent (n=42) of patients presented with no clinical symptoms but had either spinal (n=30), brain (n=4) or combined (n=8) complications. Seizures occurred in 60% of patients with polymicrogyria, 50% with megalencephaly, and 44% with a Chiari malformation. Seventeen percent of patients with an AVM experienced a stroke. Neurological impairment, such as neurogenic bladder (n=21), caused by the paraspinal lesions and AVM was common.

**Conclusion:**

Cerebrospinal manifestations in CLOVES syndrome are common with serious neurological impairment. The presence of infiltrative paraspinal lesions, arteriovenous malformation and cord compression poses the greatest risk for spinal cord injury in CLOVES. Disorders of cortical formation are frequent and associated with seizures.



**ATTRIBUTES OF HIGH QUALITY END-OF-LIFE CARE FOR CHILDREN WITH CANCER: A STAKEHOLDER-DRIVEN STUDY**

**Prasanna Ananth, Sophia Mun, Noora Reffat, Randall Li, Tannaz Sedghi, Madeline Bilodeau, Jennifer Snaman, Cary Gross, Xiaomei Ma, Joanne Wolfe**

*Yale School of Medicine, New Haven, Connecticut, United States*

**Background:**

Prior research has sought to identify measures of high-quality end-of-life care (EOLC) for adults, including avoidance of frequent hospitalizations or intensive care unit admissions in the last month of life and enrollment in hospice greater than 3 days prior to death. For children with cancer, we do not have established quality measures to evaluate or improve EOLC delivery, and adult quality measures may not apply.

**Objectives:**

We engaged key stakeholders to explore attributes of high quality EOLC for children with cancer and examine whether existing EOLC quality measures for adults are relevant to children with cancer.

**Design/Method:**

In a multi-center qualitative study, we conducted semi-structured interviews and focus groups (N=54) with adolescent and young adult patients with advanced cancer (n=10), parents of children with advanced cancer (n=13), bereaved parents (n=12), and interdisciplinary professionals (n=19). Sessions were audio-recorded, inductively coded, and analyzed using grounded theory to identify recurrent themes.

**Results:**

Participants uniformly cited direct communication with the child, optimal symptom control, honoring family preference for location of EOLC, consistency of healthcare team members, and interdisciplinary team involvement as critical elements of high quality EOLC. Many participants valued access to the emergency department and hospital for symptom management or supportive care. Several participants also favored use of chemotherapy near the end of life, particularly if chemotherapy might alleviate symptoms. Most wished to avoid mechanical ventilation or cardiopulmonary resuscitation. Notably, participants generally valued hospice, and more than half of bereaved parents had utilized hospice services. However, patients and parents held many misconceptions about hospice.

**Conclusion:**

Childhood cancer stakeholders define high quality EOLC through a combination of patient- and family-reported measures (e.g. direct communication, symptom control, location of death, care relationships) and healthcare utilization measures (e.g. hospice use, avoidance of intensive resuscitation). Many attributes of high quality EOLC for children with cancer diverge from those

in adults. This study underscores the importance of integrating patient- and family-reported outcomes into measurement of EOLC quality for children with cancer.

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Paper Session # 2015

## **SELUMETINIB IN CHILDREN WITH CLINICALLY ASYMPTOMATIC INOPERABLE NF1 RELATED PLEXIFORM NEUROFIBROMAS**

**Brittany Glassberg, Andrea Gross, Eva Dombi, Andrea Baldwin, Trish Whitcomb, Michael Fisher, Aerang Kim, Brian Weiss, Scott Paul, Seth Steinberg, Amanda Carbonell, Kara Heisey, Janet Therrien, Oxana Kapustina, Austin Doyle, Malcolm Smith, Brigitte Widemann**

*National Institutes of Health, Bethesda, Maryland, United States*

### **Background:**

Neurofibromatosis type 1 (NF1) is a genetic disorder characterized by hyperactivation of the RAS pathway. Up to 50% of people with NF1 develop histologically benign tumors called plexiform neurofibromas (PN). PN-related symptoms such as pain and airway obstruction can be debilitating, and often worsen with increasing PN volume. A phase II trial of selumetinib (AZD6244, ARRY142668), a MEK1/2 inhibitor, demonstrated PN shrinkage, growth inhibition and clinical improvement in children with baseline PN-related symptoms (stratum 1, NCT01362803).

### **Objectives:**

We characterized the effect of selumetinib in patients without clinically significant baseline PN-related morbidity (stratum 2) and determined if PN-related morbidity developed during the course of treatment.

### **Design/Method:**

Children 2-18 years-old with NF1 and inoperable PN but without clinically significant PN related morbidity were identified by history, clinical exam and MRI. Potential PN-related morbidities and associated functional assessments (motor, airway, vision) were determined based on tumor location. Patients received selumetinib PO 25 mg/m<sup>2</sup>/dose BID for continuous 4-week cycles, with volumetric MRI and functional assessments at baseline and then after every 4 cycles.

### **Results:**

Twenty-five patients (64% male) had a median age of 12.3 years (range 4.5-18.1) and median baseline tumor volume of 381 mL (range 12-3159). Eleven patients had progressive PN growth at baseline ( $\geq 20\%$  increase in PN volume within 15 months prior to enrollment). After 12 cycles of treatment, PN volume decreased by a median of 29% (range -37.9% to -2.5%), with 18 patients (72%) achieving a partial response ( $\geq 20\%$  shrinkage) and no patients with progressive disease. At baseline, functional evaluations of strength (n=12), range of motion (n=8), exophthalmometry (n=2) and pulmonary function (n=8) were within normal limits, excluding patients with non-PN related comorbidities limiting their functional status (e.g. scoliosis). There

were no statistically significant changes (improvement or worsening) in any of these measures after 12 cycles ( $p > 0.05$ ). Selumetinib was well tolerated, with only 3 patients experiencing dose limiting toxicity, one of which came off treatment due to toxicity (elevated lipase). After 12 cycles, 23 (92%) patients remain on treatment.

**Conclusion:**

Selumetinib shrinks inoperable NF1-related PN in the majority of pediatric patients enrolled on this study presenting without clinically significant morbidity. In addition, none of the patients developed PN-related morbidity during one year of treatment, and selumetinib was generally well tolerated. This suggests that treatment with MEK1/2 inhibition may provide benefit by preventing the development of PN-related morbidity, though follow-up is relatively short and additional prospective studies are needed.

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Paper Session # 2016

**LAROTRECTINIB EFFICACY AND SAFETY IN PEDIATRIC PATIENTS WITH TRK FUSION CANCER**

**Catherine Albert, Birgit Geoger, Cornelis van Tilburg, Steven DuBois, Noah Federman, Ramamoorthy Nagasubramanian, Francois Doz, Daniel Orbach, Stefan Bielack, Neerav Shukla, Brian Turpin, Michela Casanova, Sheri Spunt, Shivani Nanda, Barrett Childs, Alberto Pappo, Theodore Laetsch, Leo Mascarenhas**

*Seattle Children's Hospital, University of Washington, Seattle, Washington, United States*

**Background:**

Neurotrophic tyrosine receptor kinase (NTRK) 1, 2, and 3 gene fusions are oncogenic drivers in pediatric and adult malignancies. Larotrectinib, a Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved selective tropomyosin receptor kinase (TRK) inhibitor, was well tolerated and efficacious in pediatric patients with TRK fusion cancer enrolled in a phase 1 study (Laetsch et al. Lancet Oncol. 2018).

**Objectives:**

To report updated efficacy and safety data for larotrectinib in pediatric patients with TRK fusion cancer.

**Design/Method:**

Pediatric patients (<18 years) with non-central nervous system (CNS) TRK fusion cancers in larotrectinib clinical trials NCT02637687 and NCT02576431 were included in this analysis. Most patients were treated at the FDA- and EMA-approved dose (100 mg/m<sup>2</sup> twice daily; maximum 100 mg twice daily). Larotrectinib was administered until complete surgical resection, disease progression, withdrawal, or unacceptable toxicity. Response was investigator-assessed using RECIST v1.1.

**Results:**

At the data cut-off of February 19, 2019, 52 children with non-CNS TRK fusion cancer and

treated with larotrectinib were identified from the two clinical trials. Median age was 1.3 years (range <0.1–14.0 years); 24 patients (46%) were <1 year. Twenty-nine patients had infantile fibrosarcoma, 19 had other soft tissue sarcomas, two had thyroid cancer, and one each had melanoma and congenital mesoblastic nephroma. Gene fusions involved NTRK1 (n=20; 38%), NTRK2 (n=2; 4%), and NTRK3 (n=30; 58%; including eight patients pending confirmation). Thirty-eight patients had received =1 prior systemic therapy. In 51 evaluable patients, overall response rate was 92%. Best overall response was complete response (CR) in 16 patients (31%; including three pathological CR and two pending confirmation), partial response in 31 patients (61%; six pending confirmation), and stable disease in four patients (8%). At a median follow-up of 11.1 months, median duration of response for all confirmed responses was not reached (range 1.6+ to 29.5+ months). At data cut-off, 39 of 52 patients (75%) remained on treatment; median time on treatment was 7.5 months. Treatment was discontinued in six patients due to disease progression (n=5) or treatment-related adverse events (AEs) (n=1). AEs related to larotrectinib were mostly Grade 1–2; 9 patients (17%) experienced Grade 3 or 4 treatment-related AEs. The most common treatment-related AEs of any grade were increased alanine aminotransferase, increased aspartate aminotransferase, and decreased neutrophil count.

### **Conclusion:**

Larotrectinib demonstrated a high and durable response rate and was well tolerated in pediatric patients with TRK fusion cancer regardless of tumor type.

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Paper Session/Early Career Travel Stipend Recipient # 2024

## **DISCOVERY OF A NOVEL RAL PATHWAY DISORDER (“RALOPATHY”) WITH EARLY ONSET MYELOPROLIFERATIVE DISEASE**

**Harry Lesmana, Sushree Sahoo, Georgios Christakopoulos, Charnise Goodings-Harris, Jie Liu, William Wright, Omar Niss, Mitchell Weiss, Theodosia Kalfa, Marcin Wlodarski**

*St. Jude Children's Research Hospital, Memphis, Tennessee, United States*

### **Background:**

Ras pathway disorders (Rasopathies) predispose to the development of myeloproliferative disorders (MPD). Juvenile myelomonocytic leukemia (JMML) is a unique form of pediatric MPD caused in the majority of cases by mutations in either NRAS, KRAS, PTPN11, CBL, or NF1. Although hyperactivation of the canonical Ras-Raf-MEK-ERK cascade is the hallmark of JMML, multiple studies suggest that dysregulation of non-canonical Ras signaling pathway is sufficient to produce similar Ras-transforming capability. Ral (Ras-like) guanine nucleotide exchange factors (RalGEFs) are Ras downstream effectors that catalyze the GDP/GTP exchange on Ral G-protein leading to its activation. RGL2 is one of the four RalGEFs with a Ras-association domain that directly couples Ras to Ral pathway. Here, we describe the discovery of a homozygous RGL2 c.1020+4T>A mutation in an infant with massive organomegaly, cardiomyopathy, liver fibrosis and typical MPD-hypercellular marrow. Similar clinical phenotype was observed in the brother of the index patient who deceased as infant.

### **Objectives:**

To investigate the role of Ras-RalGEF-Ral pathway in human hematopoiesis and elucidate the molecular mechanism leading to disordered hematopoiesis.

**Design/Method:**

Using CRISPR/Cas9 technology we introduced patient’s homozygous RGL2 mutation into K562 cell-line (K562-RGL2mut/mut) cultured with/without GM-CSF. To determine the functional consequences of this mutation, we performed protein studies, RNAseq and Ral-activation assay. Finally, to investigate the role in hematopoiesis in vitro, we ablated RGL2 expression in healthy CD34+ cells using Cas9/sgRNAs followed by erythropoietic culture. Indels analysis was performed with targeted NGS and terminal erythroid differentiation was assessed using flowcytometry.

**Results:**

Compared to RGL2-wild type, K562-RGL2mut/mut cells exhibited GM-CSF hypersensitivity resembling JMML. Although protein levels were not affected, this RGL2 mutation results in aberrant distribution of RGL2 transcripts with overrepresentation of transcript lacking the CDC25-homology functional domain. This resulted in decreased catalytic activity of RGL2, compatible with loss-of-function. Distinct gene expression profile was identified in K562-RGL2 mut/mut cells, including overexpression of CXCR4, TGF-beta, IL18 and ribosome biogenesis pathways associated with disordered hematopoiesis. Finally, deletion of RGL2 in healthy CD34+ cells caused expansion of early erythroid progenitors with delayed terminal erythroid differentiation and increased apoptosis. To this end, we are investigating the effect of patient mutation in iPSC-derived hematopoiesis.

**Conclusion:**

Dysregulation of the Ras-RalGEF-Ral pathway underlies the hematological phenotype of this novel “Ralopathy” disorder characterized by hypersensitivity to GM-CSF, delayed terminal erythroid differentiation and increased apoptosis. This signifies the importance of this non-canonical Ras pathway in the regulation of hematopoiesis and a new candidate explaining the etiology of unresolved MPD.

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Paper Session # 2025

**GUT DECONTAMINATION ALTERS THE INTESTINAL MICROBIOTA DURING ALLOGENIC BONE MARROW TRANSPLANT**

**Chris Severyn, Wendy London, Paige Kao, Sophie Silverstein, Michelle Li, Kelly Verrill, Jerome Ritz, Ami Bhatt, Jennifer Whangbo**

*Stanford University, Palo Alto, California, United States*

**Background:**

Despite promising results from early preclinical studies demonstrating that “gut decontamination” can prevent the development of acute graft-versus-host disease (aGVHD) after allogeneic hematopoietic stem cell transplantation (alloHSCT), there is insufficient data supporting a clear benefit in humans. Here, we report the interim results of a randomized-

controlled trial of gut decontamination in pediatric alloHSCT patients.

**Objectives:**

- (1) Describe longitudinal differences in the intestinal microbiota composition between alloHSCT patients with and without GD.
- (2) Describe the diarrhea frequency, and GVHD and bacteremia incidence during the first 100 days post-transplant in the two groups.

**Design/Method:**

Randomized phase 2 study examining the impact of GD on intestinal microbiome composition in pediatric alloHSCT patients. 20 patients were enrolled and randomized to receive (GD) or not receive (no GD) oral vancomycin-polymyxin from day -5 through engraftment. Stool samples were collected at fixed, predetermined intervals through day +100. The primary endpoint was microbial diversity at 2 weeks post-HSCT. Secondary endpoints included the frequency of diarrhea, incidence of aGVHD and bacteremia during the first 100 days post-transplant, survival, and malignant disease relapse at 2 years after study entry. Comparisons by treatment group were performed with Fisher's exact test (binary) or Wilcoxon rank-sum test (continuous).

**Results:**

All 20 patients enrolled completed the study. Shotgun metagenomic sequencing (median count of  $1.4 \times 10^7$  reads per sample (range  $1.3 \times 10^6$  to  $3.3 \times 10^7$ ) of the microbiome in the first 10 patients (4 GD, 6 No GD) demonstrates the average change in microbial diversity (as measured by Shannon diversity) at 2 weeks is 1.7 (SD 0.86) in GD and 0.65 (SD 0.61) in No GD. No difference in diarrhea was seen between arms (GD = 4; no GD =4;  $p \geq 0.99$ ), nor aGVHD grade II or above (GD = 1; no GD =3;  $p=0.58$ ). Bacteremia within the first 100 days post-HSCT occurred in 1/10 patient in GD, whereas 5/10 patients in No GD had 8 different bacteremia events ( $p=0.14$ ).

**Conclusion:**

There is no statistical difference in the diarrhea, aGVHD, or bacteremia incidence between the two groups. Subanalysis of the gut microbiota in the first 10 patients demonstrates greater representation of the order Bacteroidales and Clostridiales in the no GD arm. Confirmed bloodstream infections were found predominantly in the class Bacilli and Gammaproteobacteria. Although not statistically significant, given the substantial difference in bacteremia, microbiome analysis from the remaining patients is ongoing.

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Paper Session # 2026

**PROSPECTIVE TRIAL OF IBRUTINIB IN CHILDREN WITH CHRONIC GRAFT VERSUS HOST DISEASE**

**Sonali Chaudhury, Peter Shaw, Alfred Gillio, Jean-Hugues Dalle, Chris Fraser, Marco Zecca, Keon Hee Yoo, Hyoung Jin Kang, Shalini Shenoy, Amy Keating, Ying Luan, Yvonne Pak, Justin Wahlstrom, Lori Styles, Paul Carpenter**

*Ann & Robert H. Lurie Children's Hospital, Chicago, Illinois, United States*

**Background:**

No therapies are currently approved for pediatric chronic graft-versus-host disease (cGVHD), a debilitating, life-threatening complication of allogeneic stem cell transplantation. Ibrutinib, a once-daily oral Bruton's tyrosine kinase inhibitor, is the only therapy approved in the US for adults with cGVHD after failure of prior systemic therapy, and has resulted in durable responses and improved quality of life.

**Objectives:**

This open-label, multicenter, international phase 1/2 study (PCYC-1146; NCT03790332) evaluates PK, safety, and efficacy of ibrutinib in children with cGVHD.

**Design/Method:**

Eligible patients had moderate/severe cGVHD (stringently defined by 2014 NIH criteria) that was either refractory ( $\geq 1$  to  $< 22$  years) or new-onset ( $\geq 12$  to  $< 22$  years). Patients aged  $< 12$  years received once-daily ibrutinib 120mg/m<sup>2</sup> (50% adult dose), escalating to 240mg/m<sup>2</sup> (100% adult dose) after 14 days without ibrutinib-related grade  $\geq 3$  toxicity; patients  $\geq 12$  years received once-daily ibrutinib 420mg. Treatment continued until no longer required, new systemic cGVHD therapy initiation, cGVHD progression, underlying disease recurrence, or unacceptable toxicity. Preliminary PK, safety, and response assessment per 2014 NIH criteria are presented.

**Results:**

Fifteen children with median age 11 years (range, 3-17) and median 3 prior cGVHD regimens (range, 1-5) were enrolled. Preliminary plasma concentration-time profiles for ibrutinib (240mg/m<sup>2</sup>) were consistent with those observed in adults with cGVHD. Four (27%) patients had grade 3 serious AEs. No invasive fungal disease was observed; one case of grade 3 pneumocystis jirovecii pneumonia was reported. At median follow-up of 1.9 months (range, 0.4-4.6), best ORR was 46% (6/13; 1 [8%] CR; 5 [38%] PR; 6 [46%] SD; 1 [8%] NE); no patients had PD. At week 5, among 13 patients with sufficient follow-up, ORR was 38% (5/13; 5 [38%] PR; 7 [54%] SD; 1 [8%] NE). At week 13, ORR was 50% (3/6; 1 [17%] CR; 2 [33%] PR; 3 [50%] SD). At time of analysis, 12 patients continue ibrutinib (median duration, 1.9 months); all 3 discontinuations were not related to NIH-defined progression or AEs.

**Conclusion:**

In this preliminary analysis of heavily pretreated children with moderate/severe cGVHD, the administered dosing regimen achieved plasma concentration-time profiles consistent with those observed in adults with cGVHD. Safety profile was consistent with known risks; no patients discontinued due to PD. Response evaluation based on strict application of 2014 NIH criteria resulted in 46% best ORR at this early timepoint, demonstrating promising activity of ibrutinib in children resistant to multiple lines of prior therapy. Enrollment continues with longer follow-up expected.

Sponsor: Pharmacyclics LLC, an AbbVie Company

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Paper Session # 2027

## CD30-DIRECTED CAR T-CELLS FOR THE TREATMENT OF PEDIATRIC HODGKIN LYMPHOMA AND NON-HODGKIN LYMPHOMA

George Hucks, Barbara Savoldo, Gianpietro Dotti, Catherine Cheng, Spencer Laing, Kimberly Kasow, Michael Winstead, Arpita Patel, Cammie Presler, Natalie Grover, Thomas Shea, Marcie Riches, Anne Beaven, Jonathan Serody

*University of North Carolina, Chapel Hill, North Carolina, United States*

### **Background:**

Chimeric antigen receptor (CAR) T-cell therapy, specifically CD19-directed, has been effective in treating B-cell acute lymphoblastic leukemia. However, the efficacy of CAR T-cell therapy for other pediatric malignancies is unknown, and alternative targets, such as CD30, are needed. CD30, a prime target, is expressed in classical Hodgkin Lymphoma (HL) and in some Non-Hodgkin Lymphoma (NHL). In adults, CD30-directed CAR-T cells are well-tolerated and have shown promising efficacy. Here, we present results of CD30-directed CAR-T cell therapy in pediatric patients.

### **Objectives:**

Determine the maximum safe dose (MSD) of CD30-directed CAR T-cells in pediatric patients with relapsed/refractory CD30-expressing HL and NHL.

### **Design/Method:**

Pediatric patients with CD30+ HL and NHL were enrolled on two trials at the University of North Carolina. Two patients were enrolled on a phase I study and received CD30-directed CAR T-cells after autologous stem cell transplant (ASCT), and 3 patients were enrolled on a phase Ib/II study and received CD30-directed CAR T-cells after lymphodepletion with bendamustine and fludarabine. Both trials continue to accrue patients to determine MSD.

### **Results:**

For all 5 patients, infusions were well-tolerated and no neurotoxicity experienced. No cytokine release syndrome (CRS) was attributed to the treatment.

On the post-ASCT study, 1 patient with HL and 1 with Anaplastic Large Cell Lymphoma (ALCL) were treated. All adverse events (AE) were less than grade 4. The patient with ALCL had progressive disease, and the patient with HL remains in complete remission (CR) 18 months following therapy.

Three patients with relapsed/refractory disease (1 HL and 2 ALCL) were treated on the post-lymphodepletion study. Most grade 4 AEs were anticipated hematologic toxicity secondary to lymphodepletion. One patient with ALCL had symptoms compatible with CRS but instead were secondary to progressive disease. This patient had other grade 4 toxicities including macrophage activating syndrome, acute kidney injury, elevated CPK, AST, ALT, hypotension, respiratory failure, and supraventricular tachycardia, and ultimately died. Autopsy confirmed progressive ALCL, which is the likely etiology of the other grade 4 AEs. The other patients achieved CR with the longest follow up being 6 months.



**Conclusion:**

This early data on CD30-directed CAR T-cells in these dose escalating studies is promising. The pediatric patients tolerated the engineered cell therapy well with CRs observed. Our results also show that not all CAR T-cell products have severe neurotoxicity or CRS and open the doors for potential uses of CAR-T cells in other malignancies.

After study initiation, UNC entered into a research collaboration with Tessa Therapeutics.

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Paper Session # 2028

**MIR29B MEDIATES EPIGENETIC MECHANISMS OF HBG GENE ACTIVATION IN SICKLE CELL DISEASE**

**Ashley Fitzgerald, Alana Smith, Biaoru Li, Betty Pace, Athena Starlard-Davenport**

*University of Tennessee Health Science Center, Memphis, Tennessee, United States*

**Background:**

Sickle cell disease (SCD) affects over two million people worldwide with high morbidity and mortality in underdeveloped countries. Therapeutic interventions aimed at reactivating fetal hemoglobin (HbF) is an effective approach for improving survival and ameliorating the clinical severity of SCD.

**Objectives:**

A class of agents, with epigenetic capabilities, that inhibit DNA methyltransferase (DNMT) activity show promise as HbF inducers because off-target effects are not observed at low concentrations.

**Design/Method:**

Blood samples were obtained from twelve patients with homozygous sickle cell anemia (HbSS) not on hydroxycarbamide (HC) therapy followed in the Sickle Cell Program at Augusta University. Subsequently red blood cells were processed in order to isolate reticulocytes for total RNA extraction using TRIzol. Isolated reticulocytes were subjected to microRNA analysis to identify high and low HbF groups. In addition to this CD34+ stem cells were used to generate human primary erythroid cells. Erythroid progenitors were transfected with human mature Micro-RNA 29B (MIR29B) or control scramble mimic and treated with or without 0.5  $\mu\text{mol/l}$  of decitabine or pretreatment with 100 nmol/l of MIR29B. Cells were subjected to reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR), western blot, and flow cytometry analysis. KU812 cells, a human leukemic cell line, were also transfected with varying concentrations of pre-MIR29B and treated with the same drug dosages as the Erythroid progenitor cells. KU812 cell were also treated with 75  $\mu\text{mol/l}$  of HC and subjected to RT-qPCR for analyses of SCD targeted genes.

**Results:**

Overexpression of MIR29B in human KU812 cells, and primary erythroid progenitors

significantly increased the percentage of HbF positive cells, while decreasing the expression of DNMT3A and the HBG repressor (MYB). Furthermore, HBG promoter methylation levels decreased significantly following MIR29B overexpression in human erythroid progenitors. We subsequently, observed higher MIR29B expression in SCD patients with higher HbF levels compared to those with low HbF.

**Conclusion:**

Our findings provide evidence for the ability of MIR29B to induce HbF, and supports further investigation to expand treatment options for SCD.

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Paper Session # 2029

**OUTCOMES OF RIGHT ATRIAL THROMBI IN CHILDREN; AN OBSERVATIONAL COHORT STUDY**

**Benjamin Barnes, William Ravekes, Grace Freire, Earnest Amankwah, Austin Sellers, David Procaccini, Neil Goldenberg, Cliff Takemoto**

*Johns Hopkins University, Baltimore, Maryland, United States*

**Background:**

Pediatric right atrial thrombosis (RAT) carries the potential for mortality and significant morbidity. However, the effectiveness and benefit of anticoagulation treatment is currently unknown. Characteristics of RAT, including larger size, increased mobility, globularity and serpiginous shape have been suggested as high-risk features associated with poor outcomes in case series. Conversely, a subset of patients without these high-risk features may have favorable outcomes, even without anticoagulation. Clinical outcomes of RAT that are treated with anticoagulation based on these risk factors have not been reported.

**Objectives:**

To compare outcomes of RAT managed with and without anticoagulation.

**Design/Method:**

Retrospective single-center cohort study at Johns Hopkins Hospital. Patients 0 to 21 years with RAT diagnosed on echocardiography from 2013 to 2018 were included. The electronic medical record was reviewed to collect demographics, treatment modalities and patient outcomes. Echocardiogram reports were reviewed for thrombi characteristics. Anticoagulation was administered based on discretion of the treating clinician but informed by the presence/absence of previously-suggested high-risk features of the RAT and assessment for increased clinically increased bleeding risk.

**Results:**

We identified 57 patients with RAT with a median age of 25 days (2 days – 20 years). The majority (n=54, 94.7%) were associated with a provoked risk factor. Twenty-seven (47%) were treated with anticoagulation while 29 (51%) were untreated.

The median thrombus dimension was larger in the treated versus untreated group (9.15 mm versus 5.7 mm). The treated group had an increased frequency of highly mobile RAT (35%) compared to the untreated group (14%).

Of the 27 patients receiving treatment, enoxaparin was most commonly prescribed (n=22), followed by unfractionated heparin (n=10), aspirin (n=3), bivalirudin (n=3) and warfarin (n=1), with several patients receiving multiple agents. Three patients underwent thrombectomy and one had an inferior vena cava (IVC) filter placed. Five (19%) experienced clinically relevant bleeding. Over half (n=14, 51%) of the treated patients had comorbidities associated with adverse outcomes compared to 13.8% (n=4) of untreated patients. Six treated patients (22%) died compared to two (6%) untreated patients. Thrombus progression was more frequent in anticoagulated patients (n=3, 11% vs n=1, 3%)

### **Conclusion:**

We report the outcomes of pediatric RAT from a single large tertiary center. We found that among patients managed without anticoagulation and with previously-suggested low risk features (e.g. smaller RAT dimension and less mobility), risks of mortality, progression, and PE were low. Future prospective studies should evaluate whether anticoagulation can be safely withheld from such patients.

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Paper Session/Advanced Practice Provider Travel Stipend Recipient # 2030

## **LONG TERM NEUROLOGICAL OUTCOMES IN PEDIATRIC THROMBOTIC THROMBOCYTOPENIC PURPURA**

**Sara Graciaa, Segun Adeagbo, Patricia McElfresh, Michael Briones, Satheesh Chonat**

*Children's Healthcare of Atlanta, Atlanta, Georgia, United States*

### **Background:**

Thrombotic Thrombocytopenic Purpura (TTP) is caused by a severe deficiency of ADAMTS13, a von Willebrand factor-cleaving protease, resulting in microangiopathic hemolytic anemia, thrombocytopenia, and ischemic organ damage. It can be immune-mediated (iTTP), due to an autoantibody against ADAMTS13, or congenital (cTTP), from mutations involving ADAMTS13 gene. Prompt recognition and initiation of treatment of this rare disorder have significantly improved the mortality, but the risk of relapse and long-term neurological morbidity remains a challenge. Pediatric TTP is underappreciated and underreported. We conducted a retrospective-prospective cohort study of all pediatric patients presenting with TTP to one of the largest pediatric hematology centers in the United States.

### **Objectives:**

We aim to describe the clinical features, laboratory trends, treatment regimens, and focus on neurological outcomes in pediatric patients with TTP.

### **Design/Method:**

Retrospective-prospective chart review between 2001 and 2019.

**Results:**

Fifteen individuals with a median age of 14 years (range: 3-19) were identified with ADAMTS13 activity of < 10% at disease onset and positive anti-ADAMTS13 antibody when available. Sixty percent of the patients were females, and 60% of patients were African American. There was a total of 9 relapses in 5 patients (33%), amounting to 24 episodes. Among the presenting symptoms; fever was reported in 2 (8%), hematological abnormalities in 21 (91%), but neurologic (75%), renal (75%), and gastrointestinal symptoms (45%) were more common than described in adults. A majority of acute cases were treated with plasma exchange (PEX) for a minimum of 5 days (73%) and corticosteroids (86%). Sixty percent received at least one course of rituximab. One patient required steroids, rituximab, and caplacizumab for refractory disease requiring 19 PEX sessions. No known deaths occurred, except for a teenage patient who had a relapse during pregnancy, resulting in fetal loss. Notably, nearly half of the patients (46%) reported persistent or worse neurologic complaints, including cognitive delay, learning difficulties, and severe depression, at least six months to 8 years from disease onset.

**Conclusion:**

Our cohort represents a distinct and previously undescribed pediatric patient population with iTTP. Children recovering from iTTP are at high risk for neurological deficits, from initial and possibly ongoing microvascular disease. Surveillance of ADAMTS13 activity during remission to detect and promptly treat early relapse, and neuropsychological testing in all children with TTP can potentially modify long-term neurological sequelae. The use of novel agents, such as caplacizumab and recombinant ADAMTS13, may vastly change the future landscape of pediatric and adult TTP management.

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Paper Session # 2031

**RESTORING THE SECRETION AND ACTIVITY OF FVIII MUTANTS BY A PROTEOSTASIS REGULATOR**

**Wei Wei, Bin Zhang**

*Genomic Medicine Institute, Cleveland Clinic Lerner Research Institute, Cleveland, Ohio, United States*

**Background:**

Quantitative or qualitative deficiency in factor VIII (FVIII) result in Hemophilia A. Cellular protein homeostasis is disturbed by FVIII mutant, and thus excessive mis-folding and degradation of FVIII mutant result in FVIII deficiency.

**Objectives:**

The folding and/or trafficking of FVIII can be enhanced by proteostasis regulators, leading to increased coagulation factor levels sufficient to restore hemostasis.

**Design/Method:**

A cell-based screening using a FDA-approved drug library and a natural compound library were

performed to look for compounds that enhance secretion of FVIII.

**Results:**

SAHA was identified increase both wild-type (WT) and a missense mutant FVIII via drug screening. We first used the WT and M614T A2 domains to detect the working time and concentration of SAHA in HEK 293T cells. The maximum effect of SAHA was achieved at 2.5ug/ml at 24 hours. We next studied the effect of SAHA on activity and secretion of several full-length FVIII mutants (A469S, R527W, R531G, I566T, N582D, S584T, R593C, R1997G, R2150C). Except for N582D, activity levels of all FVIII mutants in cell culture media were elevated 3-14 folds by SAHA (P<0.05). Antigen levels of FVIII mutants in both cell lysates and cell culture media increased by ~3 folds by SAHA (P<0.05). The increase in activities of several FVIII mutants is higher than the increase in antigen levels of the same mutants, which indicates that SAHA treatment also increased the proportions of functional proteins. To investigate the mechanism, we studied the interactions of WT FVIII and several responsive mutant FVIII (I566T, S584T, R593C and R1997C) with endoplasmic reticulum (ER) chaperones. The protein levels of BiP and calreticulin were not affected by SAHA. However, the interactions of BiP with both WT FVIII and FVIII mutants were remarkably enhanced by SAHA, while no significant differences in the interactions of calreticulin with FVIII were observed. The effect of SAHA can be blocked by simultaneously treating cells with a BiP inhibitor SubAB. We next measured mRNA levels of BiP as well as FVIII via real time PCR. Similar to protein levels, BiP mRNA levels were not changed by SAHA. However, FVIII mRNA levels were elevated by 1.2 to 3.1 folds (P<0.05) by SAHA.

**Conclusion:**

SAHA increases FVIII antigen and activity levels by increasing FVIII mRNA levels and by enhancing its folding and trafficking via specifically promoting its interaction with the ER chaperon BiP. SAHA is a potential proteostasis regulator that can increase the secretion and restore the function of certain FVIII missense mutants.

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Poster # 001

**EVOLUTION OF MODERATE APLASTIC ANEMIA INTO SUBCLINICAL PNH/AA & SUCCESSFUL TREATMENT WITH HAPLO- BMT**

**Meghana Srinivas, Jennifer Krajewski, Melanie Hankewycz, Nancy Durning, Alfred Gillio**

*Hackensack University Medical Center, Hackensack, New Jersey, United States*

**Background:**

Aplastic Anaemia (AA) is a diagnosis after exclusion of other acquired or inherited diseases presenting with pancytopenia. Pediatric AA, may often overlap with other diseases including PNH and myelodysplastic syndrome (MDS). The diagnosis is difficult and can evolve over time. There are new tests and methodologies to guide diagnosis & treatment decision making.

**Objectives:**

We describe an 18-year old girl who presented with pancytopenia, whose diagnosis evolved from

moderate AA to AA/PNH, her diagnostic evaluation & successful treatment with haplo-BMT

**Design/Method:**

Case report/literature review

**Results:**

Patient is an 18-year-old girl referred for pancytopenia. Initial WBC was  $2.4 \times 10^9/L$ , hemoglobin 9.7g/dl, platelets  $39 \times 10^9$ , ANC of 590, Absolute Retic Count 68,000 cells/mm<sup>3</sup>. Bone Marrow (BM) exam revealed a hypocellular marrow (30% cellularity) without dysplasia or blasts. Chromosomal analysis, FISH, telomere length were normal. BM failure panel targeting 60 genes was negative. PNH studies showed 2.6% erythroid, 2% granulocytes, 2.7% monocytes failing to express GPI associated anchoring proteins (GPI-APs) representing a small PNH clone, not unusual in patients with AA. These studies were c/w with moderate AA (modAA). Standard management of modAA is careful observation. Since our patient was starting college, we treated her with Immunosuppressive Therapy (IST) consisting of equine Anti-thymocyte globulin & Cyclosporine. At 24 weeks post IST, no response was observed.. Repeat PNH testing showed 2% erythroid, 5% monocytes and 4% granulocytes that were deficient in GPI-Aps. BM showed 60% cellularity and relative erythroid hyperplasia. With increasing marrow cellularity but persistent pancytopenia we began to suspect MDS. Repeat chromosomal analysis and FISH studies were normal. Foundation One myeloid panel was negative. At 28 weeks, PNH testing showed 1.3% erythrocytes, 5.6% granulocytes and 5.4% monocytes were negative for GPI-APs. Our patient had evolved from modAA to subclinical PNH/AA which accounted for the normocellular marrow. High Disease Activity (HDA) defined as LDH = 1.5 times upper limit of normal; associated with large PNH clones and can guide the use of eculizumab as pre-BMT therapy. Our patient's LDH was normal; unlikely to respond to eculizumab. Therefore she received reduced intensity conditioning & haplo-BMT. At 311 days post-BMT, she has 100% donor chimerism and PNH clone elimination.

**Conclusion:**

The case illustrates diagnostic challenges of patients presenting with pancytopenia; the overlap and possible evolution of disease classifications; concepts like HDA in PNH to help guide decision making; new diagnostic testing; the successful use of RIC and haplo BMT in a patient with PNH/AA and a normocellular marrow.

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Poster # 002

**PEDIATRIC BENIGN NEUTROPENIA: ASSESSING PRACTICE PREFERENCES IN CANADA**

**Rozalyn Chok, Victoria Price, MacGregor Steele, Catherine Corriveau-Bourque, Aisha Bruce**

*University of Alberta, Edmonton, Alberta, Canada*

**Background:**

In children, chronic isolated neutropenia is commonly a self-limiting condition with a benign

clinical course. This entity is referred to as benign neutropenia, autoimmune neutropenia (AIN), or chronic idiopathic neutropenia (CIN). Although the underlying pathophysiology is presumed to be immune-mediated peripheral destruction of neutrophils, the approach to management is often the same as that of neutropenia induced by chemotherapy or malignancy. An evidence-based approach to pediatric benign neutropenia is not well-defined in the literature.

**Objectives:**

To elucidate practice patterns in the diagnosis and management of pediatric benign neutropenia in Canada

**Design/Method:**

A case-based survey was distributed to pediatric hematology/oncology staff and trainees across Canada. The survey included multiple choice and free text questions to capture information about clinical decision-making at different time points in the presentation of benign neutropenia. Exploratory statistical analysis was performed using contingency tables to identify associations between demographic characteristics of practitioners and management of neutropenia.

**Results:**

We received 45 completed surveys for a response rate of 64%. The survey case follows a previously healthy Caucasian toddler at first presentation with fever and severe neutropenia. At initial presentation, most respondents (67%) recommended partial septic workup, but 11% recommended no investigations. Nearly 70% would treat with empiric intravenous antibiotics, while 24% would discharge home with no antibiotics. All respondents recommended follow up with observation and repeat complete blood count (CBC). For neutropenia lasting longer than 3 months, 53% would continue with observation only. The most frequently recommended investigation was quantitative immunoglobulins (42%), but a small cohort (7%) recommended bone marrow studies at this point. Nearly 60% of respondents do not use anti-neutrophil antibody testing in their practice. There was an association between level of training and use of anti-neutrophil antibody testing, with significantly more trainees reporting that they would use this test (P=0.049). The most common indications for bone marrow biopsy were initiating granulocyte colony-stimulating factor (G-CSF), recurrent/severe infection, or prolonged neutropenia. The most common indications for genetic testing were positive family history or age less than 12 months. Indications for G-CSF therapy were primarily based on severity and frequency of infection. Most respondents (84%) would not recommend prophylactic antibiotics.

**Conclusion:**

There is considerable variability in the investigation and management of benign neutropenia among pediatric hematologists in Canada. This survey highlights the need for stronger evidence and consensus guidelines to develop a more consistent approach across the country.

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Poster # 003

**A QUALITY IMPROVEMENT PROJECT TO IMPROVE THE RECOGNITION AND MANAGEMENT OF NEUTROPENIC ENTEROCOLITIS**

**Meghan McCormick, Katherine Halligan, Lisa Maurer, James Felker, Jean Tersak, Andrew Bukowski, Steven Allen, Alberto Broniscer, Scott Maurer, Julia Meade, A. Kim Ritchey, Brittani Seynnaeve**

*UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, United States*

**Background:**

Neutropenic enterocolitis (NE), or typhlitis, is a severe and life-threatening form of colitis occurring primarily in neutropenic oncology patients. Due to its rarity, there is not a standardized approach to diagnosis and management, which may lead to delayed recognition, inadequate treatment and exposure to unnecessary procedures.

**Objectives:**

Our aim is to standardize the evaluation and management of pediatric NE to improve patient outcomes. Specific aims include reduced time to definitive diagnosis through initial appropriate imaging, reduced radiation exposure, reduced nonindicated surgical interventions, decreased NPO time, improved pain management and appropriate antimicrobial coverage.

**Design/Method:**

The Pediatric Hematology-Oncology division developed consensus-based guidelines for NE management based on comprehensive literature review. Representatives from Clinical Pharmacy, General Surgery, Radiology, Palliative Care, Infectious Disease and Emergency Medicine services provided feedback, which was incorporated into revisions. Utilizing these guidelines, we collected clinical data on patients diagnosed with NE from 07/01/13 through 06/30/18. We compared management to guideline recommendations. We will repeat data collection for patients diagnosed with NE one year following guideline implementation. Pre- and post-guideline data will be analyzed by direct comparison for each variable and through a composite score measuring overall adherence. Pre-implementation clinical data are reported here.

**Results:**

There were 21 cases of NE in the pre-implementation period. Leukemia was the underlying diagnosis in 71.4% of patients. Initial admission was for concerns other than NE in 62% of patients. The classic clinical triad of abdominal pain, fever and neutropenia developed in 81% of patients. Consensus guidelines recommend abdominal ultrasound as first-line imaging, but it was the initial study in only 23.8% of cases. CT scans were obtained in 81% of cases (30% indicated as defined by guideline). The mean length of time from development of abdominal pain to first abdominal imaging was 40.1 hours. Patients were NPO in 81% of cases, mean duration 3.3 days. G-CSF was administered in 38.1% of cases. Pain management was ordered in 85.7% of cases. All patients received appropriate antimicrobial therapy (mean duration 11.1 days). All patients had blood cultures obtained with bacteremia present in 33.3% of cases. One patient required surgical intervention. There were no deaths secondary to NE in this cohort.

**Conclusion:**

Review of clinical data prior to implementation illustrates opportunities to improve care through evidence-based standardization. We aim to reduce CT scan orders, increase G-CSF use and



improve analgesia where indicated. Post-implementation follow-up will be critical to assess for impact on outcomes and the need for guideline modification.

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Poster # 004

## **BLOOD WARMERS TO IMPROVE PEDIATRIC OUTPATIENT PATIENT EXPERIENCE WITH TRANSFUSIONS: A QI INITIATIVE**

**Eleny Romanos-Sirakis, Deena Maimone, Christine Finnegan**

*Staten Island University Hospital, Northwell Health, Staten Island, New York, United States*

### **Background:**

Blood warmers may be used for simple red cell transfusions in cases of hypothermia, massive transfusions and the presence of cold agglutinins. There is some published data in the literature regarding warming IV fluids and patient comfort, however, we are not aware of any data evaluating the use of blood warmers to improve quality of experience during routine transfusions for pediatric patients.

### **Objectives:**

To evaluate the presence of discomfort during a scheduled pRBC transfusions with and without the use of a blood warmer in the outpatient pediatric hematology clinic.

### **Design/Method:**

Five patients undergoing routinely scheduled pRBC transfusions were asked to provide a numerical pain scale of discomfort (1-10) while receiving the transfusion through a peripheral intravenous line without the blood warmer. Patients were then asked to provide a numerical pain scale while receiving the transfusion with the use of the blood warmer.

### **Results:**

The patients evaluated had the diagnoses of beta- thalassemia major, sickle cell disease, and epidermolysis bullosa; all patients received regularly scheduled transfusions approximately monthly. The age range of the patients was 5-20 years of age. All patients had peripheral intravenous lines placed prior to each transfusion. One patient reported a pain scale of 0/10 with or without the use of the blood warmer. The average pain scale reported for transfusion prior to use of the blood warmer for the remaining 4 patients was 8.25 out of 10 (range 7-10). With use of blood warmer, the average pain scale during transfusion for these 4 patients decreased to 1 out of 10 (range 0-4). Three out of 4 patients using the blood warmer reported a pain scale of 0 during transfusion.

### **Conclusion:**

The use of the blood warmer for routine simple pRBC transfusions in the pediatric outpatient clinic improved discomfort associated with pRBC transfusions. This factor may contribute to improved quality of life for patients receiving transfusions, especially those on a chronic transfusion protocol utilizing peripheral intravenous lines.

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## **DOUBLE CHELATION THERAPY IN PEDIATRIC TRANSFUSION ASSOCIATED IRON OVERLOAD**

**Laura Bou-Maroun, Pragya Singh, Ahmar Zaidi, Michael Callaghan**

*Children's Hospital of Michigan, Detroit, Michigan, United States*

### **Background:**

Individuals with sickle cell anemia and thalassemias often require chronic transfusions and develop iron overload. Hepatic and cardiac failure, secondary to hemochromatosis, are major causes of morbidity and mortality. Prognosis and monitoring have improved dramatically with chelation therapy and the advent of MRI (cardiac and liver iron quantification) respectively. The standard of care has been monotherapy with deferoxamine, deferasirox or deferiprone. In view of the limited data regarding double chelation therapy in children, we report 3 cases.

### **Objectives:**

Review safety and efficacy of double chelation therapy.

### **Design/Method:**

Case reports of children with hemochromatosis in the past 5 years, requiring double chelation therapy, examining effectiveness and safety profile. Ferritin, hepatic and cardiac MRI evaluated.

### **Results:**

Monochelation was with deferasirox and double chelation a combination of deferasirox and deferoxamine.

Patient 1: 12-year-old male with HbSS disease, transfusion dependent since 3 months of age for splenic sequestration and subsequent abnormal TCD. Hemochromatosis was noted after 10 years of monotherapy, without significant change in LIC after 1.5 years of double chelation (26.5 to 26.7 mg/g dry weight liver). Cardiac T2 worsened in the same timeframe (42.0 +/- 0.7 to 25.2 +/- 0.9 ms). Ferritin levels mimicked hepatic iron trend in being uncontrolled and uptrending, despite double chelation, necessitating a dose increase of both chelators. Double chelation is ongoing.

Patient 2: 8-year-old female with beta-thalassemia major, with inconsistent treatment prior to adoption from China. Monochelation started at age 4 years. LIC after 6 months of monotherapy was 7.7 and improved to 5.6 after 1.5 years of double chelation. Ferritin levels improved on double chelation (peak of 8,763 most recent 3,951 ng/mL). Subsequently, patient has been switched back to monotherapy.

Patient 3: 19-year-old female with HbSS disease and history of CVA. At age 10 years, noted to have hemosiderosis on monotherapy (STAR MAP analysis value 8.5). Five years later, LIC was elevated between 3.1-5.9, patient was switched to combination chelation. Ferritin levels reflected a dramatic improvement following the switch (peak of 10,414 most recent 1,474ng/mL), in the

absence of a follow up hepatic T2.

Two of three patients had dramatic improvements in ferritin on double chelation. The third required an up-titration of dose. Safety profile in terms of liver and renal function, were comparable on both chelation regimens.

**Conclusion:**

Double chelation has been safely performed in transfusion dependent pediatric patients and should be considered for patients with uncontrolled iron overload on single chelation.

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Poster # 006

**EPIDEMIOLOGY OF CHILDHOOD IMMUNE THROMBOCYTOPENIA IN KOREA: INCIDENCE, PREVALENCE, AND AGE OF ONSET**

**Ji Yoon Kim, Sung Eun Kim**

*Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea*

**Background:**

The epidemiology of childhood immune thrombocytopenia (CITP) is not well known in the Asian children population.

**Objectives:**

The purpose of the present study is to investigate the prevalence and incidence of CITP in Korea.

**Design/Method:**

Data were collected from the exclusive national health claims database of Korea, which is covering more than 95% of the patient population. CITP was identified using the diagnostic code D69.38 from the Korean standard classification of diseases. Patients under 18 years-old, who had at least one claim for CITP between January 2016 and December 2017 as a primary or secondary final diagnosis, were included in the study. Data encompass both outpatient and hospitalization records. SAS 9.4 and R package was used in data extraction and cleaning.

**Results:**

We estimated sex- and age-specific prevalence and incidence of CITP during the period. The prevalence of CITP was 25.14(95% confidence interval (CI): 25.11-25.17) per 100,000 persons in 2017. The incidence of CITP was 14.48(95% CI: 14.46-14.51) per 100,000 persons in 2017. The CITP was more common in boys than in girls, with an incidence rate ratio of 1.19 and a prevalence rate ratio of 1.13. By change point analysis, the age of 3 in incidence and 4 in prevalence was detected as a descending age.

**Conclusion:**

The current study revealed the population-based incidence and prevalence of CITP in Korea. The incidence and prevalence of CITP decline after the age of 3 and 4 years-old.

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**UPDATED RESULTS FROM THE SINGLE ARM, OPEN LABEL, LONG TERM EFFICACY/SAFETY OF SC ROMI IN ITP IN PEDS**

**Charles Bowers, John Grainger, James Bussel, Michael Tarantino, Nichola Cooper, Donald Beam, Jenny Despotovic, Alexey Maschan, Kejia Wang, Melissa Eisen**

*Amgen Inc., Newbury Park, California, United States*

**Background:**

Background: Romiplostim is a thrombopoietin (TPO) receptor agonist approved for children and adults with ITP

**Objectives:**

Objective: Presenting results from a 3-year open label study evaluating safety and efficacy of Romiplostim in children with ITP

**Design/Method:**

Methods: Eligible children from 17 countries with ITP for  $\geq 6$  months and screening platelet count  $\leq 30 \times 10^9/L$  (or uncontrolled bleeding) received SC romiplostim ( $1 \mu g/kg$  titrated to  $10 \mu g/kg$  to maintain platelet counts of  $50\text{--}200 \times 10^9/L$ ). In Europe, bone marrow was evaluated at baseline and after 1 or 2 years. The primary endpoint was % time with a platelet response (platelet count  $\geq 50 \times 10^9/L$ , no rescue therapy in preceding 4 weeks) in months 0–6.

**Results:**

Results: A total of 203 patients (pts) received  $\geq 1$  dose; the median (interquartile range [IQR]) age was 10 (6–13) and median (IQR) platelet count  $14 (7\text{--}23.5 \times 10^9/L)$ . The median (IQR) duration of treatment was 145 (39–156) weeks, median (IQR) % of time with a platelet response in months 0–6 was 50% (17–83%), with 88% (179/203) of pts having a platelet response at least once. Median and lower quartile platelet counts were both consistently  $>50 \times 10^9/L$  from week 12 and 48, respectively. Eleven pts maintained platelet counts  $\geq 50 \times 10^9/L$  for  $\geq 24$  weeks. Of 75 European pts with evaluable baseline bone marrow biopsies [modified Bauermeister scores: grade 0 (no reticulin,  $n=16$ ), 1 (fine fibers,  $n=54$ ), or 2 (fine fiber network,  $n=5$ )], 27 had evaluable on-study biopsies after 1 year and 36 after 2 years. Of these, 5 pts developed increased reticulin at year 1 and 17 at year 2. 1 pt had an increase in modified Bauermeister score from baseline of  $\geq 2$  grades (increase from grade 0 to 2), 4 pts had an increase in 1 grade, 1 a decrease in 2 grades, and 3 a decrease in 1 grade in year 1. In year 2, 15 pts had an increase in 1 grade and 3 pts a decrease in 1 grade. No pts developed collagen and no bone marrow abnormalities were detected.

**Conclusion:**

Conclusion: Over the course of the study with  $>30$  months of treatment, 88% of children had a platelet response, median platelet counts were  $\geq 20 \times 10^9/L$  above baseline 79% of the time and  $>50 \times 10^9/L$  from week 12 on a median dose of  $6.9 \mu g/kg$ . Bone marrow findings showed that children, like adults, did not develop clinically important fibrosis.

## **ANALYZING PLATELET COUNTS AND OUTCOMES IN GENERAL HOSPITALIZED PEDIATRIC PATIENTS**

**Jonathan Bardahl, Pedro de Alarcon**

*OSF HealthCare Children's Hospital of Illinois, University of Illinois College of Medicine at Peoria., Peoria, Illinois, United States*

### **Background:**

Platelets are a component of blood well known for their role in primary hemostasis. Thrombocytopenia is defined as a platelet count less than 150/nL. Numerous causes of thrombocytopenia exist with those involving admission to intensive care units showing worsened outcomes. Little information is known regarding outcomes in the pediatric population with thrombocytopenia admitted to the general pediatric floors.

### **Objectives:**

Better understand the importance of platelet counts and thrombocytopenia in our general hospitalized patient population.

### **Design/Method:**

A retrospective study conducted on our pediatric patients admitted to the general floors at OSF HealthCare Children's Hospital from July 2010 to 2018. Patients' demographics, source of admission, primary diagnosis, length of stay, initial platelet count, and transfer to higher levels of care were analyzed. Platelet counts were grouped into mean platelet count +/- 2 SD and <150/nL, 150-450/nL, >450/nL for analysis. Those diagnosed with hematological or oncological diagnoses as well as subjects directly admitted to intensive care units were excluded. A T-test, multivariate model, and logistic regression model were used for statistical analysis.

### **Results:**

10,858 charts were included in the study with 48.2% being female and 51.8% male. The mean age was 4.7 ( $\pm 5.2$ ) years of age. The majority of admissions came from the emergency department with an average length of stay of 3.6 days. Surprisingly, subjects were 1.12 times more likely to have longer hospital stays for every 100/nL increase in platelet counts ( $p < .0001$ , OR 1.001 CI 1.001-1.002). The mean platelet count was 332.7/nL with a SD of 127.3. Patients with platelet counts <150/nL were 2.9 times more likely to transfer to higher levels of care than those with counts between 150-450/nL ( $p < .0001$ , 95% CI 2-4.3) and 2.2 times likely to transfer than those with counts >450/nL ( $p < .0006$ , 95% CI 1.4-3.4). Outside hospital transfers were more likely to transfer to higher levels of care compared to other sources of admission. Lastly, our top 5 diagnosis categories included: Infection, GI, Kidney/Bladder/Urinary, Neurology, and Muscle/Skeletal/Joint.

### **Conclusion:**

Previous studies in the ICUs show that thrombocytopenia is associated with worsened outcomes.

Our study suggests that this bears true in general hospitalized pediatric patients as well. Furthermore this supports the concept that providers should be aware of the potential negative impact of thrombocytopenia in general hospitalized pediatric patients.

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Poster # 009

## **CLONAL HEMATOPOIESIS IN PATIENTS WITH DIAMOND BLACKFAN ANEMIA**

**Adrianna Vlachos, Michelle Nash, Eva Atsidaftos, Maryam Hussain, Jeffrey Lipton**

*Feinstein Institutes for Medical Research, Manhasset, New York, United States*

### **Background:**

Diamond Blackfan anemia (DBA) is a rare, inherited bone marrow failure syndrome characterized by anemia, congenital anomalies and a predisposition to cancer. Patients usually present during infancy or early childhood, but can present in adulthood. In the majority DBA is due to a mutation in a small or large ribosomal protein subunit leading to haploinsufficiency. In a study of 702 patients enrolled in the DBA Registry, the observed to expected ratio for acute myeloid leukemia (AML) was 28.8 and for myelodysplastic syndrome (MDS) was 352.1. Based on reports of increasing clonal hematopoiesis (CH) with age, with only rare mutations in patients younger than 40 years of age, we embarked on a study looking for CH in patients with DBA. Our hypothesis is that patients with DBA develop CH and accumulate somatic mutations at an earlier age leading to the development of MDS earlier than in the general population. This is an interim report.

### **Objectives:**

The primary objective is to perform whole exome sequencing (WES) specifically searching for somatic mutations associated with CH.

### **Design/Method:**

A total of 100 samples are to be analyzed, mostly targeting patients older than 18 years. When available, samples previously stored in the DBA Registry Biorepository will be evaluated to determine the rate of mutation acquisition. Age- and sex-matched controls were made available in a 3:1 ratio from GeneDx who is performing the WES for the study.

### **Results:**

To date 68 patients have been accrued to the study with preliminary analysis available for 57 of these patients. There were 179 age- and sex-matched controls available. Two of the 57 patients (3.5%) were found to have somatic mutations in U2AF1 and SF3B1 at ages 20.5 and 41.2, respectively. The patient who was 20.5 years of age had a sample in the DBAR Biorepository from when he was 8.2 years which was found to have a different somatic mutation (STAG1) than was found at present. Three of the 179 controls (1.7%) had mutations in LUC7L2, GNB1, and DNMT3A at ages 39.9, 52.2 and 52.5, respectively.

### **Conclusion:**

More patients are being accrued to the study. The trend is toward patients with DBA having

mutations twice as likely as controls and at younger ages than controls. There is also the possibility that the patients with DBA have other CH mutations than what is being found in the general population and that these other somatic mutations are not being captured at this time.

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Poster # 010

## **PEDIATRIC PATIENT CHARACTERISTICS AND DIAGNOSTIC RESULT OF INHERITED BONE MARROW FAILURE GENE PANELS**

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### **Background:**

Acquired bone marrow failure can be associated with a paroxysmal nocturnal hemoglobinuria (PNH) clone and/or response to immunosuppressive therapy. Inherited bone marrow failure syndrome (IBMFS) can be associated with physical abnormalities, short telomeres (dyskeratosis congenita), or positive chromosome breakage (Fanconi anemia). A combination of tests provide the most accurate diagnoses, though advancements in genetic testing technology have identified patients previously thought to have acquired bone marrow failure to actually have an IBMFS.

Pediatric patients may have significant clinical workup before genetic testing is recommended, though the exact phenotypic predictors have not been well-characterized in context of the outcome of the gene panel.

### **Objectives:**

Compare specific phenotypic features with genetic testing result to better characterize predictors of IBMFS

### **Design/Method:**

Retrospective chart review identified 78 pediatric patients at Seattle Children's who had a next-generation sequencing panel targeted for IBMFS since 2015. Data was analyzed to compare specific patient phenotypic features (presence of a PNH clone or antineutrophil antibody, personal history of growth problems or congenital anomalies, positive family history, response to immunosuppressive therapy (IST), pathologic findings, and abnormal telomere lengths or chromosome breakage studies) with their genetic testing result as diagnostic or non-diagnostic.

### **Results:**

Fifteen patients (19.2%) had diagnostic gene panels, and each had at least one phenotypic feature suggestive of IBMFS. In comparison to the 63 non-diagnostic results, this cohort presented at a younger age (median 4y vs 8y). These patients more commonly had congenital anomalies (53% vs 24%), growth problems (40% vs 19%), and a positive family history (33% vs 22%). The most common indication for testing in the diagnostic cohort was anemia, versus neutropenia in the non-diagnostic cohort. Both cohorts had a high percentage of abnormal bone marrow pathology. The diagnostic cohort did not have PNH evaluations, and only one had antineutrophil antibody testing, which was negative. Only one IST, and did not respond. The majority (73%) of patients

with non-diagnostic results who received IST responded to it. The majority (73%) of patients with diagnostic tests had additional testing recommended, most often targeted genetic testing for at-risk family members. The majority (74%) of patients with non-diagnostic tests had no additional genetic testing recommended.

**Conclusion:**

While all patients with diagnostic results had features suggestive of an IBMFS, 49% with non-diagnostic results did. This suggests clinicians may utilize these panels as “rule-out” tests. Better characterization of specific phenotypic features in even larger patient cohorts may standardize a personalized approach for evaluation for IBFMS.

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Poster # 011

**DEFICIENCY OF SEC23B LEADS TO PANCREATIC DEFICIENCY AND GROWTH HORMONE INSENSITIVENESS IN MOUSE**

**Wei Wei, Bin Zhang**

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**Background:**

In humans, loss of function mutations in SEC23B result in Congenital Dyserythropoietic Anemia type II (CDAII), while in mice, completely deletion of Sec23b leads to perinatal death caused by massive degeneration of professional secretory tissue without any CDAII phenotype.

**Objectives:**

To investigate the pathophysiology of CDAII and the role of SEC23B in mouse professional secretory tissue, we generated mice with the same mutations as what have been commonly seen in CDAII patients.

**Design/Method:**

We generated mice with homogenous Sec23b E109K missense mutation (Sec23bki/ki mice) or compound heterozygous mice with one allele of Sec23b E109K mutation and the other allele of complete Sec23b deletion (Sec23bko/ki mice). We studied the growth of SEC23B deficient mice as well as CDA phenotype, pancreatic function and growth hormone pathway.

**Results:**

E109K missense mutation leads to decreased SEC23B protein level both in vivo and in vitro, and interestingly, E109K mutation results in lost a normal endoplasmic reticulum (ER) expression pattern of SEC23B which is evenly distributed in cell plasma. Sec23bko/ki mice did not exhibit CDAII phenotype but showed severe degeneration of pancreas but half of these mice were still able to survive to adulthood. Nevertheless, Sec23bki/ki mice showed grossly normal growth and normal histology of pancreas. Different from other SEC23B deficient mice, Sec23bko/ki mice exhibited chronic pancreatitis histology changes such as interstitial fibrosis, white blood cells infiltration as well as exocrine insufficiency. Consistent with our previous studies, increased level of ER stress had been found in Sec23bko/ki pancreas, which contributed to elevated



apoptosis. Moreover, Sec23bko/ki mice exhibited severe growth delay accompanied by significant high level of serum growth hormone and extreme low level of serum IGF-1, which indicated growth hormone insensitiveness. By exploring growth hormone receptor pathway in Sec23bko/ki liver, we identified reduced mRNA and protein levels of growth hormone receptor, less activated JAK-STAT5 signaling pathway, dramatically decreased IGF-1 mRNA. Unfortunately, we did not observe any growth delay, or alterations in serum growth hormone or IGF-1 in hepatocyte Sec23b specifically deletion mice which could rule out defect in intracellular transport of growth hormone receptor caused by SEC23B insufficiency in mouse liver. Therefore, all of these findings indicate chronic pancreatic deficiency and inflammation may be the cause of growth hormone insensitiveness in Sec23bko/ki mice.

**Conclusion:**

We further demonstrate that deficiency in SEC23B does not lead to CD4I phenotype in mice but impairs exocrine function of mouse pancreas leading to chronic inflammation, and growth hormone resistance.

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Poster # 012

**DEVELOPMENT AND QUALITY IMPROVEMENT ASSESSEMENT OF A THALASSEMIA CARE PROGRAM**

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**Background:**

As a result of population migration, adoption and new births, more individuals with thalassemia are presenting to local hematology centers. Centers with growing thalassemia populations need to develop expertise on the complex diagnosis and management of thalassemia.

**Objectives:**

Development of and quality improvement (QI) assessment of a thalassemia program at a large pediatric hospital.

**Design/Method:**

A thalassemia care program was developed with institutional treatment guidelines based on national and international thalassemia guidelines. A multidisciplinary team (hematologist, NP, RN, and dietician) provided care at a comprehensive clinic visit (CCV). After 2 years of implementation, QI was assessed by comparing pre and post-CCV guideline adherence rates for patients seen in  $\geq 1$  CCV. Pre-visit data was defined as the latest data prior to launch of the CCV, 1/1/16. Post-visit data was defined as the most recent data in the period between a patient's 1st CCV and a cutoff date of 12/31/2018. Transfusion dependent thalassemia (TDT) and non-TDT (NTDT) data were evaluated separately. For each patient, we determined percent of overall treatment goals (laboratory, imaging, and specialty referrals) met in the pre- and post-visit periods. For TDT patients, liver iron concentration (LIC) and hemoglobin nadirs were also evaluated. Data was analyzed using a paired samples t-test for TDT and NTDT.

**Results:**

Eleven NTDT patients and 21 TDT patients had  $\geq 1$  data point from the pre- and post-visit periods. Adherence to overall guidelines for NTDT pre and post-CCV showed significant improvement of parameters completed by 38.21% ( $\pm 24.2.2\%$ ,  $p < 0.0001$ ). Adherence to overall guidelines for TDT patients significantly improved by 61.52% ( $\pm 18.74\%$ ,  $p < 0.0001$ ). NTDT adherence rates improved for lab evaluations (42.73%  $\pm$  13.2%,  $p < 0.001$ ) and specialty referrals (24.73%  $\pm$  12.4%,  $p < 0.004$ ). There was no significant improvement in imaging per NTDT guidelines (3.09%  $\pm$  16%,  $p = 0.37$ ). TDT adherence rates improved for laboratory (55.24%  $\pm$  7.14%,  $p < 0.001$ ), imaging (5.07%  $\pm$  14.8%,  $p < 0.001$ ), and specialty referrals (4.38%  $\pm$  11.4%,  $p < 0.001$ ). For TDT patients, LIC significantly decreased from 13.84mmHg ( $\pm 5.25$ ) before CCV to 9.34 ( $\pm 2.95$ ) after CCV ( $p < 0.05$ ). No significant differences were seen between pre- and post-hemoglobin nadirs for TDT patients.

**Conclusion:**

Our QI efforts resulted in improvement in overall scores and laboratory evaluation for TDT and NTDT patients. TDT also showed improvement in LICs and specialty referrals. This QI project led to increased guideline adherence, expansion of our thalassemia team and improved quality of care to thalassemia patients.

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Poster # 013

**EVALUATION OF PEDIATRIC HEMATOLOGY REFERRALS AT A TERTIARY UNIVERSITY HOSPITAL IN WEST TEXAS**

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**Background:**

One in forty pediatric office visits in the US results in referral to specialty care commonly for advice on diagnosis and treatment. Poor access to subspecialty care results in delays in delivery of appropriate therapies to patients. A study done in 2016 identified that “access to affordable healthcare” and “transportation” were the top two community health needs in West Texas. Identifying possible causes of unnecessary hematology referrals could reduce some of the health-related costs to families such as lost wages and co-pays.

**Objectives:**

To evaluate the necessity of pediatric hematology referrals to Southwest Cancer Center (SWCC). Primary outcomes include common reasons for referral, appropriateness of the referral and determination of health related costs due to unnecessary referrals.

**Design/Method:**

One hundred and one pediatric patients were referred to SWCC at University Medical Center in Lubbock, TX between January 1, 2015 and September 30, 2018 for evaluation by a hematologist. A retrospective chart review was done. “Necessity” of referrals was determined by evaluation of

patient labs prior to referral, lab values at the initial specialist visit, and diagnosis that could be handled by primary care physician (PCP) without need for referral.

**Results:**

The most common reason for referral to pediatric hematology clinic was an abnormal CBC. The top three final diagnosis in decreasing frequency were: Iron deficiency anemia (IDA), leukopenia or leukocytosis, anemia other than IDA (hemolytic, aplastic, thalassemia trait). 95% of the patients were evaluated by hematologist after referral within 8 weeks. Patients had a median of 3 visits to the hematology clinic and 23% of patients only required one visit. About 33% of the referrals could be managed by PCP as the therapy had already been started and/or the laboratory findings were not abnormal at the time of first visit. The cost of unnecessary visits estimated at \$82,888 (only includes physician visits and laboratory tests). There was no significant relation between the final diagnosis and necessity for referral. Patients who travelled longer than 100 miles tended to be necessary referrals ( $p < 0.05$ ). The visits that cost more than \$5,000 were all necessary referrals.

**Conclusion:**

Our study revealed that about 32% of the referrals could have been avoided because either the labs were back to normal with therapy initiated or resolved without intervention at the time seen by hematologist. Implementation of referral guidelines for PCPs about the most common hematologic problems can improve the healthcare reducing variation of referrals.

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Poster # 014

**THE NATIONWIDE CHILDREN'S HOSPITAL SICKLE CELL CARE INDEX: A NOVEL QUALITY IMPROVEMENT METRIC**

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**Background:**

Patient outcomes for sickle cell disease most commonly focus on the reduction of emergency department visits and hospitalizations. While this is important and necessary, less attention is devoted to measuring and developing strategies to comply with standard of care outpatient practices such as penicillin prophylaxis, immunizations, transcranial doppler screening, the development of individualized pain plans, iron overload monitoring for patients on chronic transfusion therapy, and comprehensive appointments where disease counseling, anticipatory guidance, and hydroxyurea education is provided. We believe that these interventions are critically important to the health and well being of children, adolescents, and young adults with sickle cell disease and should therefore be actively monitored to ensure compliance with standard of care best practices.

**Objectives:**

Our objective was to design and test a global care metric that reflected the overall quality and

performance of our sickle cell program and use the metric to drive improvement in the quality of care provided to patients.

**Design/Method:**

The Sickle Cell Care Index (SCCI) was designed to aggregate missed opportunities in best practices into a composite score that reflects the overall clinical performance of the sickle cell program at Nationwide Children's Hospital (NCH). Eight domains were selected to assess our performance in complying with standard of care best practices. The domains included: penicillin prophylaxis, immunizations for pneumococcus and meningitis, transcranial doppler screening, adherence with comprehensive appointments, pain plan documentation, hydroxyurea utilization, transfusion plan documentation, and iron overload monitoring for patients on chronic transfusion therapy. Missed opportunities were calculated monthly and tracked over the course of one year. Lower aggregate monthly SCCI scores, therefore, reflect better care and improved overall performance. Key drivers were identified and interventions were implemented for most domains in an effort to reduce missed opportunities.

**Results:**

The SCCI was easy to calculate, deploy, and well accepted by the team. The SCCI decreased nearly every month from a maximum of 229 in January 2019 to a minimum of 119 in December 2019, representing a 52% reduction. Improvements in care were realized across most index domains with the most dramatic improvements noted in pain plan documentation and transcranial doppler screening.

**Conclusion:**

The SCCI is a valuable metric to monitor the overall performance of sickle cell programs in complying with standard of care best practices. The metric provides a composite score over time which can be used to effectively drive improvement in the quality of care provided to patients with sickle cell disease.

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Poster # 015

**INTEGRATION OF PATIENT REPORTED OUTCOME MEASURES IN NON-MALIGNANT PEDIATRIC HEMATOLOGY**

**Johann Graham, Julia Kinahan, Yamilée Hebert, Stephanie Sutherland, Dennis Newhook, Melanie Kirby-Allen, Manuel Carcao, Robert Klaassen**

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**Background:**

Patient reported outcome measures (PROMs) are questionnaires completed by patients or caregivers without the influence or interpretation of healthcare professionals, allowing patients to voice their concerns and healthcare professionals to address these concerns in an efficient manner. PROMS can be generic or disease-specific. Generic PROMs contain questions relevant to multiple disease groups while disease-specific PROMs are validated for specific conditions. Online platforms integrated into the electronic medical records (EMR) can be used to monitor

quality of life using PROMs allowing clinicians to graph and monitor quality of life.

**Objectives:**

To evaluate the integration of PROMs via a web-based platform to monitor quality of life of patients with non-malignant hematological disorders and to identify the preferred PROMs in this patient population.

**Design/Method:**

A systematic review was conducted to identify the available validated PROMs used to evaluate quality of life in four pediatric disease groups: hemophilia, sickle cell disease (SCD), immune thrombocytopenia, and thalassemia. Focus groups and interviews were conducted with affected children, parents, and pediatric hematology healthcare professionals (HCP) at The Children's Hospital of Eastern Ontario. The purpose was to elicit opinions concerning the integration of a web-based platform into daily medical practice and to identify what tools should be used on this platform. Participants were asked to rate PROMs using different colors. Green indicating that the questionnaire was useful (1 point), yellow indicating it was somewhat useful (0.5 points), and red indicating that it was not useful (0 points). Percentages were calculated using these points.

**Results:**

Thus far, 27 participants have participated in focus groups or interviews (6 children, 15 parents, and 6 HCP) to determine the pertinence of a web-based platform and to select which validated PROMs should be used. We have obtained strong support from both children and parents for disease-specific tools such as the Haemo-QoL in hemophilia (100%), the TranQoL in thalassemia (100%) and the PedsQL Sickle Cell Module in sickle cell disease (91.7%). Generic tools, such as the PedsQL Generic (68%) were met with mixed support from participants. We obtained universal support for the integration of a web-based platform to monitor quality of life amongst the hemophilia and thalassemia focus groups as well as strong support in the SCD focus groups.

**Conclusion:**

We obtained strong support for the integration of a web-based platform into daily medical practice and EMR as well as a preference for disease specific PROMs to monitor quality of life in outpatient pediatric non-malignant hematology disorders.

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Poster # 016

**A NOVEL SRP54 MUTATION ASSOCIATED WITH SEVERE CONGENITAL NEUTROPENIA**

**Myesa Emberesh, Laura Tweedie, Katie Seu, Jingfen Han, Miao Sun, Kasiani C. Myers, Robert B. Lorschach, Jose A. Cancelas, Theodosia Kalfa**

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**Background:**

Heterozygous mutations in SRP54 were recently identified as a novel molecular cause of Severe Congenital Neutropenia (SCN) and a Shwachman-Diamond-like phenotype. SRP54 encodes the

Signal Recognition Particle (SRP) 54kDa GTPase protein, a crucial component of the cytoplasmic ribonucleoprotein complex that leads the translocation of newly synthesized secretory and membrane proteins to the endoplasmic reticulum (ER). Defects in the SRP pathway have been shown to cause increased ER stress, triggering autophagy and apoptosis of neutrophil precursors in patients with SCN.

**Objectives:**

To validate the pathogenicity of a novel SRP54 variant identified in a patient with SCN and investigate the molecular mechanism of defective myelopoiesis.

**Design/Method:**

Case report, whole-exome sequencing (WES), and in vitro studies.

**Results:**

6-year-old European-American male presented at two months of age, during a febrile illness, with an absolute neutrophil count (ANC) of 380/ $\mu$ L. He had no skeletal abnormalities or other stigmata. Bone marrow evaluation confirmed the diagnosis of SCN, showing a paucity of late myeloid precursors, and arrest at the promyelocytic stage. He was started on daily G-CSF (5 mcg/kg/dose) initially, however; due to inadequate response the dose was escalated (maximum of 10, currently at 8 mcg/kg/dose). Next-generation sequencing for 21 known at the time SCN-associated genes was negative. WES revealed a de novo heterozygous SRP54 variant (c.572C>G; p.Thr191Arg). In silico prediction programs suggest this variant is deleterious, affecting a phylogenetically conserved amino acid at the G3 element of the SRP54 G-domain, critical for GTP binding and hydrolysis. Ultrasound revealed diffuse hyperechogenicity of the pancreas, compatible with fatty replacement, as seen in Schwachman-Diamond syndrome, serum amylase level was slightly decreased but lipase and immunoreactive trypsinogen were normal, and he had no laboratory or clinical evidence of malabsorption, with normal levels of lipid-soluble vitamins, and growth and development appropriate for age. His annual bone marrow evaluation has been showing dysgranulopoiesis with no evidence for dysplasia or leukemic transformation.

CD34+ cells and skin fibroblasts were isolated from the patient's bone marrow aspirate and skin biopsy respectively. SRP54 protein level was decreased in cultured patient's fibroblasts at 60-80% of normal control while a consistent increase in Light Chain 3 lipidation (LC3-II) was detected by immunoblotting indicating autophagy induction and autophagosome accumulation, consistent with SRP54-associated SCN (Bellanne-Chantelot et al, Blood 2018).

**Conclusion:**

This novel SRP54 variant is likely pathogenic for SCN. Further studies utilizing ex vivo granulopoiesis culture from CD34+ cells are ongoing to study the mutated SRP54-mediated mechanism of granulocyte autophagy.

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Poster # 017

**AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME: DEFINING A CASE OF FAMILIAL SPLENOMEGALY**

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Pennsylvania, United States*

**Background:**

Autoimmune lymphoproliferative syndrome (ALPS) is a genetic syndrome characterized by mutations in the lymphocyte apoptosis pathway leading to immune dysregulation. The defect in apoptosis results in the persistence of autoreactive lymphocytes and accumulation of lymphocytes within lymphatic tissue. Therefore, patients often present with non-infectious, non-malignant lymphadenopathy, splenomegaly, and autoimmune cytopenias. ALPS is characterized by the presence of elevated double negative T cells and pathogenic gene mutations in FAS, FAS-L and CASP-10. The lymphoproliferation typically manifests in the first years of life in individuals with ALPS-FAS.

**Objectives:**

Describe an 8-year-old patient who presented with new splenomegaly with a strong family history of splenomegaly treated with splenectomy found to have ALPS after genetic testing, altering the management of his hypersplenism.

**Design/Method:**

Case report

**Results:**

An 8-year-old male presented with abdominal pain and was found to have splenomegaly and radiographic evidence of gallbladder wall thickening and biliary sludge. Both his mother and maternal aunt underwent splenectomies due to chronic abdominal pain related to splenomegaly without definitive diagnosis and remain healthy to date with no significant hematologic or infectious disease complications. The patient was noted to have a mild leukopenia (WBC = 4) and anemia (hemoglobin = 11.1) with reticulocytosis and undetectable haptoglobin. DAT, osmotic fragility and EMA binding were normal. Infectious work-up for EBV, CMV, and Bartonella henselae was negative. Liver enzymes and bilirubin were normal and there was no evidence of liver disease or portal vein thrombosis on abdominal doppler or cross-sectional imaging, although abdominal and retroperitoneal lymphadenopathy was noted incidentally. Lysosomal storage disease work-up was negative. Pending genetic testing, given his persistent abdominal pain, his family requested splenectomy for the patient, given the family history of splenectomies. However, genetic testing revealed a FAS gene mutation in both the patient and his mother, consistent with ALPS-FAS. He demonstrated elevated double negative T cells, confirming his diagnosis. With this knowledge, splenectomy was deferred given the increased risk of sepsis in ALPS patients post-splenectomy.

**Conclusion:**

The underlying etiology of splenomegaly can be difficult to ascertain given the wide variety of causative systemic illnesses. In cases with familial splenomegaly, despite lack of history of lymphadenopathy or autoimmunity, we must consider ALPS in order to provide appropriate up

to date disease management. With the expanded knowledge of the genetic basis of diseases, we are better able to serve our patients by developing a tailored therapeutic plan and by potentially avoiding unnecessary and invasive procedures.

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Poster # 018

## **APPLICATION OF WHOLE EXOME SEQUENCING FOR THE IDENTIFICATION OF RARE HEMATOLOGIC SYNDROMES**

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### **Background:**

Prior to the advent of genetic testing, clinicians relied on their ability to recognize a constellation of symptoms as possibly being related in a grander sense. Unfortunately, even with the ability to recognize that a child may be “syndromic,” definitive identification of the disease was not always possible, given the rare nature of certain (then unknown) syndromes. This led to time-consuming and expensive diagnostic testing with uncertain or inconclusive results. MHY9-Related Disease is an excellent example of this phenomenon, as prior to genetic testing it was thought to be four separate syndromes, but later recognized to all be caused by the same mutation in the MHY9 protein. The following three case presentations all involve pediatric patients who were definitively diagnosed with rare hematologic syndromes through whole exome sequencing (WES), a genetic testing method that is becoming increasingly popular given its comprehensive and cost-effective nature.

### **Objectives:**

This case series seeks to illustrate the importance of genetic analysis by WES in evaluating patients with hematologic complaints complicated by numerous other constitutional symptoms.

### **Design/Method:**

Three patients who underwent WES in an effort to obtain a unifying diagnosis of their hematologic and extra-hematologic complaints were identified. Chart review was performed. The presentation of illness, management after diagnosis via WES, and outcome was documented.

### **Results:**

All three patients underwent numerous forms of expensive and invasive testing before being definitively diagnosed via WES. The presence of a wide array of extra-hematologic symptoms in addition to the primary hematologic complaint often clouded the clinical picture. While each patient presented with a different syndrome: MYH9-Related Disease, Hypofibrinogenemia, and Autoimmune Lymphoproliferative Syndrome Type IA; they all benefited from individually tailored medical surveillance and management after diagnosis of their rare disease.

### **Conclusion:**

Molecular diagnosis and identification of mutations has important value in terms of prognosis. WES is advantageous and cost-effective in identifying mutations that code proteins which



constitute about 1% of the human genome, and result in 85% of all known disease-related traits (Choi et al, 2009). In this case series, WES has proved to be a valuable tool in the evaluation, management and surveillance of various hematologic syndromes.

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Poster # 019

## **LATE PRESENTATION OF DIAMOND-BLACKFAN ANEMIA WITH NO ASSOCIATED ABNORMALITIES DUE TO RPL5 MUTATION**

**Loretta Parker, Lincy Thomas, Subha Mazzone, Teresa Scordino, Charles Lawrence, David Crawford**

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### **Background:**

Diamond-Blackfan Anemia (DBA) is a rare, hematologic disorder with abnormal red cell development leading to macrocytic anemia. DBA usually presents within the first year of life with transfusion-dependent anemia. Corticosteroids are often the only treatment necessary to achieve effective hematopoiesis. However, chronic steroid use and frequent transfusions result in a host of side effects, and some patients do not respond or develop other cytopenias. Definitive treatment with allogeneic hematopoietic stem cell transplantation (aHSCT) may be required.

### **Objectives:**

Recognizing the possibility of late presentations of DBA, demonstrating treatment modalities, and understanding phenotypes associated with the RPL5 mutation.

### **Design/Method:**

A 15-year-old female presented with headaches, dizziness, fatigue, and nausea, with a hemoglobin of 3.9 g/dL, MCV of 104.4 fL, and reticulocyte count of 1.8%, with no other cytopenias. She was born term with gestational age-appropriate weight, and no congenital abnormalities or malformations. Evaluations for Fanconi anemia, sideroblastic anemia, and paroxysmal nocturnal hematuria were all negative. Bone marrow evaluation showed 30% cellularity with a paucity of erythroid precursors and no dysplasia. In addition to an elevated adenosine deaminase to 2043 mU/g Hb and fetal hemoglobin of 8.3%, she was found to have a de novo pathogenic mutation via targeted CGH analysis in the Ribosomal Protein L5 (RPL5) gene resulting in a truncated protein (del 175-6GA). Corticosteroids were started but eventually discontinued due to toxicity. She became transfusion-dependent and developed MRI evidence of iron overload. Following a preparative regimen of busulfan and fludarabine, she underwent an HLA-matched sibling aHSCT. She developed BK virus-mediated hemorrhagic cystitis and Grade I GVHD of the skin and upper GI tract that responded quickly to steroids. Neutrophil engraftment was on day +13 and platelet engraftment was on day +47.

### **Results:**

RPL5 mutations occur in about 6% of patients with DBA. Of patients in the DBA registry, 84% with an RPL5 mutation had malformations, typically craniofacial and thumb anomalies. Patients

with the same pathogenic mutation involving RPL5 truncations had associated congenital abnormalities, demonstrating an imperfect genotype-phenotype correlation.

**Conclusion:**

Late presentation and lack of congenital abnormalities are unique features in this case. Although our patient responded to steroid therapy, she was intolerant of its side effects. Only 20% of those responding to steroids achieve complete remission, while only a fraction is treated with aHSCT. Although 90% of patients are diagnosed prior to 12 months of age, this case demonstrates that DBA should remain in the differential for older patients with unexplained anemia.

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Poster # 020

**INFLAMMATORY MANIFESTATIONS IN PATIENTS WITH SHWACHMAN-DIAMOND SYNDROME**

**Elissa Furutani, Ankoor Shah, Yongdong Zhao, David Andorsky, Fatma Dedeoglu, Amy Geddis, Kasiani Myers, Akiko Shimamura**

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**Background:**

Shwachman-Diamond Syndrome (SDS) is an autosomal recessive multisystem disorder characterized by exocrine pancreatic dysfunction, bone marrow failure, and leukemia predisposition. Approximately 90% of cases are due to biallelic mutations in the Shwachman-Bodian-Diamond (SBDS) gene. Additional phenotypic features variably associated with SDS include skeletal, neurologic, hepatic, cardiac, endocrine, and dental abnormalities. Characterization of the SDS clinical phenotype and natural history remains incomplete.

**Objectives:**

We report five subjects with biallelic SBDS mutations who developed a range of inflammatory manifestations, expanding the spectrum of inflammatory responses in SDS.

**Design/Method:**

Subjects were enrolled in one of two ongoing prospective cohort studies, the North American Shwachman-Diamond Registry or the Bone Marrow Failure/Myelodysplastic Syndrome Registry. Data were obtained from medical records including clinic notes, laboratory reports, imaging, and pathology reports. This case series was limited to patients with a clinical and genetic diagnosis of SDS.

**Results:**

Patients developed inflammatory manifestations at a median of 9 years (range 4 to 26 years). Three patients developed blepharoconjunctivitis, including one patient who also developed juvenile idiopathic arthritis. Single cases of chronic recurrent multifocal osteomyelitis and scleroderma are described. Treatment varied by diagnosis but included topical steroids, oral steroids, IVIG, and anti-TNF therapy.

**Conclusion:**

These cases suggest that inflammatory manifestations may be part of the phenotypic spectrum in SDS. Treatment of inflammatory manifestations in patients with SDS may be complicated by potential myelosuppressive toxicities of anti-rheumatic medications. Further research is needed to better understand the potential link between inflammatory disorders and SDS to inform effective treatment strategies.

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Poster # 021

**EVANS SYNDROME AND THROMBOTIC MICROANGIOPATHY OCCURRING SIMULTANEOUSLY IN ONE PATIENT**

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**Background:**

Hemolytic anemia and thrombocytopenia are common presenting features of both Evans syndrome and thrombotic microangiopathy (TMA) although the pathophysiologic mechanism is different. In TMA, anemia and thrombocytopenia result from formation of capillary microthrombi due to endothelial damage, while in Evans syndrome they are mediated by autoantibodies against platelets and red blood cells. A case of Evans syndrome and TMA occurring concomitantly has not been previously reported.

**Objectives:**

To describe a pediatric patient with Evans syndrome who subsequently developed TMA while being treated with steroids.

**Design/Method:**

Case report and review of the literature.

**Results:**

A 14-year-old obese female presented with dyspnea and new-onset petechial rash. Initial labs showed hemolytic anemia and thrombocytopenia with elevated reticulocytes, hyperbilirubinemia, elevated lactate dehydrogenase, and low haptoglobin. Peripheral smear showed rare spherocytes but no schistocytes. White blood cell count and differential were normal. Additional labs showed normal renal function, negative stool for Shiga-toxin, normal ADAMTS13 activity, and negative antinuclear and antiphospholipid antibodies. Direct Coombs was positive for warm antibodies. Patient was diagnosed with Evans syndrome and started on prednisone with normalization of hemoglobin and platelet count. Two months after initial presentation, while still on prednisone taper, she presented with edema, severe hypertension and acute kidney injury with elevated creatinine, hyperkalemia, nephrotic-range proteinuria, and hematuria. Renal biopsy showed microangiopathic changes with endocapillary proliferative glomerulonephritis with fragmented red blood cells but lack of fibrin microthrombi. Eculizumab was initiated for presumed atypical hemolytic uremic syndrome (HUS) with improvement in renal function. Blood counts are stable with continued weaning of steroids; Coombs remains

positive. Work-up for atypical HUS is still non-diagnostic; Factor H antibodies were negative and complement profile was normal. Genetic testing for mutations associated with atypical HUS as well as for monogenic autoimmune disorders and immunodeficiency associated with Evans syndrome is pending.

**Conclusion:**

We present a case of a patient who developed acute renal injury with findings on renal biopsy consistent for TMA while being treated with steroids for Evans syndrome. Hypertension is an expected side effect of prolonged steroid exposure, and if severe can lead to renal damage including TMA. Evans syndrome has not been previously associated with TMA, although Coombs positivity has been rarely described in patients with post-pneumococcal HUS and thrombotic thrombocytopenic purpura. TMA and autoimmune cytopenias are both important diagnostic considerations in patients presenting with hemolytic anemia and thrombocytopenia and may present concurrently.

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Poster # 022

**NOVEL MUTATION IN A CHILD OF THE GALE GENE PRESENTING WITH PANCYTOPENIA**

**Adriana Rodriguez, Ossama M. Maher, Liset Pelaez, Jorge Galvez Silva**

*Nicklaus Children Hospital, Miami, Florida, United States*

**Background:**

Galactose epimerase deficiency (GALE deficiency galactosemia) encodes UDP galactose-4-epimerase which allows the body to utilize galactose and follows an autosomal recessive inheritance. Three types of epimerase deficiency exist: generalized, peripheral and intermediate with different severities. One recent publication identified family members that had GALE mutations in which individuals did not have clinical galactosemia and presented with thrombocytopenia and intracranial bleeding.

**Objectives:**

We hereby describe a pediatric male patient found to have new pathogenic mutation on the GALE gene that presented with pancytopenia.

**Design/Method:**

A PUBMED search was conducted for queries including GALE gene mutations, galactosemia, pancytopenia, UPD-galactose-4-epimerase, galactose-1-phosphate. Relevant papers were selected for literature review

**Results:**

A 2 year-old Hispanic male with past medical history of mitral and tricuspid regurgitation with mitral valve replacement and tricuspid valvuloplasty presented with incidental pancytopenia in the setting of fever concerning for endocarditis. Presenting laboratories were normocytic normochromic anemia with hemoglobin of 9.1 gm/dL, platelets of 11 K/uL and WBC of 1.8

10K/uL with an ANC of 864 10K/uL, patient also found to have hepatosplenomegaly. Differential diagnosis included bone marrow suppression due to acute illness, Hemophagocytic Lymphohistiocytosis (HLH) or leukemia. Bone marrow biopsy showed a hyperactive marrow negative for malignancies; which results were consistent with flow cytometry. Patient had no history of vision impairment, hypotonia, developmental delays, weight loss, poor feeding or jaundice and ate a well-balanced diet with milk products. Whole exome sequencing showed a heterozygous mutation for c.151c>T p.Arg51Trp in the GALE gene presumed to have a deleterious effect on protein function. In addition, a variant of unknown clinical significance was found on the same gene, c.710G>A p.Gly237Asp. To evaluate clinical significance of these mutations galactose-1-phosphate uridylyltransferase (GALT) activity and Galactose-1-phosphate levels were taken. Results showed increased levels in Galactose-1-phosphate and normal limits of galactose-1-phosphate uridylyltransferase (GALT) activity. Patient was consulted to genetics and started on a galactose and lactose free diet.

### **Conclusion:**

To the best of our knowledge, our patient carries a novel mutation in the GALE gene that has not been previously reported in the literature. More discoveries of gene mutation profiles can help to better understand the mechanism and presentations of diseases therefore decreasing the time of diagnosis and improving outcomes.

Adam MP, ArdingerHH, Pagon RA, Wallace SE, et al. Epimerase Deficiency Galactosemia 1993. PMID: 21290786

SeoA, Gulsuner S, Pierce S, Ben-Harosh M, et al. Human molecular genetics. 2019 .Inherited thrombocytopenia associated with mutations of UDP-galactose-4-epimerase 9 GALE PMID: 30247636

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Poster # 023

## **LOOKING BEYOND THROMBOCYTOPENIA: FAMILIAL PLATELET DISORDER WITH PROPENSITY TO MYELOID MALIGNANCY**

**Rachel Leeman, Viney Hardit, Deborah Soong, Ali Sanati-Mehrziy, Joanna Davis, Fernando Corrales-Medina**

*University of Miami Miller School of Medicine/Jackson Memorial Medical Center, Miami, Florida, United States*

### **Background:**

Familial platelet disorder with propensity to myeloid malignancy (FPDMM) is a rare inherited autosomal dominant disorder caused by germline mutations in the RUNX1 gene. Only 14 pedigrees have been reported in the literature. Dysregulation of RUNX1 leads to ineffective hematopoiesis, manifesting clinically as thrombocytopenia, functional platelet defects, bleeding tendencies, and increased risk for the development of myeloid malignancies. The most common associated malignancies are acute myeloid leukemia and myelodysplastic syndrome. Onset of malignant transformation ranges from childhood to adulthood, although 20-60% develop a hematological malignancy in their lifetime.

**Objectives:**

To discuss initial presentation and diagnostic workup of an adolescent with newly diagnosed FPDMM.

**Design/Method:**

Case report.

**Results:**

A 16-year-old Hispanic female was referred to pediatric hematology for newly diagnosed thrombocytopenia. History intake was significant for epistaxis, menorrhagia, and iron-deficiency anemia. There was a strong family history of thrombocytopenia, bleeding tendency, and leukemia affecting different family members, although familial genetic testing was never performed. Patient's mother had history of refractory immune thrombocytopenic purpura requiring splenectomy at age 25 and subsequent development of mixed-phenotype acute leukemia with RUNX1 mutation at age 41. Patient's brother, maternal grandmother, and maternal great aunt were all diagnosed with thrombocytopenia. Patient's maternal aunt had history of menorrhagia and easy bruising, and a maternal first cousin was diagnosed with acute leukemia at age 8. Her personal and family history supported investigation for potential bleeding disorder.

Initial hematological workup included complete blood count with peripheral smear review and reticulocyte panel. Results revealed thrombocytopenia of 101,000/mm<sup>3</sup> with mean platelet volume of 8.8 fL. Platelet aggregation studies revealed complete absence of aggregation to ristocetin, at low and high concentrations (0.25 mg/mL and 1.0 mg/mL, respectively), associated with decreased GPIa (CD49b) to 43% (reference range > 60%) and otherwise normal GPIIb (CD41) and GPIIa (CD61) platelet surface glycoprotein receptors, indicating an unspecified platelet function disorder.

Bone marrow biopsy revealed decreased but maturing trilineage hematopoiesis without morphologic abnormalities. Genetic testing revealed a heterozygous germline mutation in RUNX1, deletion on exon 5, confirming the diagnosis of FPDMM.

**Conclusion:**

Our patient will return every three months for physical and laboratorial evaluations with annual surveillance bone marrow biopsies. Family members were encouraged to undergo genetic testing.

Due to the rarity and clinical heterogeneity of FPDMM, its diagnosis is easily overlooked, and may be more prevalent than previously recognized. It is important that pediatric providers recognize the FPDMM clinical presentation, as diagnosis in childhood will ensure early and adequate monitoring.

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Poster # 024

# ROMIPLOSTIN FOR ACUTE MANAGEMENT OF TACROLIMUS-INDUCED ITP AFTER CARDIAC TRANSPLANTATION

**Trisha Larkin, Daniel Gipson, Vandy Black**

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## **Background:**

Tacrolimus, a calcineurin inhibitor, is a widely utilized immunosuppressive therapy to prevent rejection in solid organ transplantation. Thrombopoietin analogue, Romiplostim, has been FDA approved for treatment of chronic ITP in patients 1 year of age and older. There are limited data for Romiplostim efficacy and safety in pediatric acute ITP following solid organ transplantation.

## **Objectives:**

To report the case of a pediatric cardiac transplant recipient who developed refractory, acute ITP after eight years of treatment with tacrolimus and was treated with a thrombopoietin analogue.

## **Design/Method:**

Review of the literature was performed using keywords “tacrolimus AND ITP,” yielding 11 results inclusive of adult transplant recipients.

## **Results:**

A 10-year-old Caucasian male with history of autism spectrum disorder and hypoplastic left heart syndrome status-post cardiac transplant in 2012 presented with new-onset petechiae, bruising, and a platelet count of 3,000 cells/mm<sup>2</sup>. Viral PCRs for cytomegalovirus and Epstein-Barr virus were negative. There was no evidence to suggest thrombotic microangiopathy. He was treated with intravenous immunoglobulin (IVIG) 1 gm/kg twice for presumed ITP with no response in platelets, which remained less than 3,000 despite IVIG infusions. He also received a three-day course of Solumedrol 30 mg/kg with no clinical or laboratory response. Due to concern for tacrolimus-induced ITP, patient was transitioned from tacrolimus to cyclosporine based on cases in the adult literature and exhibited no response 16 days following the immunosuppressant change. Bone marrow notable for 50% hypocellularity with trilineage hematopoiesis, in the setting of a persistent isolated thrombocytopenia. As adequate megakaryocytes were present, he received one dose of subcutaneous Romiplostim 1 mcg/kg to stimulate maturation. Peripheral counts obtained one week following Romiplostim reflected platelets up to 186,000 cells/mm<sup>3</sup> with coinciding improvement in clinical symptomatology.

## **Conclusion:**

Tacrolimus may cause a refractory ITP in children on chronic immunosuppression following solid organ transplantation. Romiplostim, a fusion protein analog of thrombopoietin that has been widely studied in adults with chronic ITP and recently FDA-approved for children with chronic ITP, may also be an effective therapeutic approach in cases of medication-induced refractory acute ITP when discontinuation of the offending agent fails. Our patient was on chronic tacrolimus when his ITP occurred and failed to respond to multiple lines of standard treatment. A single dose of Romiplostim triggered megakaryocyte maturation with a sustained hematologic response at 6 months, suggesting that thrombopoietin analogs are a safe potential

therapy for refractory medication-induced acute ITP in pediatric patients following solid organ transplantation.

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Poster # 025

## **PEDIATRIC PATIENT WITH KNOWN CHRONIC ITP FOUND TO HAVE CONCURRENT FACTOR VII AND XI DEFICIENCIES**

**Deborah Soong, Ali Sanati-Mehrizy, Viney Hardit, Fernando Corrales-Medina**

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### **Background:**

Primary immune thrombocytopenia (ITP) is defined as isolate thrombocytopenia (<100,000 plt/uL) in absence of conditions known to cause platelet reduction. This is normally caused by a autoantibody-induced platelet destruction, directed to epitopes on either glycoprotein (GP) IIB-IIIa or GPIB-IX. Clotting disorders are an entirely separate entity, caused by hereditary or noninherited forms (liver disease, blood cell disorders) reducing production of coagulation factors. Literature in which both are present are little to none, and there are minimal reports on autoantibodies to coagulation factors, which could then draw an association.

### **Objectives:**

To describe the presentation of severe menorrhagia in a child with known chronic ITP and discovered to have both Factor VII and Factor XI deficiency.

### **Design/Method:**

Case Report.

### **Results:**

An 11-year-old Hispanic female presented to the ED with her first menstrual cycle characterized by menorrhagia with blood clots requiring hourly pad changes. She denied other sites of bleeding, symptoms of anemia, or vaginal trauma or penetration.

She had previously been diagnosed with idiopathic thrombocytopenia approximately two years prior in Honduras with platelets of  $30-40 \times 10^3/uL$ . Mother revealed that the patient had been receiving intravenous immunoglobulin (IVIg) every six months at an outside hospital during this time.

She was admitted and received one IVIg infusion. Oral contraceptives were initiated to regulate her menstrual cycles. She was also started on tranexamic acid, a synthetic analog of lysine that reversibly binds plasminogen and alters its antifibrinolytic properties. Interestingly, subsequent menstrual periods continued to last about 15 days per cycle with petechial lesions on her neck, upper neck, as well as easy bruising. Consequently, an extensive bleeding disorder workup was obtained, revealing deficiencies in both factors VII and XI. Additionally, she was found to have platelet associated Anti-IIB/IIIA related to her ITP. Bone marrow biopsy did not indicate



hypocellularity.

Due to her sub-optimal response to IVg and progressively worsening thrombocytopenia over the next month, she was given a 4-week course of rituximab to ameliorate platelet counts. Her platelet count responded with this regimen though she continues with easy bruising but overall improvement.

**Conclusion:**

This case presents a child with menorrhagia with multiple causes of increased bleeding tendency. Description of chronic ITP and concurrent factor deficiency is rare. It would be prudent to investigate for factor deficiencies if similar cases become known to establish whether a currently unknown association between ITP, Factor VII, and/or Factor XI exists.

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Poster # 026

**SEVERE COAGULOPATHY PRESENTING IN ARGINASE DEFICIENCY: A CASE REPORT**

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**Background:**

Arginase deficiency is a rare autosomal recessive disorder that affects the liver-based urea cycle. More than 40 genetic mutations have been identified to cause the disease, and different phenotypes exist. Argininemia is associated with mild coagulation abnormalities that can worsen if overwhelming hyperammonemia and liver failure occur. Persistent coagulopathy has been reported only in a few cases.

**Objectives:**

Demonstrate the finding of severe coagulopathy as the initial presentation in a patient with arginase deficiency, and resolution of the bleeding and laboratory improvement with control of ammonia levels.

**Design/Method:**

Chart review.

**Results:**

Patient is a 22 month old female with history of bruising, presenting with 2 days of severe and persistent epistaxis. She was found to have prolonged prothrombin time (PT>110.0 seconds), prolonged partial thromboplastin time (PTT-47.4 sec, mixing study 1:1 resulted in correction to 26.9 sec), and abnormal liver function tests with elevated aspartate aminotransferase (102), alanine aminotransferase (157), alkaline phosphatase (60).

She was managed with parenteral Vitamin K with no improvement. Bleeding resolved with fresh frozen plasma followed by temporary improvement of coagulopathy (PT and PTT decreased to

26.9 and 39.2 secs, respectively). She had normal platelet count and platelet function assay. Dysfibrinogenemia was ruled out. Coagulation factors II, VII, IX and X were all at very low levels (27%, <6%, <1% and 29%, respectively). Genetic testing for mutations in the activation pathway of vitamin K-dependent clotting factors including VKORC1 (gene encoding vitamin K epoxy reductase complex subunit 1) and GGCx (gene encoding for gamma-glutamyl carboxylase), showed no anomalies. Testing for protein induced vitamin K absence (PIVKA-II) was normal, suggesting that the coagulation factors deficiency was not secondary to vitamin K deficiency.

Patient had persistent transaminitis, further laboratory revealed increased orotic acid and arginine levels. Genetic testing confirmed the diagnosis of Arginase deficiency with two different mutations in the ARG1 gene. Patient started a low protein/arginine diet, glycerol phenylbutyrate supplementation and nitrogen scavengers (Bupheryl). 11 months after initial presentation, despite tight control of ammonia and arginine levels, patient developed neurologic symptoms including tip toe walking, spasticity, dystonia, and hyperactivity. She is currently receiving Botox injections. Her coagulopathy normalized and remains stable. She is currently awaiting liver transplantation.

**Conclusion:**

Severe coagulopathy as the initial symptom in a pediatric patient with arginase deficiency is rare; control of ammonia levels can improve symptoms and coagulopathy, and temporarily reverse the hepatic dysfunction but does not prevent the neurologic sequelae of arginase deficiency.

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Poster # 027

**BRUISING, METAPHYSEAL HYPEREMIA AND HEMATURIA; A SEQUEL OF OVERLOOKED NUTRIENT DEFICIENCY**

**Susmita Sarangi**

*Medstar Georgetown University Hospital, Washington, District of Columbia, United States*

**Background:**

Bruising in pediatric patients is a common finding, however unexplained widespread bruising can be ominous for an underlying bleeding disorder or may warrant a child abuse workup. Loss of connective tissue morphology and fragility can also lead to subcutaneous bleeding and is an often overlooked part of the workup of these patients.

**Objectives:**

We describe a patient with bruising who was initially suspected to have a bleeding disorder due to concern for a knee joint hemorrhage on examination. A systematic laboratory workup confirmed a normally functioning coagulation system. A detailed dietary history ultimately led to pursuing the right workup and ultimately confirmed the diagnosis of scurvy in this patient. The MRI findings in scurvy show a characteristic pattern of metaphyseal signal abnormality however are not well recognized due to unfamiliarity with its interpretation.

**Design/Method:**

An 8 year old autistic boy presented to the ER due to limping for a week and gum bleeding for a day. On physical exam he was found to have friable gingivae with several large bruises on his extremities, especially around his left knee and inability to extend the left knee beyond 60 degrees. His CBC revealed Hb 10.6gm/dl, Platelet 386K/uL, WBC 10.5K/uL, with normal PT, aPTT and Platelet Function Analysis. His Urine showed microscopic hematuria with 11-30 RBC/hpf. MRI knee revealed myofascial fluid signal into bilateral popliteal fossae and symmetric metaphyseal marrow hyperemia.

**Results:**

The patient was found to have a very restricted diet almost only comprising of crackers, pasta and yogurt with no fresh fruit or vegetable intake. Scurvy was suspected and a serum vitamin C level was undetectable at <5 umol/L. He was started on oral vitamin C therapy and his limp, gum bleeding and bruising resolved within a week. His anemia and hematuria spontaneously resolved and he gained weight and had an overall improved sense of well being.

**Conclusion:**

Scurvy is a rare disorder in the modern age but must be suspected in children with picky diets. The multisystem presentation can often lead to delays in diagnosis and lead to unwarranted workup. Initiation of vitamin C therapy leads to rapid improvement.

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Poster # 028

**POLYCYTHEMIA VERA DIAGNOSIS IN A 2 YEAR OLD CHILD WITH A JAK2 EXON 12 DELETIONAL MUTATION**

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**Background:**

Polycythemia vera (PV) is a myeloproliferative neoplasm primarily characterized by erythrocytosis, isolated or in association with leukocytosis, thrombocytosis, and/or splenomegaly. Less than 0.1% of PV cases present before 20 years of age, making this disorder exceedingly rare in the pediatric population. There is increased risk for thromboembolic and hemorrhagic complications, however, common clinical presentations include headache, nausea, fatigue, arthralgias, and pruritus. JAK2 mutations comprise the molecular hallmark of PV with approximately 96% found to have a somatic mutation in exon 14 (JAK2 V617F) and 3% displaying a mutation in exon 12. Little has been standardized in regards to pediatric treatment of PV.

**Objectives:**

Present a rare case of polycythemia vera with confirmed JAK2 exon 12 mutation in a 2 year old patient.

**Design/Method:**

## Case Report

### Results:

A 2-year-old female without significant past medical history presented with microcytosis and elevated red blood cell counts and hematocrit on repeat evaluations. Lab results noted Hgb 13.7 gm/dL, Hct 49.9%, RBC 8.92 x 10<sup>6</sup>/mcL, platelet 365 x 10<sup>3</sup>/mcL, WBC 8.77 x10<sup>3</sup>/mcL, MCV 55.9 fL, and ferritin 4ng/mL. Her hemoglobin electrophoresis detected a low hemoglobin A2 level. She endorsed intermittent bilateral leg pain only. Molecular testing for JAK2 V617F, performed on a peripheral blood sample was negative. Subsequent molecular testing revealed a 6-nucleotide deletion in exon 12 of JAK2 (p.E543\_D544del), which removed 2 amino acids from the kinase domain of the protein. Based on the WHO revised 2016 diagnostic criteria for PV, she underwent a bone marrow biopsy, confirming hypercellularity with trilineage hyperplasia and pleomorphic megakaryocytes; the patient, therefore, now met the 3 major criteria for PV diagnosis.

Aspirin therapy was initiated and phlebotomy was performed with a hematocrit goal of <45%. Intermittent headaches and leg pain continued despite treatment. Despite dietary efforts, her ferritin stores remained low. Oral iron supplementation was avoided as to not exacerbate her red blood cell production. Her family became concerned about neurodevelopment, leading to initiation of peginterferon alfa-2a subcutaneous therapy. To date, she is no longer symptomatic, however given the brevity of her interferon treatment course, efficacy has not been established.

### Conclusion:

Polycythemia vera is an extremely rare condition within the pediatric population. While evidence-based treatment of PV in the pediatric population has not been established given its low incidence in this group, we have provided the therapy course that led to resolution of symptoms in this patient.

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Poster # 101

## **SPLENIC COMPLICATIONS IN SICKLE CELL DISEASE: A RETROSPECTIVE COHORT REVIEW**

**Shannon Conneely, M. Ross Mangum, Philip Lupo, Michael Scheurer, Alex George**

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### Background:

Acute splenic sequestration crisis (ASSC) is the second leading cause of death in the first decade of life in patients with sickle cell disease (SCD). It occurs prior to splenic auto-infarction with a reported incidence of 7-30% and has a high rate of recurrence. Despite the known consequences of ASSC, few large-scale studies have been performed to assess risk factors, natural progression, and current standards of therapy for splenic complications of SCD. In particular, there are limited data concerning the prevalence of splenic dysfunction in the less common sickle cell genotypes.

### Objectives:

To ascertain patterns of splenic complications in patients with various types of SCD.

**Design/Method:**

This study was a retrospective chart review of pediatric patients treated for SCD at a large academic hospital from January 2000 through December 2018. We extracted data from our electronic medical record system for patients with documented splenic complications such as splenomegaly, hypersplenism, and splenic sequestration crises based on ICD9 and ICD10 codes. We then reviewed charts for patients with these diagnoses to confirm sickle cell genotypes, dates and number of splenic events, and prevalence of surgical splenectomy.

**Results:**

We identified 1460 patients treated for SCD at our center during the study time period. Of these, 263 (18.0%) were diagnosed with a splenic complication, defined as splenomegaly, hypersplenism, or splenic sequestration. The overall prevalence of splenic complications was highest in patients with sickle beta-zero thalassemia (S $\beta$ 0) at 57.6%, compared to 17.8% in hemoglobin SS (SS) patients, 16.2% in hemoglobin SC (SC) patients, and 5% in sickle beta-plus thalassemia (S $\beta$ +) patients. ASSC events occurred in 45.5% of S $\beta$ 0 patients, 16.8% of SS patients, 13.0% of SC patients, and 2.5% of S $\beta$ + patients. The onset of ASSC occurred later in SC patients (5.3  $\pm$  3.3 years) compared to SS (2.4  $\pm$  1.9 years) and S $\beta$ 0 (3.1  $\pm$  1.5 years) patients. Splenectomy rates were highest amongst S $\beta$ 0 patients (30.3%), while they were less common in SS patients (8.0%) and rare in SC and S $\beta$ + patients (0.8% and 2.5% respectively).

**Conclusion:**

Our data indicate that the prevalence and severity of splenic problems varies widely between different sickle cell genotypes, with S $\beta$ + and SC patients having relatively mild complications while S $\beta$ 0 patients have the most severe and frequent complications.

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Poster # 102

**FEVER IN SICKLE CELL - IS IT A ONE-SHOT DEAL?**

**Kristina Emeghebo, Maire Amlicke, Abena Appiah-Kubi, Banu Aygun, Santina Bruno, Joanna Fishbein, Lorry Rubin, Charles Schleien, David Teng**

*Northwell Health/Cohen Children's Medical Center, New Hyde Park, New York, United States*

**Background:**

Children with sickle cell disease (SCD) have an increased risk of bacteremia. Although penicillin prophylaxis and pneumococcal immunizations have significantly reduced this risk, fever remains an indication for emergency evaluation and treatment.

**Objectives:**

Our study aimed to investigate the bacteremia rate for sickle cell patients who presented to the Emergency Department (ED) with fever, as well as the incubation time to positive (TTP) of pathogenic blood cultures. We hypothesized that true pathogens in febrile patients with SCD would be isolated within 24 hours.

**Design/Method:**

A retrospective chart review of children (0 to 21 years) who presented to our ED with SCD and fever (temperature >38°C) was performed. In addition to sickle cell genotype, our data included results of the complete blood count, respiratory viral panel, blood and urine cultures, chest radiographs, treatment, and outcome.

**Results:**

Over 48 months, 1197 febrile SCD patients presented to the ED. Seventeen patients had a positive blood culture with 4 (0.33%) considered “true pathogens.” (95% CI: 0.09-0.85%): *Streptococcus pneumoniae* (serotypes 3 and 15C), *Staphylococcus aureus*, and *Salmonella* Group B. The median TTP for pathogens was 17.1 hours (IQR 12.5 to 21.6; max 23 hours) compared to 30.8 hours (IQR 23.2 to 31.9) for contaminants (p=0.06). The pathogen-positive patients were between 3.8 to 19.3 years old, all had the HbSS genotype, were hospitalized, and received a course of parenteral antibiotics. The patient with *S. aureus* had a prior splenectomy and was on chronic transfusion therapy. The patients with *Salmonella* and *S. pneumoniae* serotype 15C presented with acute chest syndrome. The patient with *S. pneumoniae* serotype 3 presented with an orbital cellulitis. All patients were admitted at first presentation due to their secondary diagnoses except for the patient with *S. aureus* bacteremia who was otherwise asymptomatic and was called back to the ED after her first dose of parenteral antibiotics.

**Conclusion:**

Our data shows similar rates of bacteremia to what has been reported in the literature, ranging from 0.33% to 1.7% among febrile children with SCD. Considering the observed low rates of bacteremia in sickle cell patients and the short TTP in pathogenic blood cultures, we suggest that providing empiric parenteral antibiotic coverage for asymptomatic febrile patients for more than 24 hours may not be clinically indicated, and may increase the patient’s exposure to other infectious agents in the ED, cause work and school absences, and add a significant health care cost.

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Poster # 103

**LENTIGLOBIN GENE THERAPY IN PEDIATRICS, ADOLESCENTS, ADULTS WITH TRANSFUSION-DEPENDENT B-THALASSEMIA**

**Janet Kwiatkowski, Mark Walters, Franco Locatelli, Ashutosh Lal, Evangelia Yannaki, Andreas Kulozik, Martin Sauer, John Porter, Isabelle Thuret, Suradej Hongeng, Adrian Thrasher, Timothy Olson, Jennifer Schneiderman, Heidi Elliot, Ge Tao, Weijian Liu, Richard Colvin, Alexis Thompson**

*Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States*

**Background:**

In patients with transfusion-dependent  $\beta$ -thalassemia (TDT) hematopoietic stem cell (HSC) gene addition has the potential to increase total hemoglobin (Hb) through production of gene therapy-derived Hb and establish transfusion independence. Betibeglogene autotemcel (beti-cel;

LentiGlobin for  $\beta$ -thalassemia) gene therapy adds functional copies of a modified HBB gene to patient's HSCs through transduction of HSCs with BB305 lentiviral vector (LVV).

**Objectives:**

Describe interim results of two phase 3 studies in patients with TDT: HGB-207 (NCT02906202; non- $\beta^0/\beta^0$  genotypes); HGB-212 (NCT03207009;  $\beta^0/\beta^0$ ,  $\beta^0/\beta^+$ IVS-I-110,  $\beta^+$ IVS-I-110/ $\beta^+$ IVS-I-110 genotypes).

**Design/Method:**

CD34+ cells were collected via mobilization/apheresis, transduced with BB305 LVV, and infused into patients following single-agent busulfan myeloablation. Results are presented as median (min-max).

**Results:**

In HGB-207 and HGB-212, 21 and 13 patients have been treated with 11.6 (0.9-26.3; as of June 12, 2019) and 8.8 (2.5-20.0; as of September 30, 2019) months of follow-up, respectively. Ten patients were <12 years old and 10 were  $\geq$ 12-18 years old.

Post-infusion non-hematologic grade  $\geq$ 3 adverse events (AEs) in  $\geq$ 3 patients in either study included stomatitis (n=17), febrile neutropenia (n=14), pyrexia (n=3), epistaxis (n=3), and liver veno-occlusive disease (n=3). Drug product-related AEs included abdominal pain (n=3), thrombocytopenia (n=3), leukopenia (n=1), neutropenia (n=1), and pain in extremity (n=1).

There were no deaths.

In HGB-207, 18/20 patients (14/15,  $\geq$ 12 years old; 4/5, <12 years old) with >5 months follow-up have not received a transfusion in >3.5 months. The transfusion independence primary endpoint (TI, weighted average Hb of  $\geq$ 9 g/dL without red blood cell transfusions for  $\geq$ 12 months) was achieved in 9/10 evaluable patients. Weighted average Hb during TI was 12.2 (11.4-12.8) g/dL. Gene therapy derived HbAT87Q accounted for  $\geq$ 69% of total Hb at last assessment. Soluble transferrin receptor trended towards normal in patients who stopped transfusions (baseline: 127.6 [21.2-235.3] nmol/L, n=18; Month 12: 43.5 [20.0-69.4] nmol/L, n=9) indicating less severe ineffective erythropoiesis.

In HGB-212, 7/8 patients >12 years old and 2/3 patients <12 years old with >5 months follow-up have stopped transfusions for  $\geq$ 3 months. Two evaluable patients achieved TI including one pediatric patient. At Months 6 and 12, unsupported total Hb was 10.2 (8.5-13.2) g/dL (n=10) and 13.8 (10.3-14.0) g/dL (n=3), respectively. HbAT87Q contributed 8.3 (0-12.0) g/dL (n=11) and 11.1 (8.8-12.6) g/dL (n=3), respectively.

**Conclusion:**

Following beti-cel gene therapy for TDT in HGB-207 and HGB-212, 18/20 and 9/11 patients with  $\geq$ 5 months follow-up have stopped transfusions including 6/8 patients <12 years of age. The safety profile is consistent with busulfan myeloablation. Sponsored by bluebird bio.

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Poster # 104

**1,2,4-TRIAZOLE LSD1 INHIBITORS INDUCED FETAL HEMOGLOBIN PRODUCTION IN VITRO**

**Mayra Robinson, Joy Kirkpatrick, M Laurence Noisette, Steven Holshouser, Patrick Woster**

*Medical University of South Carolina, Charleston, South Carolina, United States*

**Background:**

The direct repeat erythroid- definitive complex (DRED) and its enzyme Lysine specific histone demethylase 1 (LSD1) promote the formation of hemoglobin A (HbA:  $\alpha_2\beta_2$ ) by methylation of Lysine 4 on Histone 3 (H3K4), during early infancy (1). Patients with sickle cell disease become symptomatic once the mutated adult hemoglobin (HbS:  $\alpha_2\beta_S$  and other phenotypes) replaces the fetal hemoglobin (HbF:  $\alpha_2\gamma_2$ ) (2). A significantly milder clinical course has been described in patients that maintain a HbF>30% (3). Complete disruption of the DRED complex via LSD1 inhibition induces the synthesis of  $\gamma$ -globin and consequently an increase in HgbF (4).

**Objectives:**

The primary objective of this research is to evaluate novel LSD1 inhibitors for the induction of  $\gamma$ -globin to treat sickle cell disease.

**Design/Method:**

K-562 and CD34+ cells were cultured separately in the appropriate media and treated for 72 hours with multiple concentrations of newly developed 1,2,4-triazole LSD1 inhibitors, known LSD1 inhibitors, HU or DMSO vehicle control. Fetal hemoglobin production was measured using  $\gamma$ - globin as a surrogate. Cells were collected, and protein and RNA were isolated for analysis of  $\gamma$ - globin using Western Blot and Real Time Polymerase Chain Reaction (rt-PCR).

**Results:**

Our newly developed 1,2,4-triazole compounds alter epigenetic regulation of  $\gamma$ - globin gene expression through modification of H3K4 methylation by reversible inhibition of the epigenetic eraser LSD1. We discovered a significant increase in both  $\gamma$ - globin protein and gene expression with a concurrent decrease in  $\beta$ - globin following treatment with our compounds. These compounds induced a significantly larger increase in  $\gamma$ - globin than standard of care treatment, HU, without additional cytotoxicity.

**Conclusion:**

These data suggest that sickle cell anemia could potentially be therapeutically treated by reversible inhibition of LSD1, using 1,2,4-triazoles to increase levels of HbF.

References:

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Poster # 105



## LENTIGLOBIN GENE THERAPY FOR PATIENTS WITH SICKLE CELL DISEASE: UPDATED RESULTS FROM STUDY HGB-206

Alexis Thompson, Lakshmanan Krishnamurti, Markus Mapara, Janet Kwiatkowski, John Tisdale, Manfred Schmidt, Alexandra Miller, Francis Pierciey Jr., Wenmei Huang, Jean-Antoine Ribeil, Julie Kanter, Mark Walters

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### **Background:**

LentiGlobin gene therapy (GT) for sickle cell disease (SCD) contains autologous CD34+ hematopoietic stem cells (HSCs) encoding  $\beta$ -globin with the anti-sickling T87Q substitution. In the ongoing Phase 1/2 HGB-206 Study (NCT02140554), GT-derived hemoglobin (HbAT87Q) levels in 7 initial patients (Group A) were suboptimal but were maintained for  $\geq 30$  months, suggesting durable transgene expression. To increase HbAT87Q production, protocol and manufacturing changes were made (Group B; N=2). HSC collection by plerixafor mobilization and apheresis was also instituted (Group C; N=19).

### **Objectives:**

Updated safety and efficacy data for LentiGlobin GT in HGB-206 Group C.

### **Design/Method:**

CD34+ HSCs were collected by apheresis following plerixafor mobilization from patients with SCD and recurrent severe vaso-occlusive crises (VOC) and acute chest syndrome (ACS). CD34+ HSCs were transduced with BB305 lentiviral vector (LVV). Patients received myeloablative busulfan conditioning and LentiGlobin infusion. LVV in transduced cells (%LVV+) was measured by qPCR in pre-infusion drug product (DP) and post-infusion CD34+ bone marrow (BM) HSCs and peripheral blood mononuclear cells (PBMCs). RBC sickling was quantified by imaging flow cytometry on RBCs exposed to 2% O<sub>2</sub>. Data are median (min–max).

### **Results:**

As of 7 March 2019, 13 Group C patients received LentiGlobin (follow-up 9.0 [1.0–15.2] months). Median HbS was  $\leq 50\%$  of total Hb in patients with  $\geq 6$  months follow-up (n=8). In these patients, total unsupported Hb at last visit was 11.5 (10.2–15.0) g/dL, with HbAT87Q levels of 5.3 (4.5–8.8) g/dL. The annualized VOC+ACS rate decreased from 5.3 (3–14) pre-treatment to 0 (0-2) post-treatment in patients with VOC+ACS history and  $\geq 6$  months follow-up (n=6). Hemolysis markers decreased post-treatment. The %LVV+ colonies from PBMCs at 9 months and BM at 12 months post-LentiGlobin (n=5) were 79.2% (67.0%–88.4%) and 81.5% (60.6%–88.1%), respectively, indicating stable engraftment of transduced cells. The % sickled RBCs from LentiGlobin-treated patients, while similar to those from trait individuals, was lower compared to untreated patients with SCD.

Most common non-hematologic Grade  $\geq 3$  AEs post-LentiGlobin were febrile neutropenia (n=10) and stomatitis (n=7). Six patients reported serious AEs (most commonly nausea and vomiting). No cases of DP-related AEs, graft failure, vector-mediated replication-competent lentivirus, or clonal dominance were reported.

**Conclusion:**

HGB-206 Group C patients with  $\geq 6$  months follow-up show stable LentiGlobin engraftment, with total Hb  $>10$  g/dL and HbS  $\leq 50\%$  of total Hb, and a safety profile consistent with busulfan conditioning. The absence of ACS or serious VOCs and improved hemolysis suggest a strong therapeutic benefit of LentiGlobin in patients with SCD.

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Poster # 106

**STUDYING THE INCIDENCE OF CANNABIS USE IN TEENAGERS WITH SICKLE CELL DISEASE, AN INTERIM ANALYSIS**

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**Background:**

There are protean manifestations of Sickle Cell Disease (SCD), but the primary issue of this debilitating disease is severe pain that occurs in both acute and chronic settings. Patients with SCD require the use of both NSAIDs and opioid pain medication to manage their pain. However, this combination often does not provide the relief that patients need, forcing patients to look for alternative and adjunct forms of pain control. With the recent legalization of marijuana in Michigan, we aim to determine the prevalence of marijuana use in adolescents and teens with SCD, to aid our effort in tracking this longitudinally. As of today, there is no data on the use of marijuana in this age group of patients with SCD.

**Objectives:**

To assess the current practices and prevalence of marijuana use amongst teenagers with sickle cell disease.

**Design/Method:**

A seven-item survey was created and distributed to patients presenting to clinic for annual visits, transfusions, and/or patients admitted to the hospital for sickle cell pain crises or fevers. This survey posed questions about marijuana usage including- frequency of use, form of marijuana used, purpose of use (medical or recreational), and lastly, perception of pain reduction.

**Results:**

At this time, 35 surveys were collected and scored. Of which, 12 (35%) had positive screens for marijuana use. Of those using marijuana, 50% were using marijuana products at least once per week. The most common form of use was inhalational (42%), followed by edible (17%), and topical (8%). 42% of patients using marijuana were combining various forms of it. Those that used more than one form were more likely to use it at least once a week, whereas those who just used inhalational were more likely to use once a month or less. Finally, and most importantly, all 12 respondents who stated they used marijuana found that it helped to alleviate their pain.

**Conclusion:**

Previous studies have showed that adults turn to marijuana use as an adjunct to their pain medication to control their sickle cell pain. The interim analysis for this study, suggests that teenagers do the same.

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Poster # 107

**SICKLE CELL AND OBESITY IN THE PEDIATRIC POPULATION IN MISSISSIPPI:  
A RESTROSPECTIVE CHART REVIEW**

**Erin Jackson, Cynthia Karlson, Whitney Herring, Victoria Okhamina, Caroline Daggett, Crystal Lim, Anne Morrow, Laura Newman, Melissa McNaull**

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**Background:**

Children with sickle cell disease (SCD) historically have higher basal metabolic rate (BMR) than healthy peers. In the past, children with SCD tended to be underweight to normal weight. Current medical treatments increase patients' basal hemoglobin level, which may in turn decrease patients' BMR

**Objectives:**

The purpose of this study is to examine the rates of overweight/obesity in children with SCD, compared to state and national norms. We hypothesized that rates of overweight/obesity in children with SCD will approach state and national normative rates, and rates of overweight/obesity will be higher in children with SCD with higher hemoglobin than lower hemoglobin levels.

**Design/Method:**

We conducted a retrospective chart review of patients diagnosed with SCD (HbSS/HbS, HbSC/HbS+), between 2-19 years, who were seen at an outpatient Pediatric Hematology appointment at the University of Mississippi Medical Center from October 2013-April 2019. All data were collected from the most recent clinic visit. Body Mass Index (BMI) and percentiles were calculated using Center for Disease Control growth charts. Mississippi and national weight status estimates for youth 10-17 years were obtained from the 2016-2017 National Survey of Children's Health. Underweight, overweight and obesity were defined as <5th, >85th and >95th percentile, respectively. Descriptive statistics, two-sample tests of proportion, and logistic regressions were calculated in Stata 16.0.

**Results:**

Chart review data were available for 787 children with SCD. For children aged 10-17 with SCD (n = 480), 24.5% were overweight/obese compared to Mississippi and national rates of 39.2% and 31%, respectively. The prevalence of 10-17 year olds with SCD who were overweight (12.7%) was not significantly different from Mississippi (13.1%) or national (15.2%) rates (p = 0.13), although prevalence of obesity in SCD (9%) was still significantly lower compared to state (26%) and national (15.8%) rates (p < 0.001). Among pediatric patients with SCD, those with

SC/SB+ genotype were 2.59 times more likely to be overweight/obese compared to patients with SS/SB°. Median baseline hemoglobin level was significantly different among patients who were underweight (8.80g/dL), normal weight (9.2g/dL), and overweight/obese (10.5g/dL), with patients who were overweight/obese having the highest median baseline hemoglobin level ( $p < 0.001$ ).

**Conclusion:**

Pediatric patients with SCD in Mississippi now have similar prevalence rates of being overweight compared to state and national norms. Patients who are overweight/obese have a higher median basal hemoglobin level than patients who are normal/underweight. The overall impact of increased BMI in SCD is unknown and additional longitudinal studies are needed.

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Poster # 108

**RETROSPECTIVE REVIEW OF PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE PRESENTING WITH THROMBOEMBOLISM**

**M Laurence Noisette, Shayla Bergmann, Amy Wahlquist**

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**Background:**

Sickle cell disease (SCD) is an autosomal recessive condition, caused by an amino acid mutation in the 6th position of the  $\beta$  globin, producing hemoglobin S.<sup>1</sup> In the deoxygenated state, the hemoglobin S (HgbS) tetramer polymerizes altering its structure to a crescent shape promoting vaso-occlusion and repeated episodes of ischemia and reperfusion loses its flexibility resulting in hemolysis. These two-mechanism lead to a cascade of events causing a hypercoagulable state in this disease.<sup>2</sup> Additionally, multiple aspects of the coagulation pathway are affected: the intrinsic and extrinsic pathways, the fibrinolytic system along with platelet activation and aggregation.<sup>3</sup> Previous studies have demonstrated a high prevalence of thromboembolism (TE) in patients with sickle cell disease.<sup>4,5</sup>

**Objectives:**

We noted an increase occurrence of thromboembolism in pediatric patients in our tertiary care center, leading us to complete a retrospective chart review of patients with sickle cell disease presenting with thromboembolism.

**Design/Method:**

We reviewed 59 charts from January 1st, 2009 to January 1st, 2019, of patients <21 years of age with any sickle cell genotype presenting with vascular thromboembolism. We collected baseline demographics of our population, recent hospitalization, characteristics of thromboembolism, thrombophilia evaluation and treatment.

**Results:**

The cohort consisted of 11 patients, with a mean age of 16.7 years  $\pm$  4.73 with a female majority. Our cohort's genotype was 55% with Hgb SS, 27% with Hgb SC and 18% with Hgb

S $\beta$ thalassemia. Most thromboembolisms were found to be pulmonary at 55%. The remainder were in the right atria, superior vena cava, abdominal aorta, and axillary, basilic and tibial veins. Pulmonary emboli occurred in slightly older patients with Hgb SC genotype, whereas with the other thrombi location were more frequent in Hgb SS genotype patients.

Despite knowing the hypercoagulable state in sickle cell disease, only 55% underwent a thrombophilia evaluation. The labs obtained were variable and provider dependent. All patients in this cohort were treated with anticoagulation.

**Conclusion:**

Despite our small population, the results of this retrospective review correlate with the current literature regarding the hypercoagulable state in pediatric patients with sickle cell disease.<sup>5,6</sup> Prospective studies of this population could answer multiple questions regarding the management of their hypercoagulability. Investigation of the increased inherited risk and/or increasing acquired thrombophilic factors and prospective studies of anticoagulation agents may help guide providers for individual management and/or prophylaxis of these patients.

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Poster # 109

**PERIPHERAL BLOOD SMEARS AND LABORATORY TRENDS AS HYDROXYUREA ADHERENCE TOOLS FOR SICKLE CELL ANEMIA**

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**Background:**

Despite decades of evidence demonstrating the benefits of hydroxyurea as the primary disease-modifying therapy for sickle cell anemia (SCA), medication adherence remains a significant challenge. As the benefit of hydroxyurea are not always felt by patients on a day-to-day basis, its protective effects may be difficult to appreciate, resulting in suboptimal adherence for some. We hypothesize that the visualization of laboratory trends and blood smear changes may improve patients' understanding of therapy, and positively impact adherence to daily therapy.

**Objectives:**

To evaluate the feasibility, acceptability and benefits of reviewing laboratory data and blood smear images as a hydroxyurea educational tool for children with SCA.

**Design/Method:**

Studying Medication Education and Adherence with Red blood cells in Sickle Cell Disease (SMEARS) is a prospective randomized trial to assess the feasibility and utility of reviewing laboratory trends and blood smear images as a tool to improve adherence. Randomization was 1:1 to the intervention (hydroxyurea education, regular review of laboratory data and blood smears) or standard of care (no additional education) arm. Blood smear images were captured electronically from Cellavision, an automated image analysis system performed with Complete Blood Counts. Caregivers and patients >11 years of age in both arms completed surveys at baseline and every three months for 1 year. The surveys included questions about medication

adherence, barriers to adherence, and their understanding of hydroxyurea therapy and its effectiveness.

**Results:**

A total of 43 participants completed the baseline evaluation, and 29 participants the entire study (16 standard arm, 13 intervention arm). At baseline visit, only 7% of participants missed >5 doses within the past month. Laboratory studies reflected good adherence with mean HbF of 28.9%. Perhaps due to the high baseline adherence, the study did not find differences in adherence patterns between the two study arms, but the educational tools were well received by families and patients. Among intervention arm participants, 100% (13/13) were able to identify healthy and unhealthy (sickled) red blood cells. In the intervention arm, 92% of participants reported that they knew how hydroxyurea helps red blood cells, compared to 55% at baseline. Commonly reported barriers to hydroxyurea therapy identified at baseline included forgetting (51%), and social difficulties (21%).

**Conclusion:**

A multi-dimensional approach to medication adherence is essential to optimize the benefits of hydroxyurea. Although further research is required, this study has shown that patients and families appreciate and learn from reviewing laboratory trends and blood smear images, which may positively impact adherence.

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Poster # 110

**PREVALENCE OF NEUROPATHIC PAIN IN ADOLESCENTS WITH SICKLE CELL DISEASE; A SINGLE CENTER EXPERIENCE**

**Latika Puri, Doralina Anghelescu, Melissa Cregan, Jane Hankins**

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**Background:**

Sickle cell pain is complex and involves both neuropathic and nociceptive pain mechanisms. Current practice for assessing sickle cell pain does not employ tools that elicit pain phenotype. It is important to evaluate for neuropathic pain so specific treatment (e.g., gabapentoids) can be used, expanding beyond non-steroidal anti-inflammatory drugs and opioids to provide optimal relief.

**Objectives:**

To evaluate the prevalence of neuropathic pain in adolescents with SCD and the utility of routine screening for neuropathic pain in this population.

**Design/Method:**

This was a quality improvement initiative undertaken at the comprehensive sickle cell center at St. Jude Children's Research Hospital. Patients between 12 and 18 years of age with any sickle cell genotype were eligible and were consecutively recruited during routine clinic visits or hospitalization for pain between June 1st and July 31st , 2019 . Participants were asked to

complete painDETECT questionnaire, a tool validated to detect neuropathic pain in patients 14 years and above.

**Results:**

Overall 88 questionnaires were completed by 83 patients - 81 in outpatient, and 7 in inpatient setting. Five patients completed survey in both outpatient and inpatient setting. Average age of patients surveyed was 15.1 ( $\pm$  2.0) years, with equal gender distribution (males, n=41; females, n=42). Disease genotypes were as follows: HbSS (n=40), HbSC (n=22); HbS $\beta$ 0 Thalassemia (n=6), other (n=15). Mean painDETECT score in outpatient cohort was 6.6 ( $\pm$ 5.5). In outpatient setting, 70 (87%) had pain score between 0-12 indicating absence of neuropathic pain; 8 (10%) patients had pain score between 13 and 18, suggesting a neuropathic component to pain and 3 (4%) patients had scores >18, suggesting a definite neuropathic component to pain. Thus only 11 (14%) patients had scores suggestive of neuropathic pain and 3 of them were receiving specific neuropathic therapy. Additionally, patients with painDETECT scores >13 had an average of 4.2 pain events (pain admissions, emergency department/acute care visits, or pain related calls) in the previous 12 months. Mean score for 7 patients hospitalized for acute sickle vaso-occlusive pain was 18.1 (+ 5.2). Three of these patients had previously documented lower painDETECT scores during routine clinic visits.

**Conclusion:**

Prevalence of neuropathic pain in adolescents with SCD at steady state was low and routine screening might not be indicated. However, patients hospitalized for pain were noted to have higher painDETECT scores suggesting a neuropathic component during acute vaso-occlusive pain. Our sample size was very small, these findings should be confirmed in a larger patient cohort.

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Poster # 111

**THE EFFECT OF CARBON MONOXIDE ON SICKLE CELL BLOOD FLOW IN A MICROFLUIDIC DEVICE**

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**Background:**

Sickle cell disease affects a large population both nationally and globally. The disease is characterized by the presence of sickle hemoglobin, HbS. HbS polymerizes the red blood cell upon deoxygenation causing several complications, most notably, vaso-occlusion. Carbon monoxide (CO) has a known effect to increase hemoglobin oxygen affinity, decreasing the likelihood of hemoglobin deoxygenation. Microfluidic devices serve as a helpful tool to study sickle cell disease allowing researchers to analyze blood flow in a controlled microenvironment while also mimicking pathophysiologic conditions.

**Objectives:**

This study investigates the effect of inhaled CO on blood flow in a mouse with sickle cell disease

using a microfluidic device. We hypothesize that given carbon monoxide's mechanism of increasing hemoglobin oxygen affinity, treated blood samples will be less sensitive to deoxygenation.

### **Design/Method:**

Townes, transgenic mice models of sickle cell disease with HbSS genotype were used in this experiment. Treatment consisted of inhaled CO at a concentration of 250 parts per million for 30 minutes. Mice were anesthetized and blood samples were drawn via intracardiac puncture. Blood was then ran through a microfluidic device in a channel with a cross sectional area of  $15\mu\text{m}\times 15\mu\text{m}$ . The microfluidic device is a multilayer polydimethylsiloxane (PDMS) construct of a gas, hydration, and blood layer. Each layer was created using standard photolithography to create a master mold. Oxygen gas was pushed through the gas layer at specific oxygen tensions while blood flow velocity was simultaneously monitored and recorded through the blood layer. Deoxygenation-oxygenation cycles were conducted using oxygen saturations from 0 to 21%, up-titrating in a step-wise fashion until oxygen-independent flow velocity was observed.

### **Results:**

Blood flow velocities at various oxygen tensions were compared between one sickle mouse treated with inhaled CO and one untreated sickle mouse. In the untreated sample, velocity decreases in response to deoxygenation until 10% oxygen saturation, when oxygen-independent flow is observed. In the treated sample, oxygen-independent flow is observed earlier at a lower oxygen saturation of 7%. Absolute maximum velocity response to deoxygenation was also reduced to about half in the treated sample.

### **Conclusion:**

Flow properties of blood from mice with sickle cell disease using a microfluidic platform have been successfully observed and demonstrate oxygen-dependent blood flow. When treated with inhaled CO at low concentrations, sickle blood flow is less sensitive to deoxygenation demonstrated by a decreased oxygen tension required for oxygen-independent flow and an overall decreased absolute velocity response to deoxygenation.

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Poster # 112

## **HYDROXYUREA USE FOR SICKLE CELL ANEMIA IS UNDERUTILIZED EVEN WITHIN A UNIVERSAL HEALTH CARE SYSTEM**

**Kirsten Miller-Jaster, Apryl Susi, Cade Nylund, Gregory Gorman, Kenneth Liew**

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### **Background:**

Sickle cell anemia (SCA) is a common hematologic disease in the US which results in severe morbidity and mortality affecting the African American population. Hydroxyurea is a safe and efficacious drug that decreases ischemic events and end-organ damage. Hydroxyurea was found in a randomized placebo controlled trial (BABY HUG) to be beneficial to children and was strongly recommended for pediatric use in 2014. There is concern that this therapy, now



considered standard of care, remains underutilized.

**Objectives:**

We aim to describe hydroxyurea use for patients with SCA in a universal open-access health care system and describe factors related to disparities in its use.

**Design/Method:**

Children aged 1-18 years old with a diagnosis of SCA were identified from military health system claims data from 2005-2017. SCA was identified by ICD9 and ICD10 codes. Patients received care at both military and civilian institutions and all patients received access to care without cost. Prescriptions for hydroxyurea were identified by American Hospital Formulary System prescription drug codes. The odds of being prescribed hydroxyurea were determined by logistic regression after adjustment for demographic factors and era effects. Socioeconomic status was determined by parent's military rank.

**Results:**

We identified 2,765 patients with SCA. The median age for initial enrollment in the military system was 3 years (interquartile range (IQR) 0-10 years) and 49.4% were female. 476 (17.2%) had a parent who was junior enlisted (JE), 1942 (70.2%) senior enlisted (SE), and 328 (11.9%) an officer. Any hydroxyurea use increased from 8.5% in 2005 to 14.4% in 2017 (OR 1.06 [95% CI 1.03-1.08]). Median time from earliest diagnosis to prescription was 2.8 years (IQR 0.4-6.0 years). With adjusted analysis, the odds of being prescribed hydroxyurea varied by increasing age (OR 1.11 [95% CI 1.09-1.13]) and Post (2016-2017) vs Pre (2005-2013) Baby HUG introduction (OR 1.93 [95% CI 1.61-2.32]). It was not significant for gender (OR 0.82 [95% CI 0.65-1.03]) or parent rank (SE vs JE 1.29 [95% CI 0.94-1.77], Officer vs JE 1.54 [95% CI 0.74-3.22]).

**Conclusion:**

Hydroxyurea use for children with SCA is increasing in the military healthcare system. There were no disparities in hydroxyurea prescription based on gender or socioeconomic factors. However, despite minimal to no cost for prescription or subspecialty care, there is an underutilization of this effective therapy. There exists overwhelming evidence regarding the benefit of hydroxyurea therapy in patients with SCA and improvements are needed to bring this life saving therapy to more patients.

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Poster # 113

**M.A.L.I. SCD: MEDICAL APPLICATION FOR LEARNING IMMUNIZATIONS IN CHILDREN WITH SICKLE CELL DISEASE**

**Gerard Hills, Seethal Jacob, William Bennett**

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**Background:**

It is estimated that about 100,000 Americans, or 1 out of every 365 African Americans, suffer

from sickle cell disease (SCD). Infection remains one of the leading causes of death in patients with SCD due to impaired splenic function. Prophylactic penicillin and a sickle cell-specific vaccination schedule aid in preventing life-threatening illnesses. However, due to the paucity of clear, accessible resources, many primary care providers (PCPs) feel uncomfortable managing the chronic care of patients with SCD, including vaccinations. It is hypothesized that the development of a web-based tool for primary care providers will improve the confidence and accuracy of vaccine administration in children with SCD.

**Objectives:**

To assess the feasibility of an online decision-support tool developed to aid primary care providers in the appropriate vaccination of children with SCD.

**Design/Method:**

We built the MALI tool using the Javascript programming language to develop a user interface that deploys a SCD-specific vaccine algorithm. This algorithm was based on CDC vaccination guidelines implemented in SCD patients based on age. The algorithm was launched via a website (utilizing Javascript/CSS), creating an application scalable to any screen size. The website was hosted on an Indiana University secure server and sent to local PCPs via email. PCPs, which included general pediatricians, internal medicine/pediatrics, family practitioners, and nurse practitioners, were randomly selected from community and academic primary care centers within the city. Data were collected in real-time.

**Results:**

Eighteen of eighty-seven eligible participants completed the survey for a 21% response rate. Participants (67% female) had a mean age range of 25-34 years. Most participants (52%) were PCPs working as general pediatricians. Desktop computers (72% of participants) and mobile phones (67% of participants) were the most utilized medium for accessing medical information in the clinical setting. 100% of individuals found that the web-tool was “easy or very easy” to navigate, and 94% of participants thought the vaccination recommendations were communicated “very well or extremely well”. The majority of participants noted the web-tool was "useful"; however, to varying degrees. The net promoter score (NPS) was +11 (scores from 0-100 indicate easy adoption of use). Feedback from participants noted the need for improvements in vaccination registry integration and website design.

**Conclusion:**

The results of this study indicate that this clinical web-tool is a feasible method for providing vaccination recommendations to providers caring for children with SCD. Future work will include modification of the tool based on feedback and adaptation for more widespread use.

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Poster # 114

**DEPICT HEALTH THALASSEMIA TO IMPROVE MANAGEMENT OF THALASSEMIA IN SRI LANKA**

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**Background:**

The thalassemias, the commonest monogenic diseases worldwide, are an escalating public health concern throughout Asia, where 90% of the world's patients reside. Most Asian patients die prematurely, related not to lack of treatment but to poor quality of care, [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(18\)31668-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31668-4/fulltext), including inadequacies arising from gaps in the organization of health records. Since 1996, our research in thalassemia in Sri Lanka has been limited by challenges in the collection, organization, and sharing of data in 25 geographically distant centers of thalassemia care around the island. We have reported that current record keeping in Sri Lanka is generally inadequate to provide information about many important aspects of thalassemia care: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0220852>. Streamlined “at bedside” data entry into our new, disease-specific, Cloud-based database, DEPICT HEALTH THALASSEMIA, will deliver point-of-care data to improve care, and collaborative research in this common disorder.

**Objectives:**

To design layouts and mock-ups of, and to evaluate the accuracy and efficiency of entering historic and current real-time data patient data into, the database DEPICT HEALTH THALASSEMIA, using data we had collected and stored over 24 years in Excel files of thalassemia patients managed in the country's largest center of care, at The National Thalassemia Center, Kurunegala.

**Design/Method:**

From our existing database, we extrapolated key fields (genotypes; transfusion records; growth; measurements of cardiac, thyroid, parathyroid, pancreatic, liver, and kidney function; medications) to design layouts for DEPICT HEALTH THALASSEMIA. Both historic and current real-time data were entered and displayed graphically on a timeline.

**Results:**

When entered into DEPICT HEALTH THALASSEMIA, the data permits clinicians and patients potentially to view (among other important endpoints): the impact of different iron-chelation regimens on parameters of iron overload; evolution of drug-induced toxic changes in liver and kidney function; the adequacy of different transfusion regimens. The efficiency of entering historical patient data was slow, but improved with practice.

**Conclusion:**

DEPICT HEALTH THALASSEMIA has the potential to improve quality of data collation, organization, and sharing for research in thalassemia. After further testing in Sri Lanka, DEPICT HEALTH THALASSEMIA should provide data to support research that builds on our earlier work, as well as improve clinical outcomes for thalassemia.

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Poster # 115

## VITAMIN D3 SUPPLEMENTATION IN CHILDREN WITH SICKLE CELL DISEASE: A PILOT RANDOMIZED CONTROLLED TRIAL

Pascale Grégoire-Pelchat, Nathalie Alos, Nancy Gagné, Niina Kleiber, Sylvie Lemay, Carine Nyalendo, Yves Pastore, Nancy Robitaille, Geneviève Mailhot

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### **Background:**

We previously showed that nearly 70% of children followed at the Sickle Cell Disease (SCD) Clinic of CHU Sainte-Justine (CHUSJ), Montreal, Canada, were vitamin D insufficient and had low vitamin D intakes with poor use of supplements. Clinically, vitamin D-deficient children had a worse hematological profile than vitamin D-sufficient children. These findings led us to pilot an intervention to overcome these issues.

### **Objectives:**

We hypothesized that administration of a single oral bolus of 300,000 IU of vitamin D3 to children with SCD resulted in the attainment of vitamin D sufficiency (25OHD levels >75 nmol/L) in 80% of participants after 3 months. The primary objectives were to assess feasibility, acceptability, and safety of the bolus while secondary objectives were related to the mean change in serum 25OHD from baseline to 3 months post-bolus and its clinical impact.

### **Design/Method:**

Children with SCD (5-17 years, all genotypes) were randomized to a single bolus of vitamin D3 (300,000 IU) or placebo. Blood was collected at baseline and 3 months post-bolus to measure serum 25OHD and calculate the change from baseline at 3 months (efficacy outcomes). Other outcomes included urinary calcium/creatinine ratio and serum calcium (safety), musculoskeletal pain, quality of life, hematological parameters and bone markers (exploratory outcomes).

### **Results:**

Of the 369 children who visited the SCD clinic of CHUSJ between November 15th, 2018 and September 30th, 2019, 142 were screened eligible (38%). Main reasons for screen failures were: children <5 years (46%, n=104) and difficult follow-up anticipated (29%, n=66). Thirty-eight children (40% girls, 63% HbSS, 29% HbSC and 8% others) were randomized to the intervention or placebo. Our preliminary blinded data showed that 54% of children had vitamin D insufficiency with mean 25(OH)D levels of 72 +/- 26 nmol/L (30-120, n= 26) at baseline. Post 3 months, the proportion of vitamin D-insufficient children decreased to 21% whereas serum 25OHD raised to 88 +/- 22 nmol/L (36-129, n=14; p=0.05 vs. baseline). No side effect related to the intervention was recorded. Complete blood counts, musculoskeletal pain and quality of life did not differ significantly between baseline and study end.

### **Conclusion:**

This study provides pilot data on the acceptability, safety and efficacy of a high-dose bolus of vitamin D3, before testing its efficacy in improving health outcomes of children with SCD in an adequately powered trial.

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## **NEW MEDICATIONS FOR PATIENTS WITH SICKLE CELL DISEASE: QI TO IMPROVE THE SPECIALTY PHARMACY PROCESS**

**Jennifer Jaroscak, Jenna Bolick, Julie Heh, Harriet McGowan**

*Medical University of South Carolina, Charleston, South Carolina, United States*

### **Background:**

There are several new medications that have been FDA approved for patients with Sickle Cell Disease (SCD). Unfortunately, these medications have initially only been available through specialty pharmacies. This process is complicated for patients and there are several steps where the process can be interrupted. As new medications are approved for our patients with SCD we want to ensure that they have access to these new therapeutic options.

### **Objectives:**

We sought to investigate the specialty pharmacy process for our patients and identify potential interventions that could increase the number of patients that receive the prescribed medications.

### **Design/Method:**

We reviewed patients with SCD at The Medical University of South Carolina (MUSC) from January 2019 through December 2019 for who were prescribed glutamine and oral iron chelators to determine if the medications could be dispensed at our institution. We determined what percentage of our patients were required to go through a specialty pharmacy. We worked with our pharmacy to identify patients that could have their medications filled at our institution.

### **Results:**

Prescriptions for glutamine or oral iron chelators were written for 152 patients during that time period. We focused on the pediatric patients with SCD who receive care in our clinic (n=65), and the remainder of patients are take care of by our adult team. For the pediatric patients we identified 38% (n=25) of patients could receive their drugs at our institution, and 62% (n=40) of patients had to get their medications through a specialty pharmacy.

The process involved with using a specialty pharmacy is complex. The prescription is written, the prior authorization is obtained by medical team (phone or web based), the prior author dictates the specialty pharmacy where the prescription can be sent. The prescription is sent, the specialty pharmacy contacts the family, the family must be at home for delivery of drug. This is multistep process has numerous potential process interruptions that all result in patients not receiving their medications as prescribed. We know that access to medication is the first step in medication adherence.

### **Conclusion:**

We identified several interventions to increase the number of patients receiving their prescribed medications as a quality improvement project.

1) Ensure patients who are able to fill their medications locally are aware of this option.

- 2) Provide patients and families with written/video instructions on the steps for specialty pharmacy process.
- 3) Measure the effect of our interventions by comparing prescription fill history pre- and post intervention.

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Poster # 117

## **BIOLOGIC AND SOCIOECONOMIC FACTORS PREDICT COGNITIVE SUBDOMAINS IN CHILDREN WITH SCA**

**Luisa Gil Diaz, Michael Binkley, Jessica Tan, Allison King, Melanie Fields**

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### **Background:**

Children with sickle cell anemia (SCA), unaffected by stroke, suffer from cognitive dysfunction that worsens with age. It remains unknown how advances in the standard of care for SCA have impacted these cognitive complications, as earlier investigations occurred prior to guidelines recommending all patients with SCA receive hydroxyurea (HU).

### **Objectives:**

Seventy-three children (22 healthy controls, 15 anemic controls, 36 SCA on HU) were prospectively enrolled to test our hypothesis that children with SCA on HU would continue to score lower within the cognitive subdomains of processing speed (PCPS) and executive function abilities composite (EF) than children unaffected by SCA, and that both biologic and socioeconomic factors would significantly impact these outcomes.

### **Design/Method:**

All participants completed the National Institute of Health Toolbox Cognitive Battery and a laboratory evaluation.

### **Results:**

There was not a difference in age (mean age for healthy controls: 12.7yr, anemic controls: 12.8yr, SCA: 11.9yr,  $p=0.507$ ) or gender ( $p=0.344$ ) between cohorts. Using a Kruskal-Wallis test, there was no significant difference between controls (PCPS:49.5 [43.0, 56.0], EF:90.8 [87.3, 103.0]), controls with anemia (PCPS:39.0 [29.0, 50.0], EF:92.3 [87.3, 104.7]) and participants with SCA (PCPS:44.0 [30.0, 57.5], EF:88.7 [81.0, 97.5]) in the PCPS ( $p=0.0779$ ) or EF ( $p=0.3240$ ) cognitive subdomains. Using the presented data for effect size,  $\beta=0.2$  and  $\alpha=0.05$ , a significant difference in PCPS would be observed between healthy controls and participants with SCA with 110 individuals per group, and 171 individuals per group for EF. To understand the role of biologic and socioeconomic covariates on cognition, multivariate general linear regression models with stepwise entry and age, hemoglobin, history of stroke, and yearly income per household member as covariates were used to predict PCPS and EF subdomains. Hemoglobin was the only significant covariate in the final model predicting PCPS (model  $R^2=0.1086$ , hemoglobin  $\beta=2.182(0.730, 3.699)$ ,  $p=0.0040$ ), while yearly income per household member was the only significant predictor of EF (model  $R^2=0.0858$ , hemoglobin

beta=4.7916 (1.0077, 8.5755), p=0.0138).

**Conclusion:**

There is no significant difference in PCPS and EF between children with SCA on HU and controls in these preliminary analyses, possibly due to small sample size. However, the multivariate analysis reinforces that socioeconomic factors do have a significant impact on cognitive ability with current standards of care. These data highlight the importance of multidisciplinary clinical care, including social workers and school liaisons, to address social challenges, in addition to the biological factors of SCA.

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Poster # 118

**ROUTINE SCREENING FOR ALLOIMMUNIZATION AFTER RED BLOOD CELL TRANSFUSION IN SICKLE CELL DISEASE**

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**Background:**

Patients with sickle cell disease (SCD) are frequent recipients of red blood cell (RBC) transfusions and are at risk for RBC alloimmunization. Patients with RBC alloimmunization should receive RBC units negative for any antigens to which they have developed antibodies. Failure to diagnose RBC alloimmunization and appropriately transfuse alloimmunized patients can cause fatal delayed hemolytic transfusion reactions (DHTRs). RBC alloimmunization is diagnosed through the pre-transfusion type and screen; however, this testing may fail to detect antibodies that have evanesced. Alloimmunized patients whose antibodies have evanesced remain at risk for DHTRs. It thus may be beneficial to screen for RBC alloimmunization after transfusion before antibody evanescence.

**Objectives:**

To evaluate the feasibility of routinely obtaining antibody screens on patients with SCD 2-6 months after RBC transfusion for an acute indication and to describe the incidence of new alloantibody detection with this screening.

**Design/Method:**

Our institution started a new clinical protocol to actively screen for RBC alloimmunization in transfused patients with SCD by recommending that providers obtain at least one antibody screen 2-6 months after transfusion. Each month, transfused patients with SCD were identified using blood bank records and reminders to order antibody screens 2-6 months post-transfusion were placed in the electronic medical record. A database was created using REDCap to track all patients who were transfused and received follow-up antibody screens. Patients not established in our hematology clinic and patients on chronic RBC transfusions were excluded. Patients were transfused with RBC units matched for C/E/K.

**Results:**

From 8/1/2018 to 5/1/2019, 110 patients with SCD received 164 RBC transfusions. At baseline, 19/110 (17%) patients had a history of an RBC alloantibody. A total of 235 antibody screens after transfusion were obtained in 104/110 (95%) of these patients. Per our RBC alloimmunization screening protocol, a follow-up antibody screen was obtained 2-6 months after 141/164 (86%) of these transfusions. In this cohort, 2 new antibodies were identified.

**Conclusion:**

It is feasible to obtain antibody screens 2-6 months after transfusion in most patients with SCD. Even with this screening, detection of new RBC antibodies is rare when patients are transfused with C/E/K matched RBC units.

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Poster # 119

**PUPIL SIZE AND REACTIVITY IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE**

**Joana Mack, Sara Frankowski, Bethany Verkamp, Shelley Cravy, Beverly Spray, Lee Crawley, Suzanne Saccente, Kathleen Neville**

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**Background:**

Pupil size and reactivity have been studied in adult and pediatric populations to objectively measure pain. Previous studies have shown that pupillometry is a promising biomarker for pain measurement. Vaso-occlusive crisis is a common complication of sickle cell disease and manifests as acute pain. Given the challenges associated with treating vaso-occlusive pain with opiates, better tools are needed since quantifying acute pain and responsiveness currently relies on subjective measures. An objective pain measurement is needed for improved assessment and treatment.

**Objectives:**

To establish normative values for pupil size and reactivity in pediatric patients with sickle cell disease so that pupillometry can be used as a tool to measure pain and response to treatment with analgesic medications.

**Design/Method:**

This IRB approved prospective study enrolled 82 patients with sickle cell disease as part of regular follow up in clinic. Eligible patients were consented. Patients were: afebrile for 48 hours (temperature < 101F), had normal vital signs, were not receiving any narcotics in the last 24 hours, and were not currently experiencing pain. Readings were performed and the following measures were collected using a NeurOptics PLR-2000 pupillometer: resting pupil size, % change in pupil size, pupil constriction velocity, and pupil dilation velocity.

**Results:**

Forty-four males and 38 females, all of African-American descent, were studied. Their median age was 11 years (range: 2-21). The mean minimum and maximum pupil sizes were 3.52mm and



5.08mm, respectively. The mean dilation velocity and maximum constriction velocity were 1.03mm/s and -4.48mm/s, respectively.

Brown et al. reported a mean maximum constriction velocity of -4.42mm/s, mean maximum pupil size of 4.97mm, mean minimum pupil size of 3.4mm for their healthy African-American participants revealing no significant difference compared to our means ( $t=0.46$ ,  $p=0.645$ ), ( $t=1.25$ ,  $p=0.216$ ), ( $t=1.84$ ,  $p=0.069$ ), respectively. However, comparing our participants with their Caucasian participants, there was a significant difference in maximum constriction velocity ( $t=3.45$ ,  $p=0.009$ ), maximum pupil size ( $t=-5.57$ ,  $p<0.0001$ ), and minimum pupil size ( $t=-3.24$ ,  $p=0.002$ ).

### **Conclusion:**

There was no significant difference in pupil size and reactivity between patients with sickle cell disease and African-American patients without the disease. However, we found a significant difference when patients with sickle cell disease were compared to the Caucasian participants in the Brown et al study. Pupillometry should be further investigated as an objective tool for pain measurement in cases of pediatric vaso-occlusive crisis.

(Brown, J Pediatric Ophthalmol Strabismus, 2015)

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Poster # 120

## **VOXELOTOR IN CHILDREN WITH SICKLE CELL ANEMIA: EFFICACY AND IMPROVEMENT IN ERYTHROCYTE PHYSIOLOGY**

**Satheesh Chonat, Earl Fields, Hannah Baratz, Amanda Watt, Mira Pochron, Sandy Dixon, Margaret Tonda, Joshua Lehrer-Graiwer, Clark Brown, David Archer**

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### **Background:**

Sickle hemoglobin (HbS) polymerizes under deoxygenation to cause sickling of RBCs. Preclinical work showed voxelotor increases HbS affinity to oxygen, thus reducing polymerization and sickling with an increase in RBC half-life. In the phase 3 HOPE trial, voxelotor significantly reduced markers of hemolysis and anemia in patients with SCD.

### **Objectives:**

To examine the effect of voxelotor on RBC physiology, anemia, and hemolysis in children with sickle cell anemia.

### **Design/Method:**

This pilot study at Emory University/Children's Healthcare of Atlanta, GA, USA, was ancillary to the GBT440-007 clinical trial of voxelotor 1500 mg/day (or weight-based equivalent; NCT02850406). Samples from children 4-11 years old, homozygous for HbS, and receiving voxelotor were analyzed at baseline and weeks 12, 24, and 36. All continued stable, optimal

hydroxyurea dosage. Measurements included Omin, EImax, Ohyper, PoS, Emin, p20, and p50. An ektacytometer laser optical rotational red cell analyzer (Lorrca; RR Mechatronics) was used to analyze deformability of RBCs at shear stress of 30 Pa at varying osmolality gradients (0-600 mOsm/kg) for Osmoscan. Oxygenscan was performed under controlled deoxygenation using nitrogen. Oxygen dissociation curves were obtained using a HemOx Analyzer (TCS Scientific Corp.). CBC parameters were determined on a clinical laboratory hematology analyzer (ADVIA, Siemens). Data were analyzed using paired t-tests (Prism).

### **Results:**

Samples were available for 10 and 7 patients through weeks 24 and 36, respectively. Mean hemoglobin (range) was 9.0 g/dL (7.6-10.0), 10.3 g/dL (8.2-12.3), 10.8 g/dL (9.6-13.1), and 10.7 g/dL (8.9-13.0) at baseline, weeks 12, 24, and 36, respectively. Mean percent changes from baseline in percent reticulocytes were -16% at each timepoint (weeks 12, 24, 36). Significant improvement from baseline in EImax on Osmoscan was noted at weeks 12 (0.49, P=0.0058) and 36 (0.54, P=0.0147). At week 36, Oxygenscan curves shifted towards normal with significant increases in EImax (0.54) and EImin (0.32). Decreases from baseline in PoS (week 12, 30.1; week 36, 35.7) during deoxygenation suggest that voxelotor-treated RBCs were more deformable at low oxygen tension. Significant reductions from baseline were observed in p50 (P=0.0011) and p20 (P=0.0001) at week 12 with a left shift of oxygen dissociation curves.

### **Conclusion:**

After 12, 24, and 36 weeks, voxelotor therapy showed marked improvements from baseline in anemia and hemolysis in children 4-11 years old. Increased EImax and EImin, combined with decreased PoS during deoxygenation in the Oxygenscan, demonstrate the ability of voxelotor to inhibit HbS polymerization and improve RBC deformability, theoretically reducing sickling and hemolysis.

Supported by Global Blood Therapeutics.

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Poster # 121

## **PERFORMANCE OF A SCREENING TOOL IN FEBRILE CHILDREN WITH SICKLE CELL DISEASE OF DIFFERENT AGES**

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### **Background:**

Children with sickle cell disease (SCD) are at increased risk of serious bacterial infections (SBI) compared to the general population and are routinely given empiric antibiotics when febrile. Screening tools are employed to identify children with SCD at high risk for SBI when admission is indicated. At our institution age <24 months is an independent risk factor for hospitalization. Our hypothesis is that age <24 months alone should not be an independent risk factor for SBI in febrile children with SCD.

### **Objectives:**

The primary objective is to compare test characteristics of our SBI screening tool for febrile patients with SCD, excluding age, between patients 6-24 months and those >24 months.

**Design/Method:**

This was a retrospective cohort study that included patients with SCD <21 years old who had fever ( $\geq 38^{\circ}\text{C}$  on presentation or prior to arrival) and were evaluated in the Emergency Department or Pediatric Hematology day hospital. Patients were considered high risk if they had any of the following: hemoglobin < 5gm/dL, platelets <100k/uL, white blood cell count <5k/uL or >30k/uL, enlarging spleen with a hemoglobin drop of 2gm/dL below baseline, ill-appearing, temperature >40°C, infiltrate on chest x-ray, cephalosporin allergy, history of Streptococcus pneumoniae bacteremia, known non-compliance with medication or unreliable caregiver as judged by the treating clinician. SBI was defined as bacteremia, meningitis, acute chest syndrome, osteomyelitis, septic joint, pyelonephritis and sepsis.

**Results:**

A total of 1,178 encounters were analyzed, 314 (27%) of those were 6-24 months of age and 864 (73%) were >24 months. SBI was present in 33 (11%) of those 6-24 months and 197 (23%) >24 months. Screening test characteristics in those 6-24 months were: sensitivity 78% (95%CI 61%-91%), specificity 83% (95%CI 78%-87%), positive predictive value (PPV) 36% (95%CI 26%-47%), and negative predictive value (NPV) 97% (95%CI 94%-99%). In those >24 months, test characteristics were: sensitivity 89% (95%CI 84%-93%), specificity 76% (95%CI 73%-79%), PPV 52% (95%CI 47%-58%) and NPV 96% (95%CI 94%-97%). There was no statistically significant difference between the sensitivity (p=0.15) or NPV (p=0.54) of the screening test in those 6-24 months and those >24 months.

**Conclusion:**

There was no significant difference in the sensitivity and NPV of our screening test to identify SBI in febrile children with SCD between 6-24 months and >24 months of age. These findings suggest that age is not an independent risk factor for SBI and the two groups should be treated similarly if they are found to be low risk for SBI.

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Poster # 122

**HEALTH LITERACY AND COGNITION IN ADOLESCENTS AND YOUNG ADULTS WITH SICKLE CELL DISEASE**

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**Background:**

Health literacy is the ability of an individual to obtain, process and understand the basic health information needed to make health decisions. Among adults, limited health literacy is associated with lower socioeconomic status, poorer overall health status and higher mortality. Despite a high risk profile, there is a paucity of literature examining health literacy and associated factors

amongst persons with SCD.

**Objectives:**

The goal of this study was to characterize health literacy amongst adolescents and young adults with SCD and explore the relationship between health literacy and cognition.

**Design/Method:**

This multicenter, cross-sectional study recruited adolescents and young adults ages 15 to 45 with any genotype of SCD. The Newest Vital Sign (NVS), a validated six-item instrument, was used to measure health literacy and numeracy. Full scale IQ (FSIQ) was assessed with the Wechsler Abbreviated Scales of Intelligence 2 subtest form (WASI-II). Additional data regarding medication history, history of stroke/silent cerebral infarct and demographics were abstracted from medical charts.

**Results:**

Seventy-nine participants completed study assessments; 52 (65.8%) had HbSS/HbS0thalassemia and 24 (30%) had HbSC/HbS+thalassemia. The mean age of participants was 20.4 years (SD 4.6). The majority (62%) of participants had inadequate health literacy; individuals with HbSS/HbS0thalassemia had lower health literacy than those with HbSC/HbS+thalassemia. Participants with a high school degree or lower had worse health literacy than those with some college education or a college degree ( $p = 0.0049$ , Fisher's Exact Test). FSIQ was lower in participants with low or inadequate health literacy ( $p < 0.0001$ ). Younger age was also associated with inadequate health literacy ( $p=0.0010$ ). There were no significant differences in health literacy based on stroke history, income, hydroxyurea use or gender.

**Conclusion:**

These results corroborate previous evidence that health literacy amongst adolescents with SCD is inadequate and also suggests that health literacy deficits persist into young adulthood. This age range coincides with the transition from pediatric to adult care, which is a well-established period of high morbidity and mortality for patients with SCD. The high prevalence of inadequate health literacy amongst younger participants who were still in school suggests that early school-based interventions to improve health literacy are needed. While health literacy was comparable in patients with and without a history of stroke, FSIQ was lower in subjects with inadequate health literacy. Cognitive testing in patients with SCD could identify those in greatest need of interventions to improve health literacy.

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Poster # 123

**SAFETY AND TOLERABILITY OF LIDOCAINE INFUSION IN CHILDREN HOSPITALIZED WITH SICKLE CELL DISEASE PAIN**

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**Background:**

People with sickle cell disease experiencing vaso-occlusive pain episodes (VOE) are typically treated with opioids and anti-inflammatory medications. Lidocaine, which inhibits voltage-gated sodium channels in peripheral sensory nerves, is frequently given intravenously (IV) for postoperative pain management. Two small studies have reported IV lidocaine for VOE management: one included only adults and the other reported four pediatric patients who also received concurrent ketamine infusion.

**Objectives:**

This project describes the tolerability and safety of intravenous (IV) lidocaine as an adjunct to IV opioids and non-steroidal anti-inflammatory medications in children with SCD hospitalized for VOE management. This intervention is important because it adds an additional therapy that could be used to alleviate pain for patients with SCD.

**Design/Method:**

This retrospective cohort study reviewed records of children with SCD who received IV lidocaine for VOE management at St. Louis Children's Hospital. All children also received opioids and NSAIDs. The protocol for IV lidocaine at St. Louis Children's Hospital is managed by the Pain Management Service and specifies continuous lidocaine infusion at 1-1.5 mg/kg/hour for up to 48 hours. Patients are monitored for lidocaine side effects including tinnitus, perioral tingling, vital sign changes, and seizures. A 24-hour serum lidocaine level is drawn to ensure levels are not supra-therapeutic. Data collected included patient demographics, pain severity, lidocaine levels, and reported side effects.

**Results:**

Twenty-four children with SCD received lidocaine infusions between January 2018 and September 2019 (median age 15 years). Together, these patients had a total of 157 hospitalizations for VOC (median 5.5 admissions/patient, interquartile range 4-9) since 2016. They had 71 lidocaine infusions during 81 hospitalizations in the study period. The mean 24-hour lidocaine level was 1.89 mcg/ml (SD 1.04). In 69 of 71 lidocaine infusions, the 24-hour lidocaine level was less than 4.5 mcg/ml, the institutional upper limit of normal. Two lidocaine infusions were stopped after 24 hours due to suprathreshold levels, but both were asymptomatic; one of them later received a lidocaine infusion without suprathreshold levels. Additionally, one child stopped lidocaine infusion due to lip paresthesia and another refused the 24-hour blood draw. One refused a lidocaine infusion due to nausea with previous lidocaine administration. No patients had seizures or cardiac arrhythmias.

**Conclusion:**

Lidocaine infusion is a safe and tolerable adjuvant for pain management in hospitalized children with SCD. Further data analysis will be conducted to ascertain effects on patient-reported pain scores and length of stay.

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Poster # 125

## **SICKLE-FIT: ADHERENCE, FEASIBILITY AND VALIDATION OF FITBIT METRICS IN SICKLE CELL DISEASE PATIENTS**

**Ahmar Zaidi, Nirmish Shah, Ryan Thomas, Muhammad Shareef, Bryan Hannan, Arshia Zaidi, Michael Callaghan**

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### **Background:**

Patients with sickle cell disease (SCD) commonly have issues with sleep disturbances and pain. We previously reported that sleep quality deteriorates leading up to and during pain, using actigraphy and patient reported outcomes. This is the first study to determine the feasibility of identifying these parameters in real time using a Fitbit® Charge 3.

### **Objectives:**

This was a 14-week pilot trial investigating the feasibility of following activity profiles and sleep fragmentation in real time by using the Fitbit® Charge 3 in ten patients with SCD.

### **Design/Method:**

The primary outcome was the percent of days data was captured (target 75%). The secondary outcomes were to determine the feasibility of real-time monitoring of actigraphy and sleep fragmentation in steady-state SCD patients and to establish baseline actigraphy and sleep fragmentation indices. Exploratory parameters include identification of variables that affect REM sleep.

### **Results:**

Data from 88.4% of possible days was captured from ten patients. On a post-study survey, patients reported no problems with the device, excellent practicality, no pain, discomfort or frustration wearing the device and complete satisfaction. One patient's data was excluded from the analysis as no sleep data was collected. A total of 748 days of data was collected from nine patients. The average time in REM sleep was 59.87 minutes (SD = 47.2). The participants walked an average of 8,297.32 steps (SD = 5842.9). They were very active for 8.35 minutes (SD = 16.9), fairly active for 19.4 minutes (SD = 30.9), lightly active for 253.84 minutes (SD = 105.6), and sedentary for 766.2 minutes (SD = 249.3). The average resting heart rate for the participants was 70.56 (SD = 8.55). The average time spent asleep was 325.31 minutes (SD = 185.9). This model explained 56.1% of the variance in REM sleep across all the participants and was significant with an F score of 137.137 ( $p < .05$ ). Every minute spent fairly active increases REM sleep by .287, lightly active increases REM sleep by .056, and sedentary increases REM sleep by .040 ( $p < .05$ ). Total time asleep is also positively associated with REM sleep and increases it by .229 ( $p < .05$ ). The strongest predictor of REM sleep is total time asleep.

### **Conclusion:**

This is the first study showing the feasibility of the FitBit® Charge 3 to be used as an actigraph in sickle cell disease patients to monitor activity and sleep and can be used as a reliable biomarker in future studies.

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## **AN ANALYSIS OF THE DETECTION OF HEMOGLOBIN VARIANTS IN PATIENTS WITH A SICKLE CELL MUTATION**

**Christineil Thompson**

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### **Background:**

There are over 1,300 hemoglobin variants.[1] In patients with sickle cell disease and sickle cell trait, the effects are often more pronounced and can frequently compound the expected manifestations of sickle cell disease or trait by either improving or worsening the signs and symptoms. Most providers are unaware of the existence of these variants and the clinical implications of their interactive effects on the morphology of the hemoglobin contained within the red blood cells.

### **Objectives:**

To evaluate existing literature to elicit trends among the detection of hemoglobin variants in sickle cell disease and sickle cell trait patients.

### **Design/Method:**

An assessment of reports of hemoglobinopathies and variant hemoglobins amongst sickle cell disease and sickle cell trait patients was performed and was analyzed by location of primary provider detection, patient presentation, the presence of sickle cell disease or sickle cell trait and the methods used to detect these variants.

### **Results:**

Six articles were included in the literature review. [2,3,4,5,6,7] All six articles were case reports. All studies discovered hemoglobin variants amongst current sickle cell disease or sickle cell trait patients. There appeared to be an increased prevalence in detection of these variants outside of the United States as 67% were detected abroad. Eighty-three percent of these variants were detected in heterozygotic patients positive for a single sickle cell allele. Another eighty-three percent of patients were symptomatic at the time of presentation. Five articles reported variants that were elicited via High performance Liquid Chromatography (HPLC) with Isoelectric Focusing (IEF) and Capillary Electrophoresis (CE). One variant was investigated using electrospray-ionization mass spectrometry (ESI MS).

### **Conclusion:**

Although the existence of the individual hemoglobin variants are rare, there are currently over 1,300 hemoglobin variants which collectively represent a significant category of unexpected presentations among sickle cell disease and sickle cell trait patients. In populations where there are increased levels of ethnic diversity and miscegenation, it is of utmost importance to consider these factors during diagnosis. A high clinical suspicion for these variants is warranted as it can assist in preventing an excessively complex work-up of the patient and determine future disease complications. As such, providers can adjust their recommendations and management of their

patients to provide a more targeted and effective care plan to prevent significant morbidity.

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Poster # 127

## **BENEFITS OF AQUATIC THERAPY IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE**

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### **Background:**

Sickle cell disease (SCD) is a condition with numerous complications including vaso-occlusive pain (VOC). Currently, opioids are the primary therapy used to treat sickle cell pain, but a growing literature has described the benefits of several non-pharmacologic approaches to the management of VOC pain. Among these interventions, aquatic therapy, which relies on movements done in the water to reduce the perception of pain, has been minimally used and studied, particularly for pediatric patients with SCD.

### **Objectives:**

To better understand aquatic therapy use and outcomes in pediatric patients with SCD, we retrospectively studied the use of this therapy at Vidant Medical Center among children hospitalized for acute VOC pain.

### **Design/Method:**

We reviewed patients between 7-18 years of age with SCD admitted for VOC between the years 2016-2018 with at least 2 days of hospital stay. Our primary aim was to quantify utilization of aquatic therapy during qualifying inpatient admissions, with our secondary aims including comparing the duration of time until re-hospitalization during admissions with and without aquatic therapy use. Fixed-effects regression was used to analyze clinical outcomes, adjusting for interdependence of hospitalizations involving the same patient.

### **Results:**

The analysis included 263 hospitalizations of 78 patients (46% female; median age at the earliest hospitalization, 12 years). The median duration of hospital admissions was 5 days (interquartile range [IQR]: 3, 7). Aquatic therapy was used in 43% of admissions, with a trend of increased utilization of aquatic therapy as adjunctive pain management. On fixed-effects Poisson



regression, use of aquatic therapy during a given admission was associated with 30% more days between hospitalizations (incidence rate ratio=1.3; 95% CI: 1.3, 1.4; p<0.001),

**Conclusion:**

As the inpatient aquatic therapy program became more robust through the years of our study, the order for aquatic therapy became part of the standard order set for admission of patients with VOC, explaining the increased utilization seen in our study. Furthermore, the increased days between hospitalizations supports the idea that aquatic therapy in conjunction with standard treatment practices for VOC has been beneficial in VOC pain management.

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Poster # 128

**SPECTRUM OF PARVOVIRUS B19 INFECTION IN CHILDREN WITH SICKLE CELL DISEASE: ATYPICAL PRESENTATIONS**

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**Background:**

Human Parvovirus B19 (P-B19) infection is known to cause aplastic crisis in patients with sickle cell disease (SCD). However, few studies have reported rare unusual complication of Parvovirus in SCD.

**Objectives:**

To describe the demographic and clinical characteristics of Parvovirus B19 infection in hospitalized children with SCD admitted to Sultan Qaboos University Hospital (SQUH) throughout the period (2009-2018), with special emphasis on atypical presentations.

**Design/Method:**

A descriptive retrospective study.

**Results:**

Out of 4688 admission episodes of pediatric patients with SCD, 108 patients (61 males & 47 females) were diagnosed with Parvovirus B19 infection evidenced by positive PCR, with an age ranging from 18 months to 13.5 years. P-B19 infection accounts for 2.3% of the total admissions in our institution. It is the 4th commonest cause of hospitalizing children with SCD, just after painful crisis, acute chest syndrome, and fever without focus respectively. Out of the 108 cases, 94 children presented with classical aplastic (erythroblastopenic) crisis, associated with variable grades of fever +/- joint pains. The majority of patients required transfusion once, although 20 of them needed twice or more transfusions. Atypical presentations were encountered in 14 patients (12.9%). The commonest is splenic sequestration coupled with aplastic crisis and marked reticulocytopenia (12 cases). The first two cases were siblings diagnosed in 2010. Since then, this complication has been increasingly recognized and we have noted a familial tendency to develop Parvovirus B19-induced acute splenic sequestration (ASSC), observed in our cohort in a much higher frequency compared to literature. Severe Parvovirus B19-induced bone marrow

failure was seen in a 7 year-old male patient, who developed marked pancytopenia associated with protracted fever and acute chest syndrome. Parvovirus B19 PCR which was persistently positive with a very high viral load. He required multiple transfusions & Intravenous Immunoglobulins (IVIg). Another interesting case is a 5-year-old boy with SCD and G6PD deficiency, who presented with acute intravascular hemolysis, combined with suboptimal marrow response evidenced by reticulocytopenia. Coombs test and flow cytometry for Paroxysmal Nocturnal Hemoglobinuria were negative. Parvovirus B19 PCR was significantly positive. The boy was diagnosed as a case of G6PD deficiency-induced hemolytic anemia triggered by concomitant Parvovirus B19 which explains the reticulocytopenia.

### **Conclusion:**

Clinical presentations of Parvovirus B19 are not confined to classical aplastic crisis. We recommend screening for Parvovirus in all cases presented with acute splenic sequestration coupled with suboptimal reticulocyte response. In severe refractory cases of Parvovirus infection, IVIg might be used as a salvage therapy.

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Poster # 129

## **PRELIMINARY SAFETY RESULTS OF DEFIBROTIDE IN SCD PATIENTS WITH ACUTE CHEST SYNDROME (IND 127812)**

**Jordan Milner, Deborah Friedman, Marise D'Souza, Sankaran Krishnan, Liana Klejmont, Erin Morris, Harshini Mahanti, Neida Otero, Adele Brudnicki, Kenneth Cooke, Mitchell Cairo**

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### **Background:**

Sickle cell disease (SCD) is a vasculopathy resulting in recurrent vaso-occlusive crises leading to endothelial dysfunction, chronic end-organ damage, poor quality of life, early mortality and the only curative therapy to date is allogeneic stem cell transplant (Talano/Cairo, EJH, 2015). Acute chest syndrome (ACS) can result in pulmonary hypertension and increase morbidity and mortality (Gladwin, NEJM, 2008, Vichinsky et al, Blood 1997, NEJM, 2000). Defibrotide primarily targets endothelium in microvascular beds and has anti-inflammatory and anti-coagulant activity, which can treat the underlying pathophysiology of ACS (Falanga et al, Leukemia, 2003 and Scallia et al, Clin Pharm, 1996 and Pescador et al, Vasc Pharm, 2013).

### **Objectives:**

To determine the safety of defibrotide in children, adolescents, and young adults with SCD-associated ACS.

### **Design/Method:**

Patients with SCD aged 2 to 40 years meeting ACS criteria (at least two of the following: fever, chest pain, cough, dyspnea, tachypnea, pulmonary infiltrate on chest imaging, or hypoxia) and eligibility were enrolled within 72 hours of diagnosis after consent was obtained (NCT03805581). Baseline studies comprised of chest radiograph, CT chest angiogram,

echocardiography with TRJ velocity and brachial artery reactivity, pulmonary function tests, and biomarkers. Defibrotide, generously provided by Jazz Pharmaceuticals, was administered at 6.25mg/kg IV q6 hours and continued for 7 days or until time of discharge, whichever occurred earlier and patients were followed until day +30.

**Results:**

We have enrolled nine patients aged 4 to 19 years with a gender ratio (M/F) of 3/6. Presenting symptoms included fever, chest pain, cough, dyspnea, tachypnea, pulmonary infiltrate on imaging, and hypoxia. Seven patients completed seven days of treatment, one patient was discharged after three days of treatment, and one patient withdrew due to recurrent fevers unrelated to defibrotide. All but one patient had resolution of fevers prior to end of treatment. Patients required an average of 1.67 days of oxygen support, with one patient requiring high flow nasal cannula, and no patients required mechanical ventilation. There were no adverse events related to defibrotide. Of the eight patients who had pulmonary infiltrates on imaging, five were evaluated on day +30, one had complete resolution of infiltrate, three had improvements, and one had no change.

**Conclusion:**

The preliminary data suggests defibrotide is safe and well tolerated in patients with SCD-related ACS. Further accrual is needed to determine the safety and efficacy of differences in pulmonary and cardiac function. This study was funded by a grant from Jazz Pharmaceuticals.

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Poster # 130

**ASSOCIATION OF OCULAR CHANGES AND COMPLICATIONS IN CHILDREN WITH SICKLE CELL DISEASE**

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**Background:**

Patients with sickle cell disease (SCD) are known to have ocular changes including proliferative sickle cell retinopathy (PSR) due to repeated microvascular occlusions. Several studies have been published attempting to correlate severity of SCD, including frequency of vasoocclusive crises (VOC), acute chest syndrome (ACS), and stroke, to the presence of PSR (1). However, little data exists on the presence of other ocular changes (refractive errors, visual field defects, and color vision changes) in relation to disease severity. Identification of patients with concerning risk factors would help to identify those who require closer monitoring with ophthalmologic examinations and early non-surgical interventions.

**Objectives:**

We aimed to evaluate the association between laboratory values, SCD complications, and ocular changes in children with SCD.

**Design/Method:**

We performed a retrospective chart review of patients with SCD followed at St. Christopher's Hospital for Children in hematology and ophthalmology between 2015 and 2019. Ophthalmologic measurements were changes in refraction index, color vision, and presence of retinopathy. Data obtained were markers of hemolysis and the presence or absence of clinical outcomes including history of stroke, splenectomy, ACS, VOC and asthma. Descriptive statistics were generated. Differences in optical abnormalities associated with patient characteristics, laboratory markers, and evidence of disease severity were explored with Analysis of Variance (ANOVA) and chi square or Fisher's exact tests.

**Results:**

Thirty patients met criteria (21 HgbSS, 8 HgbSC, and 1 HgbS Beta+thalassemia) with a mean age of 12.9 years (range 6 – 24). While many patients demonstrated refractive index errors, only two patients had retinopathy, 1 had visual field defects, and 1 had imperfect color vision. No significant differences were found in ocular abnormality totals in association with any of the disease severity, medical history variables or laboratory markers. Of note, all patients with ocular abnormalities and refraction errors were SS phenotype, although this number did not reach statistical significance.

**Conclusion:**

No significant differences were seen between patients with clinically more severe SCD and those with ocular changes in any SCD phenotype. Studies over a longer period with a larger sample size would be required for further investigation

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Poster # 131

**HIGH ACUTE CARE USE IN ADOLESCENTS WITH SICKLE CELL DISEASE PERSISTS INTO ADULTHOOD**

**Rachel Alade, Lydia Pecker, Sophie Lanzkron, Joon Boon**

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**Background:**

Adolescents with sickle cell disease (SCD) have higher rates of acute care utilization, incur greater expenses, and have poorer health outcomes than people with SCD in other age groups. Frequent use of acute care leads to delayed transfer to adult hematologic care, minimizes opportunities for initiation of disease modifying therapies, and perpetuates reliance on acute care.

**Objectives:**

This study describes the trajectory of acute care use by adolescents and young adults (AYA) with SCD at a single institution as they transfer from pediatric to adult hematology care.

**Design/Method:**

This is a retrospective chart review of AYA with SCD and at Johns Hopkins. Eligible subjects were 16-19 years old between 2006-2009 and had high acute care use ( $\geq 3$  acute care encounters/year) during that time period. Demographic data, number of opioid pills prescribed

(as an estimate of opioid exposure), number of hematologic visits, and number of acute care encounters were collected for each year through 2016. Analysis was performed with SPSS using a linear mixed model regression.

### **Results:**

We identified 106 adolescents aged 16-19 between 2006-2009; 30 (28%) had high acute care use. They were 57% female, 80% had hemoglobin SS or S $\beta$ 0, with a median age of 17.4 years (IQR=17.2-19.1); 41% took hydroxyurea, and 28% received chronic transfusions. At enrollment, subjects averaged 22.3 acute care visits/year. There was one death and no change in the number of acute care encounters/year over 10 years of follow-up (22.3 to 20.3 visits, p=0.06). The average number of short-acting opioids prescribed per year increased from 38 to 224 pills (p=0.02). The average time from last pediatric to first adult hematology appointment was 1.3 years. Subjects' mean number of outpatient clinic was the same in pediatric and adult care (1.98 pediatric vs. 2.2 adult hematology appointments annually, p=0.4).

### **Conclusion:**

In this study, 28% of adolescents with SCD had high acute care use, which remained stable over a decade of follow-up. Over the same interval, the number of opioid pills prescribed more than quintupled, and the number of outpatient appointments remained low. As treatment options for SCD expand, AYA with high acute care use and infrequent outpatient encounters may miss opportunities to optimize disease-modifying therapies. Studies are needed to identify interventions to reduce acute care use among adolescents, which may reduce acute care reliance after transfer to adult care.

Support provided by the American Society of Hematology Minority Medical Student Award Program.

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Poster # 132

## **SICKLE CELL DISEASE IS ASSOCIATED WITH MARKED CHANGES IN AMINO ACID PROFILE**

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*Children's National Medical Center, Washington, District of Columbia, United States*

### **Background:**

Nitric oxide (NO) depletion from deficiency of the amino acid arginine has been shown to play an important role in the pathophysiology of vaso-occlusion in sickle cell disease (SCD). However, there are no studies that have comprehensively evaluated plasma and intracellular red blood cell (RBC) amino acid profile in SCD, which may support investigation of novel treatments for acute pain.

### **Objectives:**

To compare plasma and intracellular RBC amino acid profile in sickle cell subjects during

steady-state, during sickle cell pain crises and healthy controls.

**Design/Method:**

Demographic, genotype, and medication history was collected in 52 participants enrolled to date. Amino acid analysis was performed by reverse phase high performance liquid chromatography (HPLC) for 22 different amino acids and its related compounds (Aspartic acid, Glutamic acid, Glutathione, Asparagine, Serine, Glutamine, Histidine, Glycine, Threonine, Citrulline, Arginine, Ornithine, Alanine, Taurine, GABA, Tyrosine, Valine, Methionine, Cystine,  $\beta$ -Alanine, Tryptophan, Isoleucine, L-alloisoleucine, Homocysteine, Leucine, and Lysine).

**Results:**

Of a total of 52 subjects (57% female), 21 with steady-state SCD, 20 with sickle cell pain crisis, and 11 healthy controls (no SCD). The mean $\pm$  S.D age was 10.51 $\pm$ 5.47 years. In patients with SCD, the genotypes were: hemoglobin SS (N=24), hemoglobin SC (N=14), hemoglobin S $\beta$ +thalassemia (n=3). 24 were taking hydroxyurea and 2 were taking L-glutamine. Compared to healthy controls, SCD patient has significantly lower levels of plasma glutamic acid (p=0.014), plasma glutamine (p=0.008), plasma citrulline (p<0.0001), plasma ornithine (p=0.019), and plasma cystine (p=0.006). In addition, SCD patients had significantly lower levels of RBC glutamic acid (p<0.0001), RBC serine (p=0.01), RBC Citrulline (p=0.019), and RBC methionine (p=0.016). Moreover, compared to steady-state SCD, patients with sickle cell pain crisis had significantly lower levels of plasma asparagine (p=0.024), plasma serine (p=0.02), plasma histidine (p=0.024), plasma arginine (p=0.002), and plasma methionine (p=0.009).

**Conclusion:**

SCD especially during acute pain is associated with significantly lower levels of amino acids which supports further investigating use of these amino acids as novel therapy for managing acute SCD pain.

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Poster # 133

**INTRAVENOUS IRON IN PEDIATRIC PATIENTS: AN INSTITUTIONAL ASSESSMENT OF EFFICACY AND ADVERSE EFFECTS**

**Jennifer Nestor, Faraz Afridi, Rafat Ahmed, Richard Suarez, Joey Kareem, Krystal Hunter, Michael Hardiman, Christine Rickette**

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**Background:**

Iron deficiency, even without a diagnosis of anemia, can be neurodevelopmentally dangerous in pediatric patients. Oral iron supplementation has been the treatment of choice but is associated with poor adherence for several reasons including metallic taste of the tablets, gastric irritation, severe constipation, and daily dosing for several weeks. Intravenous iron has been safely used in adult populations for iron supplementation, but is not commonly used in pediatrics. It is hypothesized that pediatric patients with iron deficiency anemia (IDA) who receive intravenous iron infusions will show normalization of hematologic parameters.

**Objectives:**

The aim of this study was to assess the safety and efficacy of intravenous iron sucrose infusions to pediatric outpatients.

**Design/Method:**

This is a retrospective chart review. EMR of patients aged 1-21 who received at least one intravenous iron infusion at Cooper University Hospital between 2016 and January 2019 were reviewed. Pre-infusion lab values including Hgb, MCV, RBCs and RDW were compared to post-infusion values to determine if values normalized after intravenous iron infusion. Patient demographics including ethnicity, cause of IDA, prior oral iron treatments and adverse effects of oral and IV iron were also analyzed.

**Results:**

There were 33 subjects enrolled in this study. The average age of the subjects was 12.8 (+/- 5.1) years of age and 79% were female. The most prevalent indication for IV iron was menorrhagia (55%), while GI pathology accounted for 18% and inadequate dietary intake accounted for 27% of all cases. The mean baseline HGB was 8.3 (+/- 1.7) while the mean final HGB increased to 11.5 (+/- 1.4) ( $p < 0.001$ ). The mean baseline MCV was 69.2 (+/- 9.3) and the mean final MCV increased to 76.1 (+/- 6.8) ( $p < 0.001$ ). The mean baseline RBC was 4.2 (+/- 0.82) and the mean final RBC increased to 4.9 (+/- 0.6) ( $p < 0.001$ ).

**Conclusion:**

IV iron sucrose infusions administered to pediatric outpatients were safe and effective in children and adolescents with IDA. Hematologic parameters improved with IV iron infusions. Adherence to IV iron was subjectively better than adherence to oral iron without statistical significance. Further analysis of patient demographics and characteristics of diagnosis needs to be performed to elucidate benefits of this therapy. As a single institution study, the results are limited to a regional patient population and their specific demographics.

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Poster # 134

**IRON DEFICIENCY ANEMIA AND THROMBOPOIESIS: EFFECT OF ETIOLOGY AND SEVERITY ON PLATELET COUNTS**

**Margarita Dionysiou, Bruce Bernstein, Nataly Apollonsky**

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**Background:**

Iron deficiency anemia (IDA) remains the most common acquired cause of anemia and the most common nutritional deficiency in children in the United States. Anemia typically leads to increased erythropoietin levels, which commonly result in thrombocytosis. Although less frequently, thrombocytopenia has been reported in cases of severe anemia. It has been proposed that factors contributing to thrombocytopenia include competition of platelet and erythroid precursors for iron, direct inhibition of thrombopoiesis, and preferential differentiation of a

common erythrocytic and megakaryocytic precursor into erythroblasts.

**Objectives:**

To evaluate how platelet counts are affected in patients with iron deficiency anemia depending on the etiology (nutritional causes vs bleeding) and to explore an association between severe anemia (Hgb<7g/dl) and thrombopoiesis.

**Design/Method:**

We conducted a retrospective review of medical records for pediatric patients with iron deficiency anemia followed at St. Christopher’s Hospital for Children. Patients were divided into two groups based on the etiology of iron deficiency. Hematological parameters and iron studies were followed during the treatment. Associations of diagnostic categories with changes in platelet counts and IDA severity were assessed with chi-square or Fisher’s exact tests, as appropriate.

**Results:**

The study included 210 children with Iron Deficiency Anemia (IDA), 71.8% had nutritional IDA and 28.2% had IDA due to bleeding: mean age 10 years ( $\pm 7$  SD), 60% female patients, 26% African American, 43% Hispanic, 21% Caucasian and 10% Asian. Mean Hgb at diagnosis was 8 ( $\pm 2.38$  SD) g/dl and mean platelet count 401.21 ( $\pm 186.57$  SD). Nutritional IDA was more frequently associated with thrombocytosis at presentation compared to IDA due to bleeding (51.7% vs 22.4%),  $p<0.001$ . Patients with nutritional IDA less frequently presented with severe anemia (<7g/dl) than patients with IDA due to bleeding (28.6% vs 50.8% respectively),  $p = 0.003$ . Only 7 patients (3.4%) had thrombocytopenia at presentation. There was no statistically significant association between severe anemia and thrombocytopenia in the two groups,  $p=0.745$ .

**Conclusion:**

Patients with Iron Deficiency Anemia (IDA) due to nutritional causes less frequently had severe anemia at presentation and anemia was more frequently associated with thrombocytosis compared to IDA due to bleeding. Our data doesn’t support the hypothesis of thrombocytopenia at severe IDA.

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Poster # 135

**RED BLOOD CELL DISTRIBUTION WIDTH (RDW) IN PEDIATRIC  
OSTEOMYELITIS: NEW INFLAMMATORY MARKER?**

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**Background:**

Decrease in serum iron levels with production of active leukocytes is a protective host defense mechanism during infection. This happens at the expense of shorter life span of erythrocytes and



decreased erythropoiesis. On the patient side, it is reflected as anemia that starts around the first week of infection and worsens during chronic infection/inflammation. Traditionally RDW has been used in differentiation of anemia and shows variation in the size of current erythrocytes. Recent studies have revealed that RDW can be a potential marker of inflammation.

**Objectives:**

To evaluate RDW levels during osteomyelitis therapy in pediatric patients and evaluate whether it correlates with other inflammatory markers.

**Design/Method:**

After proper IRB approval, we conducted a retrospective chart review of 82 children with osteomyelitis followed at our practice, both inpatient and outpatient. We collected data on demographics, predisposing medical condition to osteomyelitis, presenting symptoms, serum inflammatory markers, blood culture results, number of incision & drainage, length of therapy & hospital stay, and related morbidity. The serum laboratory values including complete blood cell count (CBC), C-reactive protein (CRP), sedimentation rate (ESR) were recorded at presentation, during therapy and at the end of the therapy. Data was then analyzed.

**Results:**

The mean age of our patients was 13.9 years. Of the patients 62% were males and 89% were white. Mean value of RDW increased from 13.9% at presentation (95% CI 13.4-14.3) to 14.8% after completion (95% CI 14.5-15.4) the therapy. The RDW negatively correlated with absolute neutrophil count (ANC) ( $r = -0.21, p = 0.001$ ), ESR ( $r = -0.17, p = 0.007$ ) and CRP ( $r = -0.21, p = 0.001$ ). There was no correlation between RDW on one hand and length of hospital stay, length of total therapy (total intravenous & oral) and blood culture positivity, on the other.

**Conclusion:**

We showed that RDW increased during pediatric osteomyelitis therapy. Its increase was inversely related to CRP, ESR and ANC. Our findings suggest considering RDW as a potential inflammatory marker. Further studies are warranted to determine its validity in following up of pediatric osteomyelitis, especially at resource limited healthcare settings.

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Poster # 136

**EXPLORING THE ASSOCIATION OF RETICULOCYTE COUNT IN DIFFERENT FORMS OF HPFH DURING THE INFANCY PERIOD**

**Christina Abrams, Emily Meier, Marcus Carden**

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**Background:**

Hereditary persistence of fetal hemoglobin (HPFH) can be protective in patients with sickle cell anemia (SCA) because elevated hemoglobin F (HbF) prevents hemoglobin S (HbS) polymerization. In infancy, Mendelian-inherited deletional and non-deletional forms of HbS/HPFH are difficult to distinguish from SNPs in quantitative trait loci (QTL), such as XMN1-HBG2 without informative genetic studies. Absolute reticulocyte count (ARC) in the first year of life can predict disease severity in children with SCA (Meier et al., AJH, 2012), but similar descriptions of ARC in children with HbS/HPFH are lacking.

**Objectives:**

To describe our findings regarding hematologic parameters in a series of patients with deletional and non-deletional HbS/HPFH, and HPFH in SCA with the XMN1-HBG2 SNP (rs7482144).

**Design/Method:**

Retrospective chart review of 16 patients seen in our pediatric SCA clinic diagnosed with HbS/HPFH and genetic confirmation based on send out testing for gamma-globin sequencing and/or beta globin deletion/duplication analysis (Mayo Clinic Laboratories, Rochester, MN). Medical records were reviewed for hematological parameters and clinical outcomes. All values were at steady state and none of the patients were receiving hydroxyurea during this study period, which ages ranging 2-15 months of age.

**Results:**

Three representative patients with HbS/HPFH were identified: Patient 1 (P1) has deletional HbS/HPFH, Patient 2 (P2) has non-deletional HbS/HPFH (promoter), and Patient 3 (P3) has XMN1-HBG2 SNP (c.-158C>T). All patients had FS on newborn screen. P1 had HbS 61.5%, HbF 35.8% and normal hemoglobin (Hb) (12.1-13.4 g/dL) with ARC ranging 22-91x10<sup>9</sup>/L, and MCV range 73-93fL. Patient 2 had HbS 14.2%, HbF 85.8% and normal Hb (11.2-12.7 g/dL), with ARC ranging 56-104x10<sup>9</sup>/L, MCV range 76-79fL. P3 had HbS 17-67%, HbF 30-83% and mild anemia (Hb 10.2-11.3 g/dL) with ARC ranging 80-347x10<sup>9</sup>/L, MCV range 77-88fL. His disease course includes dactylitis twice and one hospitalization for pain.

**Conclusion:**

Pediatric hematologists should be aware that a more global assessment of level of hemolysis, as evidenced by ARC and degree of anemia, coupled with HbF levels should be made before determining if a child has HPFH. We found elevations in ARC in a patient with HbS/HPFH due to the XMN1-HBG2 SNP (rs7482144) who has had SCA complications and seek to determine if ARC can predict genetic changes associated with HPFH in pediatric patients with SCA. Further investigation is needed to support our findings but would likely indicate need for closer follow up given the potential for complications and concern for end organ damage in the children with XMN1-HBG2 SNP.

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Poster # 137

**CORRELATION BETWEEN ZINC AND HEMOGLOBIN F**

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**Background:**

Sickle cell disease (SCD) affects millions of people around the world. SCD is the most common inherited disease in the United States, affecting 1 of 1800 births and 1 of 400 African American births. Patients with SCD have improved clinical course when Hemoglobin F (HbF) level is increased which is the basis for hydroxyurea as disease modifying therapy. Children with SCD have a high incidence of zinc deficiency; this has been associated with poor wound healing and growth retardation. Adults with SCD showed increased red blood cell (RBC), hemoglobin (Hb) and hematocrit levels after 3 months of zinc supplementation compared to the placebo group. Pilot in vitro studies in our (Peterson lab) has demonstrated increased gamma globin gene transcription in response to zinc supplementation. No studies have been done evaluating for a relationship between HbF and serum zinc.

**Objectives:**

To describe the relationship between HbF and serum zinc levels in children with SCD

To assess baseline zinc status of SCD patients in our clinic

**Design/Method:**

Single center, retrospective chart review. Patients aged 2-21 years with diagnosis of SCD treated at our institution from 1/15/2019 until 08/15/19.

**Results:**

A total of 40 patients (age range 2 to 20 years; 55% female) were included. There were 24 patients with Sickle Cell Anemia (Hemoglobin SS and Hemoglobin S $\beta$ 0thalassemia), 12 patients with Hemoglobin SC, 2 patients with Hemoglobin S $\beta$ +thalassemia, 1 patient with Hemoglobin S/HPFH (hereditary persistence of fetal hemoglobin) and 1 patient with Hemoglobin S $\delta$  $\beta$ -thalassemia. Spearman's correlation was used to evaluate the relationship between serum zinc, HbF and serum Hb both overall and separated by diagnosis and based on use of hydroxyurea. All p-values were found to be >0.1 and therefore no significant correlations were found between zinc and HbF or Hb. The mean zinc level was 70.68mcg/dL with a standard deviation of 13.42, 48 % of patients had zinc deficiency based on lab cutoff of 70 mcg/dL.

**Conclusion:**

We hypothesized that patients with SCD would have zinc levels that positively correlated with HbF levels, the results showed no correlation. Results are limited by small sample size as well as timing of zinc testing in relation to food intake and lack of serum copper levels. Prospective studies are needed, but our study could serve as background for future studies evaluating zinc as a potential low-cost therapy option for patients with SCD. In addition, we illustrate the need to evaluate for zinc deficiency in pediatric SCD centers.

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## **ADDING FUEL TO THE FIRE: MANAGEMENT OF HYPERHEMOLYSIS IN BETA THALASSEMIA WITH COMPLEMENT BLOCKADE**

**Richard Zanetti, Lauren Vasta, Kristen Romanelli, Megan Kachur, Michael Devan, Thomas Newton**

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### **Background:**

Hyperhemolysis is a rare, but life-threatening condition, occurring most commonly in the setting of chronic transfusion therapy, resulting in hemolysis of all red blood cells. Evidence is lacking for definitive management options of hyperhemolysis. Delayed transfusion reactions, specifically hyperhemolysis, have been shown to involve complement mediated hemolysis. Prior cases have demonstrated the effective use of aggressive immunosuppression and novel use of eculizumab in hyperhemolysis for sickle cell disease, however its use in beta thalassemia is less established.

### **Objectives:**

Review novel use of eculizumab for acute and chronic hyperhemolysis in beta thalassemia major.

### **Design/Method:**

Case review of acute and chronic management of hyperhemolysis in beta thalassemia.

### **Results:**

This patient is a 19-year-old male with beta thalassemia major, on chronic transfusion therapy receiving phenotypically matched packed PRBCs every 3 weeks. He presented with myalgias, fatigue, and low-grade fever twelve days after a transfusion and was found to have a hemoglobin of 5.5 g/dL with evidence of hemolysis. DAT showed panagglutination. He was admitted for acute management with immunosuppression including intravenous immunoglobulin (IVIG) and high-dose corticosteroids. After 2 days, his hemoglobin continued to drop to 4.4 g/dL, at which time he was given eculizumab and started on erythropoietin. At that time, his DAT was negative. After 6 days, despite high-intensity immunosuppression (corticosteroids, IVIG, Rituximab, two doses of eculizumab) and erythropoietin, his hemoglobin continued to decline to 2.9 g/dL. The decision was made to transfuse PRBCs. Subsequently his hemoglobin rose without significant increase in hemolysis. After immunosuppression initiation with eculizumab, the DAT was subsequently positive for anti-Sda antibody, suggesting a successful complement blockade. Mild chronic hemolysis resumed two weeks after the second dose of eculizumab. Eculizumab therapy was reinitiated every two week along with continuation of immunosuppression with corticosteroids. Sirolimus was added for steroid replacement. He is currently stable, tolerating transfusions, on the current regimen.

### **Conclusion:**

Hyperhemolysis is unique in beta thalassemia due to the underlying dysfunctional erythropoiesis and dependence on transfusions. Immunosuppression with eculizumab successfully slowed the

hemolysis and allowed for safe transfusion. The chronic course had a shared phenotype with paroxysmal nocturnal hemoglobinuria. Ongoing use of eculizumab has allowed for weaning of immunosuppression without flairs of hemolysis. Lastly, complement blockade with eculizumab enabled more accurate antibody identification in the setting of hyperhemolysis for safer selection of blood products. This case can act as a model for the successful management of this rare, life threatening syndrome.

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Poster # 139

## **AN UNUSUAL CASE OF NEONATAL G6PD DEFICIENCY, PRESENTING WITH HYPERBILIRUBINEMIA AND THROMBOCYTOPENIA**

**Zara Ilahi, Eleny Romanos-Sirakis**

*Staten Island University Hospital, Northwell Health, Staten Island, New York, United States*

### **Background:**

Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency is one of the common red-cell enzyme disorders associated with neonatal hyperbilirubinemia. It is not typically accompanied by thrombocytopenia. We present a rare case of a newborn with hemolytic anemia and thrombocytopenia who was found to have G6PD deficiency.

### **Objectives:**

Describe a variant presentation of G6PD in the neonate with thrombocytopenia.

### **Design/Method:**

Case report.

### **Results:**

Transcutaneous bilirubin (TcB) at 24 hours of life (HOL) was 5.5 mg/dL, low intermediate risk, but increased to high risk bilirubin of 16.1 mg/dL at 41 HOL. Serum indirect bilirubin at 42 HOL was 19.4 mg/dL; phototherapy was initiated. Hematocrit (HCT) was 44.9%. Bilirubin trended up and platelets were 175,000/uL. Intravenous hydration was added and bilirubin improved. At 57 HOL indirect bilirubin increased to 22.5 mg/dL. Newborn underwent double exchange transfusion. Prior to exchange transfusion, platelet count was 73,000/uL, with HCT of 40.2%, and decreased to 42,000/uL post-exchange transfusion with a HCT drop to 25.2%. Due to unclear etiology of the worsening thrombocytopenia in the context of hemolysis, IVIG was also administered.

Indirect bilirubin improved after double exchange transfusion to 13.3 mg/dL. Platelets trended up to normal without further intervention. No evidence of infection was found with negative blood and urine cultures, and infant was treated with 48 hours of empiric antibiotics were started after noting thrombocytopenia. Glucose-6-phosphate dehydrogenase test came back low at 1.2 units/g Hgb confirming the diagnosis of G6PD deficiency.

### **Conclusion:**

While G6PD is a known cause of hyperbilirubinemia in the newborn, it is not typically associated with thrombocytopenia. We are aware of a case report of a 4 year old who presented with hemolysis, thrombocytopenia, and acute kidney injury, treated for atypical HUS, but was found to have G6PD deficiency after he returned twice more with hemolysis and thrombocytopenia without renal involvement. We are not aware of any reported cases of newborns with G6PD deficiency presenting with hemolytic anemia and thrombocytopenia. While newborns may present with thrombocytopenia, no causes for the thrombocytopenia were found in this case. G6PD deficiency should remain on the differential diagnosis list when evaluating patients with hemolysis and thrombocytopenia.

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Poster # 140

## **NOVEL HETEROZYGOUS MUTATIONS FOR PYRUVATE KINASE DEFICIENCY**

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### **Background:**

Red cell pyruvate kinase deficiency (PKD) is glycolytic defect causing congenital non-spherocytic hemolytic anemia secondary to mutations in the PKLR gene. Pyruvate kinase converts phosphoenolpyruvate to pyruvate and its deficiency leads to reduction in ATP and shortened red cell lifespan. Pyruvate kinase enzyme activity is poorly specific and confirmation with molecular diagnosis is now clinically available.<sup>1</sup> Clinical features vary widely, from mild anemia to severe requiring regular transfusions with complications similar to other hemolytic anemias: jaundice, gallstones, iron overload along with thrombosis and osteopenia.<sup>2</sup> Management is supportive with red blood cell (RBC) transfusions, splenectomy, folic acid supplementation and iron chelation therapy. Curative treatment with hematopoietic stem cell transplantation is possible, although it is difficult to assess the risk to benefit ratio of transplantation due to elusive stratification of PKD severity.<sup>1,3</sup>

### **Objectives:**

We present a boy with novel heterozygous mutations resulting in severe pyruvate kinase deficiency.

### **Design/Method:**

A 6-month-old male presented with jaundice, splenomegaly and cholelithiasis on abdominal ultrasound at his WCC. Mother noticed jaundice at 2 months of age, with an otherwise unremarkable prenatal and neonatal history. His labs were the following: haemoglobin was 5.3 g/dL, retic count 32.8%, potassium 5.5 mEq/L, indirect hyperbilirubinemia of 3.6 mg/dL, uric acid 7.2 mg/dL and lactate dehydrogenase of 2,509 units/L. Pyruvate kinase activity level and RBC membrane defect obtained prior to RBC transfusion were unremarkable. His newborn screen, Hb electrophoresis and beta globin gene analysis were normal. Evaluation for hereditary spherocytosis and thalassemia resulted in one gene deletion for alpha-thalassemia trait. At 8 months of age, a next generation sequencing confirmed pyruvate kinase deficiency due to the inheritance of two heterozygous mutations of the PKLR gene described as c.970G>T

(p.Asp324Tyr) and c.1172T>A (p.Val391Asp), a heterozygous pattern found in each parent. He is managed with folic acid supplementation, RBC transfusions, with close monitoring of ferritin level.

**Results:**

Since his referral he has required monthly transfusions to maintain his Hb  $\geq 7$  g/dL, while closely monitoring his ferritin level. We plan for splenectomy once he reaches 24 months of age.

**Conclusion:**

PKD is a rare hemolytic anemia, with a substantial variation in clinical features in patients with this disorder impacting various aspects of their quality of life.<sup>4</sup> This disorder has been managed symptomatically, with limited case reports offering curative treatment with hematopoietic stem cell transplantation. We will hopefully have more therapies available for our patients with current clinical trials consisting in enzyme replacement.<sup>5</sup>

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Poster # 141

**IDIOPATHIC PULMONARY HEMOSIDEROSIS: AN UNDERDIAGNOSED  
CONDITION IN PEDIATRICS**

**Vanessa Howard, Parul Rai**

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**Background:**

Idiopathic pulmonary hemosiderosis (IPH) while rarely seen in children, can be associated with a poor prognosis if the diagnosis and treatment are delayed. It usually presents with the classical triad of respiratory symptoms (hemoptysis, cough, dyspnea), radiographic findings (pulmonary infiltrates) and iron deficiency anemia (IDA). However, the initial clinical presentation may be misleading, especially if the characteristic respiratory symptoms accompanying IDA are mild and missed on history, and chest imaging is not obtained. Herein, we review the clinical presentation of four patients referred to us for severe IDA not responding to IDA-directed therapy, who were eventually diagnosed with IPH.

**Objectives:**

The aim of this case series is to identify patients diagnosed and managed for IDA, who need to be further evaluated for IPH.

**Design/Method:**

Case Series

**Results:**

Four subjects, between the ages of 12 months and 3.5yrs diagnosed with IDA and managed with iron supplementation and transfusions, were referred to hematology at St Jude Children's Research Hospital for concerns of persistent anemia. All four patients presented with laboratory findings significant for severe anemia (2.5- 4.0g/dl) which was normocytic (MCV 78.6 -90.5fL),

and iron studies which were incongruent for isolated IDA. The low transferrin saturation (4-8%) in the absence of low ferritin (ranging from 59- 195 ng/ml) suggested functional iron deficiency secondary to inflammation. However, the reticulocytosis (2-14%) accompanying this normocytic anemia couldn't be explained by IDA or anemia of inflammation (AI), and was concerning for ongoing hemolysis or hemorrhage. In the setting of negative direct antiglobulin test, mild LDH elevation (423 -809 U/L), and mild bilirubin elevation to 4.2mg/dl in only one subject, hemolysis didn't appear to be contributing to the anemia. While no overt source of blood loss was identified, detailed history revealed three patients to have complaints of asthma or dry cough, with two reporting few episodes of blood streaked sputum, attributed at that time to forceful coughing. Given these mild respiratory symptoms chest x-ray was obtained, and all reported findings concerning for diffuse bilateral pulmonary infiltrates, leading to further evaluation and diagnosis of IPH.

**Conclusion:**

Severely anemic patients not responding to iron-directed therapy and with a discordant laboratory picture, where iron studies suggestive of hyporegenerative anemia (IDA, AI or both) are accompanied by reticulocytosis, should be evaluated for concomitant blood loss or hemolysis. This work-up should include chest imaging to evaluate for IPH, especially if the clinical history indicates presence of any respiratory symptoms.

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Poster # 142

**NOVEL RAC2 MUTATION AS THE MOLECULAR CAUSE OF HEREDITARY HEMOLYTIC ANEMIA**

**Chana Glasser, Mark Weinblatt, Myesa Emberesh, Diamantis Konstantinidis, Anna Ottlinger, Theodosia Kalfa**

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**Background:**

Ras-related C3 botulinum toxin substrate 2 (Rac2), encoded by the RAC2 gene, expressed only in hematopoietic cells, is a Rho family GTPase that regulates a wide spectrum of cellular functions. RAC2 loss-of-function and, more recently, a novel gain-of-function RAC2 mutation, have been reported to cause immune deficiency with altered neutrophil migration and superoxide production. Although Rac GTPases play a role in maintenance of the mouse red blood cell (RBC) cytoskeleton (1), there have been no reports to date of a hemolytic anemia associated with RAC2 mutation.

**Objectives:**

Report a case of chronic hemolytic anemia in a child and her mother with a novel gain-of-function RAC2 mutation

**Design/Method:**

Case report, whole exome sequencing (WES), and in vitro functional studies.



**Results:**

5-year-old girl presented at age 12 months with severe anemia and splenomegaly (hemoglobin 3.1g/dL, MCV 98fL, and reticulocytes 18%). She was diagnosed with Coombs-negative acute hemolysis in the setting of an infection. Hemoglobin 2 months prior was 7.5g/dL with no other prior hemoglobin. There was no history of neonatal jaundice. There was a maternal history of lifelong splenomegaly, hemolytic anemia episode, mild leukopenia with lymphopenia, and chronic upper respiratory infections in childhood. Peripheral blood smear revealed polychromasia, mild anisocytosis and poikilocytosis with acanthocytes. Comprehensive workup for RBC membranopathies, enzymopathies, and hemoglobin disorders was negative. Bone marrow evaluation demonstrated erythroid hyperplasia. The patient required multiple packed RBC transfusions over the first 2 years of life for recurrent hemolysis in the setting of viral illnesses, but transfusion needs diminished as she grew older. Chronic anemia (hemoglobin ~9g/dl) with reticulocytosis (~10%) and mild leukopenia with lymphopenia persist at baseline. WES with family-trio analysis revealed a heterozygous RAC2 p.D63N variant in the proband and her mother, located in the highly conserved Switch II domain, just next to the recently described p.E62K gain-of-function mutation causing lymphopenia and neutrophil dysfunction (2). Neutrophil oxidative burst was evaluated to follow-up on the novel Rac2 variant and was found increased in both proband and mother (2-6fold compared to control). RBC ektacytometry and actin/spectrin ratio in the RBC cytoskeleton were normal; however, increased cysteine oxidation was detected in RBC membrane proteins using biotin-iodoacetamide (BIAM), indicating increased erythrocyte oxidative damage, likely mediating decreased RBC survival.

**Conclusion:**

This is the first case report of hereditary hemolytic anemia associated with a functional RAC2 gene mutation causing increased oxidative stress and RBC membrane damage.

- 1.Kalfa et al, Blood 2016
- 2.Hsu et al, Blood 2019

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Poster # 143

**HEMOGLOBIN HAMMERSMITH PRESENTING AS ASYMPTOMATIC ANEMIA IN 1-YEAR OLD FEMALE**

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**Background:**

Hemoglobinopathies are one of the most common inherited disorders worldwide, with an estimated incidence of 300,000 cases of mutations of the hemoglobin gene occurring each year. Over 1200 variants have been described; of these, mutations causing Hemoglobin S, Hemoglobin C, and thalassemia account for the majority of cases. Approximately 150 of these variants are described as unstable globin molecules. These rare variants exist at frequencies below 1% and are typically caused by spontaneous mutations. While typically asymptomatic, some unstable

forms can present with severe hemolytic disease in the neonatal or early childhood period. Hemoglobin Hammersmith [ $\beta$ 42(CD1)Phe→Ser, TTT>TCT] is one such hemoglobin variant with an unstable tertiary structure and decreased affinity for oxygen. Patients typically present with severe congenital hemolytic Heinz body anemia, hyperbilirubinemia, and transfusion dependence. Our case describes a unique presentation of this rare hemoglobinopathy in a young girl with asymptomatic anemia discovered during a well-child exam.

**Objectives:**

Our objective is to discuss the presentation of a rare hemoglobinopathy in a toddler in order for clinicians to consider this as part of their differential.

**Design/Method:**

Single subject case report

**Results:**

This patient first presented to her primary care provider for her 1-year well-child check with no complaints. She was found to be anemic and received iron supplementation for a month, but her anemia persisted (hemoglobin 8.1 g/dL, elevated mean cell volume 94.6 fL, normal ferritin 132 ug/L). Her diet was complete and supplemented with Similac. She had no prior hospitalizations or illnesses and had no family history of blood disorders. She was born full-term and received phototherapy for hyperbilirubinemia for one day. On physical exam, she was hypoxic at 79%, had pale conjunctiva, a 2+ systolic ejection murmur at the left sternal border, and no hepatosplenomegaly. She was found to have a macrocytic anemia with reticulocytosis and elevated total bilirubin and lactate dehydrogenase, with no other morphologic abnormalities seen on peripheral smear. She was diagnosed with Hemoglobin Hammersmith by sequencing and gel electrophoresis. Since this diagnosis, the patient has been growing normally and meeting all developmental milestones. She has been transfused once due to a drop in her hemoglobin to 5.4 g/dL following a viral illness.

**Conclusion:**

The present case report highlights the importance of timely diagnosis of unstable hemoglobin variants. While rare, these hemoglobinopathies are capable of causing hemolytic anemia in infancy along with splenomegaly and cholelithiasis later in life.

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Poster # 144

**HEREDITARY HEMOLYTIC ANEMIA ASSOCIATED WITH NOVEL SPTA1 & NT5C3A ALTERATIONS**

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**Background:**

Hereditary elliptocytosis (HE) encompasses a group of red blood cell (RBC) membrane disorders with phenotypes ranging from asymptomatic to severe, transfusion-dependent hemolytic anemia.

Phenotypes presenting with significant neonatal/infantile hemolytic anemia include HE with infantile poikilocytosis and hereditary pyropoikilocytosis (HPP). The former is typically due to autosomal dominant alpha or beta spectrin defects whereas cases of HPP are typically due to autosomal recessive inheritance of homozygous or compound heterozygous alpha-spectrin gene (SPTA1) alterations. Hereditary pyrimidine 5' nucleotidase deficiency is another cause of hereditary hemolytic anemia due to autosomal recessive inheritance of cytosolic 5' nucleotidase IIIA (NT5C3A) mutations

**Objectives:**

To report a case of hereditary hemolytic anemia associated with novel gene mutations.

**Design/Method:**

Case Report

**Results:**

We describe a male neonate delivered at 33 5/7 weeks gestational age after a pregnancy complicated by pre-eclampsia and oligohydramnios, noted to have worsening symptomatic anemia in the first few days of life. Hemoglobin at birth was 11.2 g/dL, which decreased to 9.2g/dL with 8% reticulocytosis by day of life 5, requiring RBC transfusion. Neonate also had unconjugated hyperbilirubinemia requiring phototherapy for 2 days. Initial investigations revealed negative Coombs test, normal G6PD and pyruvate kinase levels, normal hemoglobin electrophoresis and typical neonatal peripheral blood smear. After discharge, he required RBC transfusions twice, at 1 and 2 months of life, with hemoglobin levels of 5.9 g/dL and 6.7 g/dL respectively. Repeat peripheral smears showed elliptocytes, microspherocytes, poikilocytes and schistocytes. Parental blood smears were normal. Further investigation showed increased osmotic fragility and normal protein band 3. Next generation sequencing for congenital hemolytic anemia revealed a novel nonsense in exon 16 of SPTA1 (c.2173C>T; p.R725\*), believed to be an inactivating mutation and considered likely pathogenic. Three variants of unknown significance were also identified: two in SPTA1 (c.1369\_1371del; p.N457del and intronic alteration c.5665-24%>C; p.?) and one in NT5C3A (c340A>C; pK114Q). The infant is now 15 months old. He has not required RBC transfusion since 2 months of age. He continues to have a moderate, well-compensated hemolytic anemia with hemoglobin levels ranging from 10 to 11.5 g/dL and 3-4% reticulocytosis over the past 6 months.

**Conclusion:**

This is a case of hereditary hemolytic anemia associated with a novel, likely pathogenic inactivating SPTA1 mutation. This may be an autosomal dominant alteration causing HE with infantile poikilocytosis or may be an autosomal recessive compound heterozygous case of HPP involving variants currently of unknown significance. Clinical course and parental mutation analysis will help with further classification.

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Poster # 145

**AN UNSUAL CASE OF HEMOLYTIC DISEASE OF THE NEWBORN INFANT DUE TO ANTI-JKB ANTIBODIES**

**Zara Ilahi, Eleny Romanos-Sirakis**

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**Background:**

Alloimmune hemolysis is most commonly due to RhD incompatibility or ABO maternal/fetal incompatibility. A rare presentation of hemolytic disease of the newborn occurs due to Kidd antigens. We are only aware of thirteen documented cases of anti-Jkb related hemolysis in the newborn, with only four requiring phototherapy and one requiring packed red blood cell (pRBC) transfusion.

**Objectives:**

Describe a newborn with alloimmune hemolysis secondary to Kidd antigens and his course of treatment.

**Design/Method:**

Case report.

**Results:**

A 37 week gestational age male was born by NSVD to a G6P4 mother. Maternal history was significant for two intrauterine fetal demises at term and positive titers for anti-C, anti-e, and anti-Jkb antibodies. Other maternal prenatal labs were negative. Maternal blood type was O+; newborn was blood type O+, coombs positive and anti-Jkb positive.

Newborn exam was within normal limits and he was admitted to regular nursery where he was monitored for signs of acute hemolytic anemia/jaundice. At 2.5 hours of life (HOL) bilirubin (total/direct) was 3/0.2 mg/dl, hematocrit was 39.5% with 6.3% reticulocytes. At 13 HOL, bilirubin was 5.6/0.2 mg/dl and phototherapy was initiated; phototherapy was discontinued at 35 HOL and rebound bilirubin was stable.

Hematocrit dropped from 39.5% at birth to 29.4 % at 41 HOL with 8.4% reticulocytes. The newborn was transferred to NICU and received intravenous immunoglobulin (IVIG) and a packed red blood cell (pRBC) transfusion. Phototherapy was reinitiated at 81 HOL due to rising bilirubin and was discontinued after less than 24 hours of treatment. The patient was discharged home and was monitored closely in the outpatient clinic to assess for potential delayed hemolytic anemia.

**Conclusion:**

Kidd antibodies can cross the placenta, bind to complement, and produce hemolysis. Kidd antibodies are not always detected by routine screening as they have the tendency to disappear after the first few months of exposure. Kidd antibodies can cause both immediate and delayed hemolytic transfusion reactions secondary to a strong response in a later re-exposure to antigen positive RBC.

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Poster # 146

# CONTROL OF REFRACTORY AUTOIMMUNE HEMOLYTIC ANEMIA WITH IVIG IN AN 11 WEEK OLD

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## **Background:**

Autoimmune hemolytic anemia (AIHA) is rare in infants and can be due to an immune deficiency and/or infection. Steroids are first-line therapy; however, resistance or dependence can occur. Second-line therapies are not well established for children but include Rituximab or splenectomy. Unfortunately, these modalities can cause prolonged hypogammaglobulinemia and/or life-threatening infections. There are limited reports where Intravenous Immune Globulin (IVIG) is successful.

## **Objectives:**

To describe an infant with refractory AIHA who responded to IVIG.

## **Design/Method:**

Case report

## **Results:**

An 11-week Hispanic male presented with diarrhea, poor po intake, fevers, and anemia. Initial labs showed Hemoglobin (Hgb) 6.8 g/dL, retic 3.8%, direct antiglobulin test (DAT) IgG+/C3-, blood type O+ (mother A+), and total bilirubin 4.6 mg/dL. White blood cell count and platelet count were normal. Peripheral blood smear showed polychromasia and spherocytes.

High dose (4 mg/kg/d) IV steroids were immediately started. Hemolysis continued, requiring daily blood transfusions to maintain hemoglobin > 6-7 g/dL. On day 6, IVIG (1g/kg) was trialed with minimal response. On day 11, Rapamycin was trialed for 1 week with no clinical change despite adequate trough levels. On day 14, IVIG was repeated and led to the longest time (4 days) between blood transfusions. Monthly IVIG was continued. On day 30, he was started on Valganciclovir for 1 month after blood Cytomegalovirus (CMV) polymerase chain reaction (PCR) and urine were positive (mother CMV seronegative during pregnancy). Congenital CMV was ruled out. Blood CMV PCR was then negative, but hemolysis continued.

Positive DAT was later thought to be artifact after discovery of patient having an antibody to test gel medium. Evaluation for Autoimmune lymphoproliferative syndrome (ALPS) and scurf (FOXP3) protein were negative. While on steroids, flow cytometry showed decreased CD4 T-cells with inverted CD4/CD8 ratios, and absence of natural killer (NK) cells. B cells elevated proportionally. Discontinuance of steroids showed trend towards normalization, but inverted CD4/CD8 ratios persisted. Hemolytic panel was unrevealing.

Last blood transfusion given at 23 weeks of age. Steroids slowly weaned off at 31 weeks of age, and IVIG continued 2 weeks after. He has been in remission for 5 months and continues to undergo evaluation for an underlying immunodeficiency.

## **Conclusion:**

We report an infant with DAT negative refractory AIHA that responded to IVIG. Approximately

30% of children with AIHA respond to IVIG. We recommend to trial IVIG for at least 2 doses in refractory AIHA prior to starting other second-line therapies, which can have life-threatening side effects.

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Poster # 147

## **CTEPH IN A HOMOZYGOUS SICKLE CELL PATIENT WITHOUT SIGNIFICANT RIGHT HEART DISEASE**

**Stacey Rifkin-Zenenberg, Gabriel Rama, Donna Lee**

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### **Background:**

Pulmonary hypertension (PH) affects approximately 10% of adults with sickle cell disease. The etiology is multifactorial and it is currently classified as WHO Group 5. It is characterized clinically by a spectrum ranging from asymptomatic to being oxygen dependent reflected by baseline hypoxia, abnormal pulmonary function testing and echocardiographic and cardiac catheterization findings. Pathological findings can affect all layers of the pulmonary arteriolar wall including the intima, media and adventitia as well as, laying organized thrombi causing stenosis or complete luminal occlusion. PH is usually heralded in childhood by abnormal echocardiographic findings such as elevated tricuspid regurgitant jet velocity (TRV) and right ventricular (RV) hypertrophy and dysfunction.

### **Objectives:**

We report a 21 year old male patient with homozygous sickle cell disease who has a normal right heart evaluation on echocardiogram but with WHO class 5 PH based on lung histology.

### **Design/Method:**

Case Report/Literature review

### **Results:**

We report a 21 year old with homozygous sickle cell disease with frequent vaso-occlusive pain crises and acute chest syndrome but without history of intubation with progressive dyspnea and hypoxia. The patient had been on hydroxyurea for several years with compensatory macrocytosis. He became oxygen dependent as evidenced on PFTs with decreasing diffusion over 10 months. Transthoracic echocardiogram was normal with no evidence of pulmonary hypertension based on right ventricular size and function, septal position and pulmonary insufficiency jet. There was no significant tricuspid regurgitation thereby limiting TR jet evaluation. Right heart catheterization showed mildly elevated RV and pulmonary artery pressures but with a normal pulmonary vascular resistance (1.56 HRU). Lung biopsy was consistent with chronic thromboembolic pulmonary arterial hypertension.

### **Conclusion:**

This is the one of the youngest sickle cell patients reported to have pulmonary hypertension based on lung findings with normal right heart anatomy and function on echocardiogram. The

literature supports that the earliest sign of PH in sickle cell is the TRV function being abnormal. This patient unfortunately still passed the initial noninvasive screening only to develop more ominous complications of CTEPH later.

(Kato, *Pediatr Hematol Oncol* 2007)(Klings, *Am J Respir Crit Care Med*, 2014)(Simonneau, *JACC* 2013)

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Poster # 148

## **PATIENT WITH SICKLE CELL TRAIT HAS UNUSUAL PRESENTATION ON STATE NEWBORN SCREEN**

**Urania Dagalakis, Ashley Munchel, Regina Macatangay**

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### **Background:**

New York State first implemented a Newborn Screen (NBS) for Sickle Cell Disease (SCD) in 1975 and by 2006 it was universally in place in all U.S. states, Puerto Rico and the U.S. Virgin Islands. Since its implementation over 2 decades ago there have been over 40,000 confirmed cases of SCD and 1 million of sickle cell trait (SCT) diagnosed. Accurate identification via newborn screen of genetic disease can dramatically improve survival and quality of life for patients as well as their families.

### **Objectives:**

Describe a pediatric patient with a newborn screen that initially was diagnosed with Hemoglobin S/Beta Plus Thalassemia that at 20 months was later confirmed to be SCT.

### **Design/Method:**

Case report

### **Results:**

A 20-month-old male was diagnosed with Hgb FSA on the Maryland Newborn Screen indicating Hemoglobin S/Beta Plus Thalassemia. Family history revealed that mother and older brother both had Sickle Cell trait while father's status was unknown and has refused further genetic testing. After diagnosis at 5 weeks he was started on penicillin prophylaxis. At 6 months of age experienced episode of dactylitis which resolved with ibuprofen and heat packs. At 12 months of age confirmatory lab work showed a mild normocytic anemia and normal hemoglobin electrophoresis that was incongruent with his diagnosis. At 20 months of age a second hemoglobin electrophoresis was done which showed 56% Hemoglobin A, 40% Hemoglobin S with 4% Hgb A2. Due to this inconsistency genetic testing was done which confirmed SCT.

### **Conclusion:**

This case demonstrates the importance of close follow up and verification of newborn screen results. There are many long-term complications and risks that are attributed to different hemoglobinopathies that affect both a patient's quality of life as well as that of their family.

Genetic counseling has important implications for treatment modalities, family planning as well as informing families regarding the morbidity and mortality they need to be aware of.

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Poster # 149

## **ENTEROGENOUS SULFHEMOGLOBINEMIA IN A NEWBORN WITH CYSTIC FIBROSIS RELATED MECONIUM ILEUS**

**Kisha Beg, Hala Chaaban, Arpan Sinha**

*Jimmy Everest Section of Pediatric Hematology/Oncology, Department of Pediatrics, University of Oklahoma Health Sciences, Oklahoma City, Oklahoma, United States*

### **Background:**

Sulfhemoglobin is formed when a sulfur atom incorporates into the heme moiety of hemoglobin and excessive sulfhemoglobin in blood leads to sulfhemoglobinemia. Sulfhemoglobinemia typically occurs due to exogenous drugs/toxins and is potentially lethal due to tissue hypoxia from ineffective oxygen transport.

### **Objectives:**

We describe a neonate with enterogenous sulfhemoglobinemia, to increase the index of suspicion for sulfhemoglobinemia in patients presenting with an intestinal pathology.

### **Design/Method:**

Case report and review of literature.

### **Results:**

A term male neonate with failure to pass meconium developed progressive generalized dusky, green/blue skin discoloration around day of life (DOL) 4-5. On DOL 7, he required mechanical ventilation for presumed hypoxic respiratory failure with pulse oximetry saturation of 60-70% on room air. Arterial blood gas analysis, however, showed a normal arterial oxygen tension (PaO<sub>2</sub>), corresponding appropriately to increasing oxygen delivery (FiO<sub>2</sub>). Although his pulse oximetry saturation improved on 80-100% oxygen his cyanosis did not improve. Initial workup ruled out cardiac or pulmonary causes for these findings.

Multiple normal methemoglobin levels by co-oximetry excluded methemoglobinemia. In addition, hemoglobin electrophoresis did not identify any abnormal hemoglobin variant. Sulfhemoglobinemia was considered, however, no exogenous factors were identified. On reviewing the literature, we found isolated reports of sulfhemoglobinemia associated with intestinal overgrowth of a sulfate-reducing bacteria. We hypothesized that ileus led to disruption of normal intestinal microbiome and overgrowth of sulfate reducing bacteria generating hydrogen sulphide, causing overproduction of sulfhemoglobin. Diagnosis of sulfhemoglobinemia was confirmed, with elevated sulfhemoglobin of 21% by spectrophotometry. We simultaneously found that our patient had underlying cystic fibrosis (CF) with a confirmed homozygous deltaF508 mutation which predisposed him to have ileus after birth. He received blood transfusion for anemia which led to resolution of hypoxia and cyanosis, and ileus was treated conservatively.



**Conclusion:**

We describe a rare case of enterogenous sulfhemoglobinemia in a neonate with CF. A high index of suspicion for sulfhemoglobinemia and timely testing with sulfhemoglobin levels should be considered in a patient with unexplained cyanosis and intestinal motility disorders. In patients with underlying CF, not all cyanosis/hypoxia may be pulmonary, especially if they have signs of intestinal obstruction. Stool studies may be helpful in identifying sulfate reducing bacteria.

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Poster # 150

**HEREDITARY SPHEROCYTOSIS DUE TO A NOVEL VARIANT, P.Q1034X, IN THE BETA SUBUNIT OF THE SPECTRIN GENE**

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**Background:**

Hereditary Spherocytosis (HS) is the most common red cell membrane disorder. 25-30% of cases involve the SPTB gene which encodes for  $\beta$ -Spectrin, a protein that maintains red blood cell shape. Heterozygous variants in SPTB are associated with autosomal dominant HS and elliptocytosis. While genetic testing is not routinely done to confirm HS, it is useful in atypical presentations.

**Objectives:**

To present a novel variant, p.Q1034X, in the beta subunit of the spectrin gene found to cause HS in an infant.

**Design/Method:**

A 1 week old male presented to the pediatric hematology/oncology clinic for anemia. He was born late preterm and had a history of hyperbilirubinemia requiring phototherapy, failure to thrive and developmental delay. On exam, he was noted to have hypotonia. There was no known family history of hematologic problems. Based on these constellation of signs and symptoms, he had a comprehensive hematologic and genetic workup.

**Results:**

On lab evaluation, his peripheral blood smear showed normocytic normochromic red blood cells with some spherocytes, significant polychromasia, normal WBC and platelet morphology. His newborn screen was normal, direct coombs negative, osmotic fragility test was positive, and protein band 3 reduction was abnormal. His abdominal ultrasound was normal. Whole exome sequencing with variant segregation analysis was significant for heterozygosity of the p.Q1034X variant of the SPTB gene. This variant in the SPTB gene has not been previously reported.

**Conclusion:**

We found a novel, de novo variant in an infant with HS through whole exome sequencing. This variant is predicted to cause loss of normal protein function either through protein truncation or

non-mediated mRNA decay resulting in fragile red blood cells. While neither parent was found to carry this mutation, germline mosaicism should not be excluded. Physicians should be aware that prenatal diagnosis is available to address the risk of recurrence in future pregnancies.

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Poster # 151

## **BORDETELLA HOLMESII BACTEREMIA IN A PATIENT WITH SICKLE CELL DISEASE**

**Charyse Diaz, Anca Dumitriu**

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### **Background:**

Pediatric patients with sickle cell disease (SCD), due to functional asplenia, were highly susceptible to bacteremia with streptococcus pneumoniae and haemophilus influenza prior to the advent of immunizations and prophylactic antibiotics. Bordetella holmesii is a rare gram-negative pathogen frequently seen in asplenic patients with only 30 cases of bacteremia between 1983-2000 reported by the CDC. Isolation and speciation are slow with some laboratories unable to speciate Bordetella by PCR, delaying clinical management.

### **Objectives:**

We present the clinical course and management of a 16 year old male with HbSS disease who was subsequently diagnosed with Bordetella holmesii bacteremia in the setting of vaso-occlusive crisis.

### **Design/Method:**

A 16-year-old male with hemoglobin SS presented to the emergency department (ED) with fever to 39.3, chills, vomiting, cough and headaches. There was no obvious source of infection on physical exam. Influenza test performed was negative. Due to patient's allergic history to cephalosporins and penicillin, he received a dose of azithromycin after peripheral blood culture was obtained. NS bolus and antipyretics were administered which improved his symptoms. Complete blood count and reticulocyte count were near patient baseline and outpatient follow up arranged.

He returned to the ED five days later after developing pain to his back, chest and lower extremities consistent with previous crises that did not resolve with his home medications. He was admitted for pain management with patient-controlled analgesia (PCA). On the day of admission, his initial blood culture was reported positive for gram negative rods. Repeat blood culture obtained and started on IV clindamycin. B. holmesii was isolated after 96 hours with susceptibilities.

### **Results:**

Patient was initially started on clindamycin due to penicillin allergy but with guidance from infectious disease after speciation, he was transitioned to IV Ciprofloxacin. Due to incompatibility with PCA and access issues, he was transitioned to IV Levaquin. Due to

persistent fevers, an echocardiogram was obtained due to historical reports of endocarditis in patients with *B. holmesii* bacteremia. This was negative. Patient completed the course of recommended antibiotics. Follow up blood cultures remained negative.

**Conclusion:**

*B. holmesii* bacteremia remains a rare presentation among patients with sickle cell disease with antibiotic susceptibilities for fluoroquinolones and carbapenems not empirically administered to this patient population. Providers who care for patients with SCD should be aware of this pathogen and laboratory capabilities for identification.

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Poster # 152

**MALARIA AND HYDROXYUREA TREATMENT IN SICKLE CELL DISEASE: WHAT DO WE KNOW?**

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**Background:**

Sickle cell disease (SCD) is among the most commonly inherited hemoglobinopathies in Sub-Saharan Africa. Hydroxyurea (HU) is the most effective treatment for SCD with a proven safety and efficacy profile. However, its effect on malaria is controversial. This report compares two siblings exposed to malaria and their difference in presentation.

**Objectives:**

To emphasize the protective role of HU in the acquisition of malaria as well as disease severity. To highlight the need for anti-malarial prophylaxis for all SCD patients.

**Design/Method:**

Case report with literature review.

**Results:**

Case 1: 15-year-old female with SCD and persistent HbF, non-compliant with anti-malarial prophylaxis, presented with intermittent fever, chills and headache for three days following a recent trip to West Africa. Laboratory work demonstrated severe hemolytic anemia (Hgb 5.5 gm/dL with 21% reticulocytosis), hyperbilirubinemia, and transaminitis. A peripheral smear revealed red blood cells with intracellular Plasmodium ring forms, confirming malaria. The patient was hospitalized for supportive care, required two blood transfusions and completed a three-day course of oral atovaquone-proguanil. She was discharged in good condition.

Case 2: 9-year-old male with SCD, on HU therapy and compliant with antimalarial prophylaxis, was closely monitored through serial blood work given his recent travel to West Africa and two siblings diagnosed with malaria. Laboratory work confirmed mild hemolysis, however the peripheral blood smear did not show any intracellular Plasmodium ring forms. Patient received a

blood transfusion and was empirically treated with oral atovaquone-proguanil as outpatient.

**Conclusion:**

In-vitro studies suggest HU increases malaria severity in SCD via HU-associated neutropenia and increases Plasmodium replication via up-regulation of cell surface receptor ICAM-1. However, both NOHARM and REACH trials concluded that HU decreased the incidence of malaria and its severity in SCD. The mechanism for protection via HU therapy is as of yet unknown. Some clinical trials attribute the increase in HbF as the protective factor. Other studies concluded there was no significant difference in the growth of *P. falciparum* parasite between hemoglobin A (HbA) and HbF red cells. Our study supports this finding since the patient with persistent HbF developed malaria. We conclude that HU provides a protective effect against malaria though other mechanisms such as nitric oxide donation or increased erythrocyte adherence. Further studies are needed to elucidate the exact mechanism of action. Our study also emphasizes the significance of anti-malarial prophylaxis on all SCD patients travelling to endemic areas.

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Poster # 153

**PEDIATRIC HYPOFERRITINEMIA WITHOUT ANEMIA: AN ENIGMATIC HEMATOLOGICAL CONDITION**

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**Background:**

Serum ferritin is an important marker in assessing iron deficiency as it reflects tissue iron storage. A decrease in serum ferritin precedes the decrease of serum iron. Hypoferritinemia without anemia(HWA) is rare, reported to occur with a female predominance(1:1.7M:F) in 18/100,000 patients with hypoferritinemia. Laboratory evaluation of blood counts, however, are normal in contrast to iron deficiency anemia. Etiology of hypoferritinemia may be secondary to poor dietary iron intake/absorption due to bowel pathologies such as IBD/celiac disease. Rarely, hypoferritinemia may occur from disorders of iron metabolism.

**Objectives:**

To discuss the presentation, workup, and treatment of two pediatric cases of hypoferritinemia without anemia.

**Design/Method:**

Case reports

**Results:**

Case Presentations:

1. A three-year-old female patient presented in March/2018 with three weeks of pallor and URI symptoms. Laboratory evaluation, significant for hemoglobin 2gm/dL, MCV 60fL, high-RDW,

Mentzer-index >13, iron <10 mcg/dL and ferritin 6 ng/mL. Hemoglobinopathies, parvovirus-induced-aplastic-crisis, antibody-mediated-hemolysis, intestinal infections, GI-bleed, and anemia-of-chronic-disease were excluded. Received 10 mL/kg of PRBC-transfusion. She was discharged upon dietary education and establishment of follow-up. At the hematology clinic in August/2018, laboratory studies showed hypoferritinemia in the absence of anemia. Ferrous sulfate supplementation (5 mg/kg/day) prescribed by her PCP did not correct hypoferritinemia. Intravenous iron infusions were administered and better tolerated. Follow-up visit in September/2019 revealed hemoglobin 13 gm/dL, MCV 70.3 fL, iron 31 mcg/dL and ferritin 8 ng/mL. The patient's iron-refractory-iron-deficiency anemia (IRIDA) testing was negative. She resumed intravenous iron supplementation, providing an additional 10 mg/kg. In the event of no improvement whole genome sequencing will be performed.

2. A three-year-old female patient, at 2-years-of-age presented with a hemoglobin 4 gm/dL. Patient was refractory to PO iron supplementation, hematology started 15 weeks of IV iron therapy. However, once the IV iron was discontinued she did not increase iron stores on her own. CT-imaging and bone marrow biopsy were normal. GI studies have not been revealing. The patient had extensive testing for inherited-hemolytic and dyserythropoietic-anemias. Follow-up visit in December/2019 laboratory studies showed hemoglobin 11.8 gm/dL, iron 59 mcg/dL, and ferritin 9 ng/mL. The patient's IRIDA test was negative, inherited hemolytic and dyserythropoietic-anemias test revealed variants of unknown significance in glutathione-synthetase and spherocytosis (SPTA1, SPTB). Patient will continue intravenous iron supplementation of 120 mg.

### **Conclusion:**

These cases illustrate the issues encountered in diagnosis and management of hypoferritinemia without anemia. HWA is a masked hematological condition of exclusion which would benefit from new nomenclature to help providers distinguish it from iron deficiency anemia to properly manage as hypoferritinemia is shared by both.

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Poster # 154

## **AUTOSOMAL RECESSIVE SPHEROCYTOSIS: A SERIES OF FIVE CASES WITH COMPOUND HETEROZYGOUS SPTA1 MUTATIONS**

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### **Background:**

Autosomal recessive (AR) hereditary spherocytosis (HS) is a rare, and challenging to diagnose, erythrocyte disorder. Patients with AR HS vary in their anemia severity, transfusion dependence, response to splenectomy, and disease complications. Patients may present with severe anemia in-utero and/or anemia with reticulocytopenia, complicating the differential diagnosis. Here we present five patients with severe, transfusion-dependent anemia ultimately diagnosed with AR HS by genetic testing.

**Objectives:**

To describe five patients with AR HS, including their initial presentations, management and complications, along with their specific mutations and genotype-phenotype correlations.

**Design/Method:**

Five patients with a confirmed diagnosis of AR HS at our institution were identified. Their electronic health records were reviewed for clinical and laboratory data, genetic testing results, and maternal obstetric data, if available.

**Results:**

All five patients had compound heterozygous pathogenic variants in SPTA1, two of whom were siblings. Three patients were male, and all five self-identified as White, Hispanic. The diagnosis of AR HS was made via whole exome sequencing (n=2), a targeted custom next-generation panel (n=1), and a commercially available hemolytic anemia next-generation panel (n=1). Known familial variant sequencing was obtained in the fifth patient based on the affected sibling's results. All patients have at least one SPTA1 variant leading to loss of function (LOF) due to resulting frameshifts, while the other variants affect either splicing or signaling, which are also expected to result in LOF.

All five patients have been transfusion-dependent since birth. Four were diagnosed with fetal anemia, two suffering from hydrops fetalis (HF), with all four requiring intrauterine transfusions. One had no abnormal intrauterine findings detected but was anemic with severe conjugated hyperbilirubinemia at birth. Reticulocytopenia was present within the first week of life in all patients, with two initially undergoing evaluation for suspected red cell aplasia. All remain transfusion-dependent; two additionally receive chelation therapy. Total splenectomy (n=1) and partial splenectomy (n=1) did not eliminate transfusion dependence. Two patients are also followed by a renal geneticist for persistent hypertension, potentially related to the SPTA1 variants.

**Conclusion:**

We describe a cohort of five patients with AR HS secondary to compound heterozygote SPTA1 mutations. All remain transfusion-dependent, demonstrating a severe clinical phenotype beginning in-utero or at birth. Given the lack of typical hemolytic findings, genetic testing for AR HS should be considered by hematologists and maternal-fetal-medicine obstetricians early in the pre- or post-natal course for fetal anemia and/or non-immune hydrops fetalis.

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Poster # 155

**EMERGENCY DEPARTMENT RELIANCE AND HOUSEHOLD MATERIAL  
HARDSHIPS IN CHILDREN WITH SICKLE CELL DISEASE**

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**Background:**

High emergency department reliance (EDr) in children and adolescents with sickle cell disease (SCD) is associated with worse outcomes and increased costs [1,2]. For patients with SCD, lower household income is associated with increased emergency department (ED) utilization, but it is unknown if household material hardships (HMH)- housing, utility, or food insecurity- impact utilization [3,4]. Because these may represent modifiable risk factors for high ED utilization, we aim to determine the association between HMH and ED reliance in pediatric patients with SCD. Our hypothesis is that increased number of HMH will be associated with increased ED reliance.

**Objectives:**

To analyze the association between household material hardships and ED reliance in children with sickle cell disease.

**Design/Method:**

We performed a retrospective review of patients with SCD between the ages of 12-months and 18-years who receive care in the Boston Medical Center network in Boston, Massachusetts, USA and were screened for HMH during a quality improvement initiative between August, 2017 and June, 2019. EDr, defined as the percentage of healthcare visits that occur in the ED, was obtained via review of the electronic medical record for the preceding year.

**Results:**

Of 101 eligible patients, 60 (59.4%) reported one or more material hardship. The mean EDr of patients without HMH was 5.9% compared to an EDr of 16.0% for patients reporting at least one HMH ( $p < 0.0001$ , confidence interval 5.0-15.0%). Using linear regression, each 1 unit increase in material hardship reported was associated with an increase of 7.7 in EDr ( $p < 0.0001$ ), adjusting for age, sex, language, insurance type, and transportation hardship.

**Conclusion:**

Experiencing more household material hardships significantly increases ED reliance in children with SCD, regardless of transportation hardship or insurance type. The ED reliance in our population was not high, but each added material hardship was associated with patients receiving an additional 7.7% of their care in the ED. Through screening for HMH, providers and health systems can attempt to identify modifiable risk factors for high EDr and to identify patients at-risk for these utilization patterns to connect them with resources.

1. Brousseau, JAMA, 2010
2. Blinder, J Emerg Med, 2015
3. Glassberg, Acad Emerg Med, 2012
4. Bilodeau, Pediatr Blood Cancer, 2018

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Poster # 201

**TREATMENT OUTCOMES OF PEDIATRIC MAY-THURNER SYNDROME-ASSOCIATED DEEP VENOUS THROMBOSIS**

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**Background:**

May-Thurner Syndrome (MTS), obstruction of the left lower extremity venous outflow tract due to compression of the left common iliac vein by the right common iliac artery, may predispose an individual to lower extremity deep venous thrombosis (DVT) development. Literature about this condition in pediatrics is limited, and studies evaluating safety and effectiveness of therapy as well as outcome data and risk factors predicting outcome in pediatric MTS-associated DVT are lacking.

**Objectives:**

We reviewed treatment outcomes of children and young adults with MTS-associated DVT at a tertiary care hospital and to identify predictors of DVT recurrence.

**Design/Method:**

With Institutional Review Board approval, we conducted a retrospective chart review of children and young adults with MTS-associated DVT seen from 2009 to 2018, and analyzed their clinical features, radiologic findings, management strategies, and outcomes.

**Results:**

Sixteen patients met inclusion criteria (9 male, 7 female), with a median age of 16.4 years (range 6.7-17.9 years). Five patients (31.3%) had pulmonary embolism. Thrombophilic risk factors included obesity (n=5, 31.3%), antiphospholipid syndrome (n=5, 31.3%), estrogen exposure (n=4, 25.0%), heterozygous Factor V Leiden (n=3, 18.8%), recent surgery, infection, protein C and S deficiency, and frequent video game playing (n=1, 6.3% for each variable). All patients received anticoagulation including unfractionated heparin (n=12, 75.0%), enoxaparin (n=16, 100%), warfarin (n=6, 37.5%), and direct oral anticoagulant (n=4, 25.0%). Nine (56.3%) had site-directed tissue plasminogen activator at initial presentation. Thirteen (81.3%) had interventional therapy, with 69.2% (9/13) requiring repeat procedure. Seven (43.8%) had thrombectomy, 8 (50.0%) had stent placement, and 9 (56.3%) had angioplasty. Complications of interventional therapy included bleeding (n=2; 12.5%) and immediate re-thrombosis (n=4; 25.0%).

Eleven (68.8%) had DVT resolution with median time to resolution of 61 days. Six out of 14 patients (42.9%) had DVT recurrence with median time to recurrence of 572 days. After adjusting for variables found to be independently associated with DVT recurrence, warfarin use (adj. HR 28.01, 95% CI: 4.60, 170.55) and common femoral vein involvement (adj. HR 33.21, 95% CI: 3.41, 323.73) were associated with a higher risk of DVT recurrence.

**Conclusion:**

This study represents the largest series of MTS-associated DVT focusing on children and young adults. Common femoral vein involvement and warfarin use, the latter possibly related to non-compliance in younger patients, may be associated with a higher risk of DVT recurrence. Future



studies may help to develop a risk-stratified approach to optimize the care of MTS-associated DVT in adolescents and risk of recurrent DVTs.

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Poster # 202

## **VTE IN HOSPITALIZED PEDIATRIC PATIENTS: IMPLEMENTING A RISK ASSESSMENT TOOL**

**Joanna Robles, Marissa Just, Ashley Frazier, Karan Kumar, Andrew Yazman, Heather McLean, Jennifer Rothman, Kristy Pahl**

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### **Background:**

The incidence of venous thromboembolism (VTE) in hospitalized pediatric patients is increasing due to the growing medical complexity of pediatric patients and the increasing use of central venous catheters (CVCs). While incidence, risk factor identification, and preventative strategies are well established in hospitalized adults, this information is limited in the pediatric population. There are currently no standardized VTE risk screening tools or thromboprophylaxis guidelines for children at Duke Children's Hospital.

### **Objectives:**

Determine the baseline incidence of hospital acquired VTE (HA-VTE) at a large pediatric tertiary care center. Develop and implement a risk stratification tool allowing medical providers to identify patients that may benefit from VTE prophylaxis.

### **Design/Method:**

Electronic medical records (EMR) of pediatric patients hospitalized at Duke Children's Hospital June 2018 through November 2018 were reviewed to identify patients diagnosed with HA-VTE during their hospitalization or within 14 days of discharge. A VTE risk calculator was created using standardized risk factors associated with HA-VTE. Quality improvement methods were used to test implementation of a VTE screening tool on one pediatric medical surgical unit. Nurses received education about VTE screening and prevention. Nurses tested the screening tool for patients ages 12 to 18 years over a 2-week period. The complexity of the screening tool increased with each Plan-Do-Study-Act (PDSA) cycle.

### **Results:**

Out of 4,176 total pediatric admissions, 33 VTE events were identified (incidence = 0.98 per 1000 patient days). Patients with CVCs comprised the majority of the cohort. During the QI phase, nursing completion of screening assessments decreased with each PDSA cycle as the complexity of the screening tool increased. There was a 71% decrease in forms completed from 1st to the 3rd PDSA cycle. In the initial cycle, 39% of nurses reported that the screening assessment tool negatively impacted their work flow. Feedback noted difficulty locating body mass index (BMI), family history or personal history of thromboses in the patient's chart. Nurses also requested that the screening tool be implemented in the EMR.

**Conclusion:**

The increasing complexity of the VTE risk calculator tool correlated with decreased completion of the assessment. The completion rate was not affected by efforts to reinforce education or the implementation of daily reminders. Future PDSA cycles planned will include testing the feasibility of the EMR VTE risk calculator tool, reliability of screening by nurses, and eventually focus on the effectiveness of the tool to decrease the incidence of HA-VTE.

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Poster # 203

**AN INSTITUTIONAL EXPERIENCE WITH EMICIZUMAB IN PEDIATRIC PATIENTS WITH HEMOPHILIA A**

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**Background:**

Emicizumab is a recombinant, humanized, bispecific monoclonal antibody that substitutes for the function of FVIII by binding to activated factor IX and X. It is currently indicated for routine prophylaxis in adults and children of all ages with hemophilia A, with or without inhibitors. Despite basic guidelines provided by MASAC and the drug package insert, there is significant inter-institutional variability regarding monitoring and follow up in patients on Emicizumab.

**Objectives:**

To outline our institutional experience in pediatric patients on Emicizumab.

**Design/Method:**

Retrospective and prospective chart review of our patients on Emicizumab. Information collected included age of patient, hemophilia severity, presence and titer of inhibitors, age when Emicizumab was initiated, bleed management and monitoring.

**Results:**

We have 20 pediatric patients on Emicizumab. Three with moderate and seventeen with severe hemophilia A. Age at initiation of therapy ranged from 11mo-16years. The four youngest patients were started on primary prophylaxis with Emicizumab by age 2. Five patients had inhibitors, two with high titer inhibitors. Prophylactic factor therapy was discontinued when Emicizumab was initiated.

Labs included chromogenic FVIII activity and inhibitor within a month prior to starting therapy. Repeat levels are done at 3mo and then annually. Initial dose with teaching is done in clinic. Parents have the option to follow up weekly if needed. Scheduled visit are at week 5, 3mo, 6mo and 6 monthly thereafter. PTT is checked at each follow up. An educational checklist is completed by the provider and a nurse at the initial visit. Dose is recalculated at each visit based on weight. FEIBA is noted as a drug allergy in the patient's chart. Central lines are removed after 3mo of Emicizumab therapy. Single dose of factor product at 50 IU/kg or recombinant factor VII at 60-70mcg/kg has provided adequate hemostasis for minor surgical procedures. Most dental procedures have required only antifibrinolytic therapy. Majority of joint and soft tissue injuries

are managed with observation and RICE alone or a single dose of factor if there is a bleed. Most patients are on q2 or q4 week dosing for maintenance based on convenience and number of injections needed at a time.

**Conclusion:**

The custom educational check list at our HTC has proven to be the most useful tool for our staff, patients and families. This has ensured consistent teaching and uniform monitoring for all the patients. A multi-institutional collaboration will help establish Emicizumab monitoring guidelines for patients across the globe.

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Poster # 204

**VWF LEVELS IN CHILDREN WITH POSTOPERATIVE BLEEDING FOLLOWING TONSILLECTOMY**

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**Background:**

Bleeding is an important complication in children following tonsillectomy, and postoperative bleeding can lead to diagnosis of clotting disorders such as von Willebrand disease. Screening with coagulation tests prior to procedure has become common to assess bleeding risk in the perioperative period despite inconsistent data to support this practice. ASH/ASPHO Choosing Wisely guidelines recommend against routine PT/PTT testing, but there is little data on assessing VWF antigen (VWF:Ag).

**Objectives:**

To compare VWF:Ag levels among patients with postoperative bleeding following tonsillectomy to evaluate bleeding risk.

**Design/Method:**

Subjects aged 0 to 18 without significant personal or family history of major bleeding who were planning to undergo tonsillectomy with or without adenoidectomy were recruited from the Children's Hospital of Wisconsin Ear, Nose, and Throat Clinic into this prospective study following attainment of informed consent and IRB approval. Plasma VWF:Ag levels were drawn at time of anesthesia administration. VWF:Ag was tested using ELISA. Surgical and postoperative bleeding data was gathered via patient diary supplemented by medical chart review. Severity of bleeding, time of onset of first bleeding event, and recurrence of postoperative bleeding were assessed. Statistics were performed using GraphPad Prism.

**Results:**

1,454 subjects had fully evaluable data for VWF:Ag and postoperative bleeding scores, with mean age of 6 years and mean VWF:Ag of 92 IU/dL. Postoperative bleeding occurred in 239 cases. Mean VWF:Ag was 91 in patients with postoperative bleeding scores of 1-2 (n=188), 88

for scores 3-4 (n=39), 82 for scores 5-6 (n=6), and 94 for scores >6 (n=6), with no significant difference between groups (p=NS). Of the patients who experienced multiple days of postoperative bleeding, the median VWF:Ag was 90 (n=61), compared to 91 in subjects with only one day of bleeding reported (n=178), p=NS. We then evaluated VWF:Ag for subjects whose first reported bleed was early as compared to those whose first reported bleed was later in the postoperative course. Mean VWF:Ag was 94 for those who experienced bleeding on postoperative days 0-1 (n=93), 88 for days 2-7 (n=117), and 92 for days 8-14 (n=29). None of these differences were statistically significant (p=NS).

**Conclusion:**

VWF:Ag does not correlate with severity of bleeding, time of onset of first bleeding event, or recurrence of bleeding in healthy children with postoperative bleeding following tonsillectomy. These data do not support routine screening for von Willebrand disease prior to surgery if the patient has a negative personal or family history of bleeding.

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Poster # 205

**CLINICAL CHARACTERISTICS AND EPIDEMIOLOGY OF PATIENTS WITH FACTOR VII DEFICIENCY**

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**Background:**

Factor VII deficiency is the most common among rare autosomal recessive bleeding disorder with an overall national incidence of 1 in 500,000. Only small amounts of FVIIa are needed to trigger coagulation however bleeding phenotype varies from asymptomatic to severe life-threatening bleedings including central nervous system (CNS) and gastrointestinal (GI) bleeding. However, studies refer lack of a direct correlation between plasma levels of coagulation Factor VII and bleeding manifestations making treatment more challenging.

**Objectives:**

Our main objective is to describe demographic characteristics of our population with Factor VII Deficiency in New Orleans. Also, we aim to determine if there is any correlation with Factor VII level and the bleeding phenotype in our patients with Factor VII Deficiency.

**Design/Method:**

We performed a retrospective chart review from 2011-2019 evaluating patients diagnosed with Factor VII deficiency in Children's Hospital of New Orleans during that period. Fourteen patients were diagnosed with Factor VII deficiency in Children's Hospital of New Orleans during the period 2011-2019. We analyze the following variables: age, gender, race, Factor VII Level at diagnosis, bleeding phenotypes and treatment received. We used descriptive statistics such as median(range) and frequencies (percentages) to analyze the data collected.

**Results:**

The majority of our patients with Factor VII deficiency (86%) were classified as Mild Factor VII Deficiency (FVII level 20%-50%). Only one patient presented with Severe Factor VII Deficiency (FVII level <10%) associated with symptoms of menorrhagia and microcytic anemia. The most common bleeding phenotype was epistaxis (35%). Treatment varied depending on the setting, for trauma or major surgery Factor VII recombinant was given and for mucosal bleeding Aminocaproic Acid was used as first-line treatment.

**Conclusion:**

Our main population of Factor VII deficiency in New Orleans is African American and classified as Mild Factor VII Deficiency. As indicated in previous studies there is a great variability associated with bleeding phenotype and Factor VII level. Future studies needed to evaluate for genotype and how this compares between Ethnicities and their bleeding phenotypes.

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Poster # 206

**THE PBRAQ AS A RISK STRATIFICATION TOOL FOR SURGICAL BLEEDING RISK IN PEDIATRIC PATIENTS**

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**Background:**

The current standard of care in the pediatric population is the use of coagulation testing to screen for surgical bleeding risk. However, this practice is not based upon clear guidelines and often results in false positives, leading to further blood work and hematology consults which may delay surgeries and increase parental stress and costs. In fact, several studies reject the use of PT and aPTT in asymptomatic patients as predictors of clinical bleeding. In 2018, we adopted the Pediatric Bleeding Risk Assessment Questionnaire (PBRAQ) in our pre-surgical testing (PST) unit to assess its utility in predicting clinical bleeding outcomes and as a surrogate for laboratory testing in children undergoing surgery.

**Objectives:**

1. To assess sensitivity and specificity of the PBRAQ for those who completed the questionnaire
2. To assess the proportion of patients who were identified by the PBRAQ as being at high risk of bleeding (score  $\geq 2$ )
3. To assess the proportion of patients who were identified by the PBRAQ as being at low risk of bleeding (score < 2), but still had labs drawn per surgeon preference

**Design/Method:**

A retrospective chart review was conducted of patients seen at PST in January, February, April, May, July, August, October, and November of 2018. PBRAQ scores, labs, and bleeding outcomes were recorded. Patients with a history of bleeding disorder were excluded along with repeat visits to PST among patients.

**Results:**

Of 1208 charts reviewed, 955 patients (79.0%) completed the PBRAQ. 2 patients (0.17%) experienced perioperative bleeding, both of whom scored < 2.

1. The sensitivity of the PBRAQ tool was 0.0% (95% CI: 0.0% to 84.0%), and the specificity of the screening tool was 92.3% (95% CI: 90.5% to 94.0%).

2. Of 955 patients, 73 (7.6%) scored  $\geq 2$ , none of whom bled.

3. Of 955 patients, 882 (92.0%) patients scored < 2, 66 (7.5%) of whom had PT/PTT drawn.

### **Conclusion:**

Preliminary analysis suggests that the PBRAQ could be a specific screening tool for eliminating laboratory testing in children undergoing surgery. Our preliminary data suggests that laboratory testing can be avoided in children at low bleeding risk (PBRAQ score < 2). Study limitations include inadequate administration of the PBRAQ by our PST, resulting in potential lack of a representative sample target patient population, which may affect PPV and NPV.

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Poster # 207

## **THE IMPACT OF CONCURRENT X-CHROMOSOME ABNORMALITIES ON BLEEDING PHENOTYPE IN PEDIATRIC HEMOPHILIA**

**Elizabeth Soffer, Karlene Coleman, Shannon Meeks, Glaivy Batsuli**

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### **Background:**

Early diagnosis of hemophilia is essential for effective bleeding prophylaxis and optimizing patient quality of life. As an X-linked recessive disorder, patient sex and family history are significant determinants of a patient's risk of disease and play a major role in whether or not a child will receive genetic screening. However, the presence of other X-chromosome abnormalities may skew this risk of disease and should be considered when assessing possible diagnoses and management of these patients.

### **Objectives:**

To describe the impact of X-chromosome abnormalities on hemophilia phenotype and demonstrate the importance of multi-disciplinary collaboration to obtain a thorough family history and recognize the possibility of multiple diagnoses in one child.

### **Design/Method:**

A retrospective chart review of 4 children with mild to severe hemophilia A or B followed at the Emory University Pediatric Hemophilia Treatment Center, 3 of whom have concurrent X-chromosome abnormalities, was conducted to determine the effect of chromosomal abnormalities on factor levels and bleeding phenotype.

### **Results:**

Our patient cohort includes: Patient 1, a 21-year-old (yo) female with moderate/severe hemophilia A (FVIII <1-4%) and skewed X-inactivation; Patient 2, a 6 yo female with severe

hemophilia A (FVIII <1%) and Turner Syndrome (karyotype 45, X); Patient 3, a 6 yo male with mild hemophilia B (FIX 34%) and Klinefelter Syndrome (karyotype 47, XXY); and Patient 4, a 2 yo male (46, XY) with severe hemophilia B (FIX <1%) and the brother of Patient 3. Diagnosis of hemophilia was delayed in the case of Patient 1 by 10 months and in Patient 3 by 4 years despite their bleeding histories as well as family histories of hemophilia. Patient 1 also had a history of fluctuating FVIII levels between <1-4% throughout childhood that contributed to her severe bleeding phenotype and need for FVIII prophylaxis. Patient 2 was diagnosed with a FVIII level <1% shortly after birth due to severe intracranial hemorrhage in her deceased twin sister with similar karyotype and FVIII <1%. She immediately started FVIII prophylaxis but developed a low titer inhibitor at 17 months that was successfully tolerized. Patient 3 demonstrated an unexpectedly lower FIX level of 34% believed to be the result of skewed X-inactivation with 47, XXY karyotype.

**Conclusion:**

In the setting of various X-chromosome abnormalities, the presentation of hemophilia may differ. Although rare, vigilant evaluation of patient and family histories by providers remains a critical aspect of the diagnosis and management of patients with hemophilia.

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Poster # 208

**CHARACTERISTICS, RISK FACTORS AND MANAGEMENT OF PEDIATRIC SUPERFICIAL VEIN THROMBOSIS**

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**Background:**

Thrombophlebitis and thrombosis of the superficial veins is frequently encountered in hospitalized children. Recent studies in adults with superficial vein thrombosis (SVT) suggested non-negligible risk of development of deep vein thrombosis (DVT) and/or pulmonary embolism (PE). The management of SVT is poorly defined and there is no pediatric data describing characteristics, risk factors and management of SVT.

**Objectives:**

To describe the characteristics, risk factors and management of SVT in pediatric patients followed at our center.

**Design/Method:**

In this retrospective study, we identified all patients with a radiologically confirmed SVT who were managed at our center between January 1, 2014, and December 31, 2019. Patients were identified by searching radiology reports using MONTAGE Search and Analytics (MONTAGE Search and Analytics; Nuance communications Inc, Burlington, MA) for specific key words followed by chart reviews to identify true cases. Relevant data extracted from electronic medical records were summarized using descriptive statistics. Analysis was limited to patients with

isolated SVT (i.e.: no concurrent DVT at diagnosis).

**Results:**

During the study period, 122 patients were found to have an SVT [isolated SVT in 37 patients (30%), concurrent SVT and DVT in 85 patients (70%)]. The median age of patients with isolated SVT was 15 years (range 2 weeks-21 years) and 20 patients (54%) were females. SVT affected the superficial veins of upper extremities in 24 patients (65%), lower extremities in 12 patients (32%) and both extremities in 1 patient (3%). Of the 37 patients, 17 (46%) exhibited clinical evidence of phlebitis. SVT was a hospital-associated event in 33 patients (89%). One or more risk factors for SVT were identified in 34 patients (92%). The most common risk factor was venous catheterization [24/37 patients (65%)] which included peripheral venous catheter (PVC) placement in 13 patients (54%) or peripherally inserted central catheter (PICC) placement in 11 patients (46%). Sixteen patients (43%) received anticoagulation with significant variation in intensity, duration of therapy and follow-up. Propagation to DVT occurred in 3 patients and 1 patient developed PE. All 4 patients were receiving lower-intensity prophylactic anticoagulation.

**Conclusion:**

Our study suggests that pediatric SVT is a common thrombotic event especially in hospitalized patients. Venous catheterization (PVC or PICC) was the single most common risk factor in our cohort. A significant number of patients required anticoagulation but management was highly variable with a subset of patients developing DVT/PE despite receiving prophylactic anticoagulation. Multicenter, prospective studies are needed to develop more optimal evidence-based risk stratified management approaches.

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Poster # 209

**HEAVY MENSTRUAL BLEEDING AS AN IMPORTANT PRESENTATION OF VON WILLEBRAND DISEASE IN ADOLESCENTS**

**Anna Sowa, Nataly Apollonsky**

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**Background:**

Von Willebrand Disease (vWD) is the most common inherited bleeding disorder. In adult females with vWD rates of heavy menstrual bleeding (HMB) range from 60% to 90% with reports of up to 20% of participants undergoing hysterectomy to prevent further HMB episodes. There is limited data on HMB in postmenarchal adolescents with vWD.

**Objectives:**

To evaluate the prevalence, risk factors and complications associated with HMB in postmenarchal adolescents with vWD.

**Design/Method:**

We performed a retrospective chart review of consecutive female adolescent patients with vWD seen in the St. Christopher's Hospital for Children hematology outpatient clinic between April



2015 and June 2017. To compare groups, we performed Student's t-test, Mann-Whitney test and chi squared when appropriate. Two-tailed p-values less than 0.05 were considered significant.

### **Results:**

In 62 postmenarchal female patients (mean age of referral= $10.1 \pm 5.3$  SD) with vWD, 77% (n=48) had HMB. HMB was the most common reason for referral to Hematology clinic (44% of patients, n=27). Age of referral of patients with HMB was higher than those without HMB (mean  $\pm$  SD;  $6.1 \pm 3.0$  vs.  $11.3 \pm 5.2$ ,  $p < 0.001$ ). Among patients with HMB there was a higher prevalence of iron deficiency in comparison to patients without HMB (50%, n=24 vs. 14%, n=2 respectively; OR=6.0,  $p = 0.038$ ) and they were prescribed iron therapy more frequently (54%, n=26 vs. 7%, n=1; OR=15.4,  $p = 0.005$ ). Seven patients (11%) required pRBC transfusion and the most common reason for transfusion was HMB (57%, n=4). The results yielded no statistically significant association between characteristics such as: BMI percentile for age, ethnicity, reason for referral, positive family history of bleeding, presence of other bleeding symptoms, presence of coagulation abnormalities and risk of HMB, anemia, iron deficiency, iron treatment prescription or transfusion ( $p$  values  $> 0.05$ ). Baseline Von Willebrand Factor Antigen level, von Willebrand Factor Activity and Factor VIII activity were not significantly different between patients with and without HMB.

### **Conclusion:**

In our study, the majority of postmenarchal female patients with vWD had HMB and is was the most common reason for referral among those patients. HBM was associated with higher odds of iron deficiency and need for iron treatment and it was the most common cause of pRBC transfusion. Our findings provide evidence that HMG is highly prevalent and it renders substantial health implications in adolescents with vWD. Therefore, it might be beneficial to inquire female adolescents of symptoms of HMB and screen for VWD in those with menorrhagia.

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Poster # 210

## **PREDICTIVE VALUE OF ISTH-BAT SCORES IN THE DIAGNOSIS OF MILD BLEEDING DISORDERS**

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### **Background:**

The International Society on Thrombosis and Hemostasis - Bleeding Assessment Tool (ISTH-BAT) is a validated diagnostic tool used in subjects with suspected inherited bleeding disorders. While the current literature validates the use of questionnaires for clinical diagnosis and assessment of bleeding severity in pediatric patients with von Willebrand disease, there is paucity of data on its clinical utility in mild bleeding disorders, particularly in low von Willebrand factor (VWF) and delta storage pool deficiency (DSPD).

### **Objectives:**

To describe the predictive value of an ISTH-BAT score in the diagnosis of laboratory confirmed mild bleeding disorders among pediatric patients referred to hematology clinic.

**Design/Method:**

A retrospective chart review of all patients referred to University of Louisville Pediatric Hematology for evaluation of bleeding symptoms from October 2017 to December 2018. ISTH-BAT scores were assigned based on symptoms documented in the initial encounter. Only patients with at least one of the following studies obtained were included: VWD Diagnostic Panel (BCW), platelet function study, or platelet electron microscopy (PEM).

**Results:**

A total of 406 charts were reviewed, of which 96 met inclusion criteria. Of these, 67 had a positive bleeding score of  $\geq 3$  (70%) while 29 had an initial bleeding score of  $\leq 2$  (30%). In the positive bleeding score cohort, only 23 of 67 (32%) were diagnosed with either low VWF or DSPD. Forty-one of 67 (63%) had a negative workup. In the negative bleeding score cohort, 13 of 29 (43%) had confirmed diagnosis of a mild bleeding disorder while the workup was negative in the remaining 15 (51.7%). The overall positive predictive value of a positive bleeding score was 36%.

There was no difference in mean ISTH-BAT scores ( $t(90) = 0.2826, p=0.78$ ) between those with either low VWF or DSPD (3.67) and those lacking a bleeding disorder diagnosis (3.54). Furthermore, there was no significant correlation between ISTH-BAT scores and PEM ( $R=-0.0748, p=0.62$ ), VWF GP1bM activity ( $R=0.1688, p=0.38$ ), VWF collagen binding activity ( $R=0.0633, p=0.74$ ) or VWF Ag ( $R=-0.1294, p=0.5$ ).

The most common symptoms reported in patients with a confirmed diagnosis were menorrhagia (61%), bruising (50%), oral bleeding (33%), and epistaxis (31%). However, clinically significant bleeding symptoms as reported above were only seen in 18%, 11%, 22%, and 12%, respectively.

**Conclusion:**

A positive ISTH-BAT bleeding score is a poor predictor of subsequent diagnosis of laboratory confirmed mild bleeding disorders. Limitation of its use in pediatric patients likely results from lack of exposure to hemostatic challenges in this population.

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Poster # 211

**RISK FACTORS FOR PEDIATRIC CEREBRAL SINUS VEIN THROMBOSIS**

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**Background:**

Cerebral sinus vein thrombosis (CSVT) is a type of stroke consisting in thrombosis of the dural sinus and/or cerebral veins. The estimated incidence in children is 0.6 per 100,000 children per year. Poor outcomes, including death, happen in 9 to 29% of patients. In addition, neurologic

deficits, primarily cognition and behavior, are seen in 50% of affected children. Despite new progress on pediatric stroke, CSVT is under-recognized and its risk factors are not well established.

**Objectives:**

In an effort to increase recognition of Pediatric CSVT, we wanted to identify the risk factors associated with pediatric CSVT together with its signs and symptoms at presentation.

**Design/Method:**

We conducted a single-center review of pediatric patients diagnosed with CSVT between 2008 and 2018, seen by the Hematology service at Cook Children’s Medical Center (CCMC). Patients with radiographically confirmed CSVT were identified.

**Results:**

We identified 87 patients; 59% had neurological symptoms at diagnosis: headache (32%), increased intracranial pressure (9%), altered mental status (9%), cranial nerve palsy (5%), focal weakness (5%), diplopia (3%), papilledema (3%), ataxia (2%), and hemiparesis (1%). Other symptoms included fever (29%), vomiting (28%), and nausea (11%).

Risk factors included mastoiditis (26%), otitis media (24%), Lemierre’s syndrome (10%), retropharyngeal abscess (5%), and severe anemia (hemoglobin <7 gr/dl; 5%).

Thrombophilia testing was done in a limited number of patients. We found Antithrombin III deficiency in 4 (n=37 tested); deficiency of protein C in 5 (n=30) and protein S in 5 (n=29); and elevated lipoprotein A in 1 (n=3). There was a positive lupus anticoagulant in 4 (n=26), positive Anticardiolipin IgM antibodies in 4 (n=36), Anticardiolipin IgG in 1 (n=38), Anti beta-2 glycoprotein IgM Antibodies in 2 (n=26), and Anti beta-2 GP IgG antibodies in 4 (n=28). Positive Factor V Leiden mutation in 2 (n=30) and positive Prothrombin gene mutation in 1 (n=30).

The most common locations for CSVT included the right sigmoid sinus (39%), superior sagittal sinus (38%), right transverse sinus (38%), internal jugular vein (37%), left transverse sinus (32%), left sigmoid (26%), and cortical veins (15%).

**Conclusion:**

Infectious causes such as otitis media, mastoiditis and retropharyngeal abscess can be common contributors of pediatric CSVT. An important but often overlooked risk factor is anemia which presented in 5% of our patients. Thrombophilia on the other hand, was rather rare. We suggest that if these entities are diagnosed, there should be a high index of suspicion if any neurological symptoms are present.

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Poster # 212

**INHERITED FIBRINOGEN DISORDERS AT A SINGLE CENTER: ATYPICAL PRESENTATIONS AND UNMET NEEDS**

**Mohamed Elshinawy, Shamsa Alkaabi**

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**Background:**

Inherited fibrinogen disorders are relatively common in Oman due to consanguineous marriage.

**Objectives:**

We aim to study the demographic and clinical characteristics of patients with special emphasis on atypical presentations and access to service.

**Design/Method:**

The retrospective arm of this ambidirectional study included all pediatric patients diagnosed with inherited fibrinogen disorders in Sultan Qaboos University Hospital, Muscat, Oman till December 2017 and the prospective arm included patients diagnosed since January 2018 onwards. Electronic data, lab results & imaging studies have been reviewed. All patients and caregivers were interviewed.

**Results:**

Twenty-four patients with fibrinogen disorders were identified, constituting the third most common inherited bleeding disorder, after von Willebrand disease and hemophilia. The majority of patients had hypofibrinogenemia (17/24), followed by afibrinogenemia (5/24) & dysfibrinogenemia (2/24). Consanguineous marriage was encountered in 22 cases and all patients have at least one affected sibling and/or cousin. The age at diagnosis varied from 2 days to 13 years. Male: Female ratio was 1:1. The most frequent presenting manifestations were mucocutaneous bleeding, post-tooth extraction hemorrhage, bleeding from umbilical stump and menorrhagia. Atypical presentations include an infant with massive orbital hematoma who developed panophthalmitis resulted in enucleation, an adolescent girl who suffered from ruptured hemorrhagic ovarian cyst and an 8-year-old boy who developed concealed hemorrhage secondary to a splenic laceration. Selective embolization failed to control bleeding and the patient required emergency splenectomy. Two siblings developed painful hemorrhagic bone cysts and they benefited from intensified prophylactic therapy with fibrinogen concentrate. 11/24 patients (46%) have severe bleeding phenotype and receive prophylactic monthly replacement therapy. Only two adolescent girls required hormonal therapy as an adjuvant treatment for uncontrollable menorrhagia. As regards patient satisfaction, 42% of families requested more frequent follow up visits and/or provision of fibrinogen concentrate as a substitute of cryoprecipitate in peripheral hospitals.

**Conclusion:**

Clinical presentations of hypo/dysfibrinogenemia can be life-threatening in some patients. Establishing a nation-wide registry and performing molecular studies are highly recommended.

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Poster # 213

**EFFECTIVENESS OF THROMBOPROPHYLAXIS FOR PICC-ASSOCIATED VTE IN PEDIATRICS: A CASE-CONTROL STUDY**

**Matt Speckert, Sophie Lamontagne, Ken Tang, Ewurabena Simpson**

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**Background:**

Venous thromboembolism (VTE) is a rising cause of morbidity and mortality in the Canadian pediatric population [1]. Central venous access devices (CVAD) have been identified as the most important risk factor in the development of VTE in pediatric patients [2]. At this time there is conflicting evidence supporting the use of prophylactic anticoagulation [3, 4], and institutional practices vary. CHEO, a tertiary pediatric hospital in Ottawa, Canada, currently administers prophylactic anticoagulation to pediatric patients with peripherally inserted central catheters (PICC) based on the presence of elevated biochemical and hematological markers of inflammation. To date, there has been no review of the effect of this practice on the burden of catheter associated VTE at our institution.

**Objectives:**

The primary objective of this study was to evaluate the effect of thromboprophylaxis on the risk of PICC associated VTE at our institution.

**Design/Method:**

This is a single-centre retrospective case-control study at a medium-sized pediatric hospital. We included all patients with PICC line associated VTE at CHEO between January 1, 2005 and June 30, 2018, excluding patients with previous thrombosis or known thrombophilia. Information about PICC line insertion, VTE characteristics and inflammatory markers were abstracted from patient charts. Controls were assigned to patient cases of VTE at a 1:1 ratio, and matched according to the presence of comorbid malignancy, inflammatory bowel disease and year of PICC insertion.

**Results:**

Ninety-nine patients had PICC-associated VTE between January 1, 2005 and June 30, 2018. Most VTEs occurred in patients less than 3 months of age (49.5%), followed by adolescents over 12 years of age (22.2%). Fifty-two (52.5%) patients had symptomatic VTE and 58 (58.6%) of VTEs were occlusive on imaging. Of 199 patients in our sample 27 (13.6%) received thromboprophylaxis with a similar number of recipients in both the VTE case and non-VTE control groups. Thromboprophylaxis was commonly prescribed to adolescents (78%) and rarely given to infants under 3 months of age (1, 3.7%). In our multi-variable regression model we observed no statistically significant association between VTE and thromboprophylaxis, age, female sex, year of placement, ultrasound guidance or raised inflammatory markers. There was an observed association between increasing age and odds of receiving thromboprophylaxis.

**Conclusion:**

This case-control study did not demonstrate a reduction in the probability of PICC-line associated VTE for patients that were prescribed thromboprophylaxis and in our sample, neonates represented the largest population of patients with PICC line associated VTE but were the least likely to receive thromboprophylaxis.

## **EFFICACY AND SAFETY OF FIBRINOGEN CONCENTRATE FOR CONGENITAL FIBRINOGEN DEFICIENCY IN CHILDREN**

**Bruce Schwartz, S Lohade, Fulton D'Souza, G Latha, Claudia Khayat, O Zekavat, Irina Kruzhkova, Cristina Solomon, Sigurd Knaub, Flora Peyvandi**

*Octapharma, Hoboken, New Jersey, United States*

### **Background:**

Congenital fibrinogen deficiency (CFD) is a rare, inherited bleeding disorder affecting normal blood clotting function, with an estimated incidence of 1:1000000. Symptoms usually present in childhood, where patients experience severe and/or frequent bleeding episodes (BEs). Treatment with human fibrinogen concentrate (HFC) can prevent and arrest bleeding. The rarity of CFD makes it difficult to perform pediatric prospective clinical trials. Here we report safety and efficacy data evaluating the treatment of HFC in pediatric patients (<12 years old) with CFD.

### **Objectives:**

FORMA-04, a multinational, multicenter, prospective, open-label, uncontrolled, Phase III study, aimed to determine the efficacy and safety of HFC (Fibryga®, Octapharma AG), and single-dose pharmacokinetics (reported separately) for treatment of acute BEs and surgical prophylaxis in this pediatric population.

### **Design/Method:**

Hemostatic efficacy in the treatment of BEs, as well as intra- and post-operative efficacy during surgical prophylaxis, was assessed by the physician/surgeon/hematologist with final adjudication by an Independent Data Monitoring and Endpoint Adjudication Committee (IDMEAC) using an objective 4-point scale. Overall hemostatic efficacy was defined as 'success' (excellent or good) or 'failure' (moderate or poor) from the adjudicated scores. Maximum clot firmness (MCF) measured from baseline to 1-hour after each infusion for all BEs served as a surrogate parameter of hemostatic efficacy. Safety was assessed by monitoring adverse events (AEs).

### **Results:**

Fourteen pediatric patients with afibrinogenemia received HFC, of these 8 received HFC for the treatment of 10 BEs (2 major, 8 minor). Mean ( $\pm$ SD) HFC dose per infusion for treatment of BEs was 62.52 mg/kg ( $\pm$ 22.56). Overall hemostatic efficacy for on-demand treatment of BEs was rated as 100% successful by the IDMEAC (95% CI 69.15–100.00). Fibrinogen plasma level and MCF significantly increased from pre-treatment to 1-hour post-infusion, coinciding with hemostatic efficacy. Three patients received HFC for surgical prophylaxis (1 major, 2 minor); intra- and post-operative hemostatic efficacy was rated as successful for all surgeries (100%; 95% CI 29.24–100.00). Overall, 10 AEs occurred in 4 (28.6%) patients. Of these, 2 AEs in 1 patient (pyrexia and portal vein thrombosis) were assessed as possibly related to treatment. The latter AE was classified as serious; occurring after splenectomy performed for a spontaneous spleen rupture, which led to discontinuation from the study. No allergic/hypersensitivity

reactions and no deaths were observed.

**Conclusion:**

This data set demonstrates that treatment with HFC in pediatric patients with congenital afibrinogenemia was efficacious and safe for on-demand treatment of acute BEs and surgical prophylaxis. Study funded by Octapharma AG.

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Poster # 215

**PHARMACOKINETICS OF FIBRINOGEN CONCENTRATE FOR CHILDREN WITH CONGENITAL FIBRINOGEN DEFICIENCY**

**Bruce Schwartz, S Lohade, Fulton D'Souza, G Latha, Claudia Khayat, O Zekavat, Irina Kruzhkova, Cristina Solomon, Sigurd Knaub, Flora Pevvandi**

*Octapharma, Hoboken, New Jersey, United States*

**Background:**

Congenital fibrinogen deficiency (CFD) is a rare, inherited bleeding disorder affecting normal blood clotting function, with an estimated incidence of 1:1000000. Symptoms usually present in childhood, where patients experience severe and/or frequent bleeding episodes. Human fibrinogen concentrates (HFC) can help to prevent and arrest bleeding. Herein we report the single-dose pharmacokinetics (PK) of HFC in pediatric patients (<12 years old) with CFD.

**Objectives:**

FORMA-04 was a multinational, multicenter, prospective, open-label, uncontrolled, Phase III study to determine the efficacy and safety (reported separately), and single-dose PK of a HFC (Fibryga®, Octapharma AG) in pediatric patients with CFD (afibrinogenemia or severe hypofibrinogenemia).

**Design/Method:**

Thirteen afibrinogenemic pediatric patients underwent PK analysis after a single HFC infusion (70 mg/kg), following a 14-day washout period. Blood samples were collected within 30 minutes before HFC infusion, at 1- and 3-hours post-infusion, and at follow-up on Days 2, 5, 7, 10 and 14. Fibrinogen plasma concentration and activity after HFC treatment were calculated and PK parameters analyzed.

**Results:**

The median (range) age was 6.0 (1.0–10.0) years. After the wash-out period, fibrinogen plasma level was at or below the limit of detection of the fibrinogen antigen or activity assays. The mean ( $\pm$ SD) HFC dose administered in the PK population was 73.5 mg/kg ( $\pm$ 0.00). Fibrinogen plasma level increased from baseline (0.0 mg/dL) in all patients ( $p < 0.0001$ ), with a mean peak level observed at 1-hour post-infusion (106.1 mg/dL [ $\pm$ 17.04] with a median [range] of 100.0 mg/dL [92.0–154.0]). Mean ( $\pm$ SD) maximum plasma concentration ( $C_{max}$ ) determined by measuring fibrinogen activity was 1.07 g/L ( $\pm$ 0.17), half-life ( $T_{1/2}$ ) was 63.33 h ( $\pm$ 11.97) and in vivo recovery (IVR) was 1.46 mg/dL/(mg/kg) ( $\pm$ 0.23). Area under the concentration-time curve

(AUC) was 96.60 g\*h/L ( $\pm 21.00$ ), mean residence time (MRT) was 88.03 h ( $\pm 16.82$ ) and clearance was 0.79 ml/h/kg ( $\pm 0.15$ ). Time to reach maximum plasma concentration (Tmax) was 1.46 h ( $\pm 0.88$ ) and volume of distribution (VSS) was 67.63 mL/kg ( $\pm 7.07$ ). The PK profile of HFC was comparable to previous data in patients  $\geq 12$  years old (FORMA-01) for Cmax, VSS, clearance and IVR, and slightly lower for AUC, T1/2, Tmax and MRT.

**Conclusion:**

Results from this study describe the PK profile of pediatric patients with congenital afibrinogenemia after infusion with HFC. The PK profile was comparable to that in adults except for lower AUC, T1/2, Tmax and MRT. The study was funded by Octapharma AG.

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Poster # 216

**VON WILLEBRAND STUDIES DURING ACUTE HEAVY MENSTRUAL BLEEDING MAY BE HELPFUL IN DIAGNOSIS OF VWD**

**Megan Brown, Robert Sidonio Jr.**

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**Background:**

Acute heavy menstrual bleeding (HMB) is common for adolescent females, and inherited bleeding disorders are common. The timing and extent of hemostatic workup for acute HMB in adolescents is extrapolated from adults, and a work up including von Willebrand (VWD) studies is recommended at presentation. Factor VIII (FVIII) and Von Willebrand studies are known to be increased in the setting of physiologic stress and supplemental estrogen use, questioning their diagnostic accuracy in the setting of acute bleeding. Repeat testing is often required for diagnosis of VWD. A von Willebrand factor antigen (VWF:Ag) or VWF ristocetin cofactor level (VWF:RCo) over 100IU/dL has been shown to have a high negative predictive value (NPV).

**Objectives:**

Determine the utility of VWD studies obtained at the time of acute HMB.

**Design/Method:**

We instituted an acute HMB protocol in the emergency departments across our institution as a quality improvement initiative to improve the evaluation and management of adolescents with HMB. Subjects were included if they presented with acute HMB as determined by an adapted Philip Menorrhagia Screening Tool; exclusion criteria include previously diagnosed bleeding disorder, ITP, rheumatologic disease, cancer, or anticoagulation. Descriptive statistics summarized demographic and clinical characteristics. Patients with a positive screen underwent uniform laboratory evaluations. Follow up with hematology and gynecology was encouraged. Data was extracted using various heavy menstrual bleeding ICD-10 codes from January 1, 2017 to December 31, 2018. Individuals with von Willebrand studies at baseline and follow up were identified. T-tests and Wilcoxon rank sum tests were utilized to compare VWF:Ag, VWF:RCo and FVIII at baseline and follow up.



**Results:**

Over the 2-year period, 221 adolescents were evaluated with acute HMB, with 86 (38.9%) requiring admission and 6 (2.7%) requiring intensive care. The population was primarily African-American (63%) with a median age at presentation of 14.8 years (IQR 13.1-16.7). The majority of adolescents had the standard hemostatic labs (55.6%). Forty individuals had baseline and follow-up VWD studies. VWF:Ag, VWF:RCo and FVIII were significantly higher at presentation than follow-up. Of those with a baseline VWF:Ag or VWF:RCo > 100, there was a 92.3% and 95% NPV respectively for VWD. For patients with a normal FVIII level, a VWF:Ag or VWF:RCO >100 had a 100% NPV against VWD.

**Conclusion:**

Among adolescents with acute HMB with confirmatory VWD testing, initial VWF:Ag or VWF:RCo >100 has high NPV, and accuracy is improved with a normal FVIII level. Poor follow-up may give false reassurance against a VWD diagnosis.

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Poster # 217

**ANALYZING COAGULATION DYNAMICS DURING TREATMENT OF VASCULAR MALFORMATIONS WITH THROMBOELASTOGRAPHY**

**Joana Mack, Beverly Spray, Carol D'ann Pierce, Richard Nicholas, Spencer Lewis, Gresham Richter, Shelley Crary**

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**Background:**

Slow-flow vascular malformations are abnormal vessels that can lead to coagulation derangement known as localized intravascular coagulopathy (LIC). LIC occurs due to stagnant blood flow in these lesions, leading to activation and consumption of coagulation factors and thrombosis. Most clinical and research evidence of vascular malformation hemostasis relies on conventional coagulation studies, which may not provide a complete picture of the balance between bleeding and clotting. Thromboelastography (TEG) can provide a real-time assessment of a patient's coagulation dynamics and may allow for a more individualized treatment approach at the bedside.

**Objectives:**

We hypothesized that patients will have changes in TEG parameters during and after procedures that will help predict the need for antiplatelet, anticoagulant or antifibrinolytic therapy.

**Design/Method:**

IRB approved prospective study of patients with slow-flow venous malformation undergoing a sedated procedure between January and September 2019. TEG and conventional coagulation studies (hemoglobin, platelet count, PT, PTT, D-dimer, fibrinogen, von Willebrand (vW) antigen) were obtained pre-procedure, at 15 minutes after start of procedure and if possible, at 30 minutes.

**Results:**

Twenty-five patients were enrolled. Median age 15 years (range 3-47 years). Three patients had laser only, 13 had laser and sclerotherapy and 9 had sclerotherapy only. There were no changes in TEG parameters (R time, K time, alpha angle, max amp, LY 30) from baseline to 15 minutes or 30 minutes. The following decreased from baseline to 15 minutes: fibrinogen 313 to 287 mg/dl (p=0.001), D-dimer 1.3 to 1.1 mg/L (p=0.02), hemoglobin 12.8 to 11.8 g/dl (p=0.001), platelet count 272,000 to 256,000 (p=0.006) and vW antigen 110 to 101% (p= 0.001). There were no significant changes in baseline to 30 minutes (n=8) for conventional coagulation parameters. No patient had a bleeding or thrombotic complication during or within 1 week post-procedure.

**Conclusion:**

In minor procedures, we saw no change in TEG parameters despite changes in the conventional studies, suggesting conventional coagulation studies are not as useful in determining risks of bleeding or thrombotic complications peri-procedural. The study was limited due to the number of patients and short, non-invasive quality of procedures. No patient had significant pre-procedure LIC in this cohort of patients, which may be due to concomitant sirolimus use in 4 patients and peri-procedural prophylactic lovenox in 3 patients due to history of thrombosis and LIC. No patient developed significant coagulopathy post-procedure. vW antigen showed significant decrease during the procedure and additional studies to evaluate this further are warranted.

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Poster # 218

**DIFFICULTIES TO TRANSITION TO ADULT HEMATOLOGY CARE IN VASCULAR ANOMALIES: SURVEY OF ADULT PATIENTS**

**Ionela Iacobas, Mellene Finger, Lisa Klepper, Francine Blei**

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**Background:**

The quality of life and prognosis of patients with vascular anomalies (VA) have improved significantly with advances in surgical/interventional techniques and medical therapies. Since most of the conditions present at birth or during childhood, pediatric specialists are coordinating the care for these patients, who have ongoing medical needs requiring multidisciplinary management. Majority of children's hospitals and clinics have established age cut-offs, after which patients can no longer be followed at pediatric institutions. While for surgical or endovascular interventions it may be easier, adult patients with VAs have great difficulties finding adequately trained physicians willing to take over their medical care.

New targeted agents are on the market with potential for major improvement in symptomatology. Even though the number of adult patients with VAs is significantly higher than the pediatric ones, clinical trials open and are enrolling a disproportionate number of children due to lack of providers for the adult population.

**Objectives:**

To ascertain the challenges adult VA patients face, we collected data from patients  $\geq 18$  years of age with vascular anomalies in collaboration with patient advocacy groups, who posted our anonymous survey on their websites and social media.

**Design/Method:**

Over a 6-month period 238 adult patients responded.

**Results:**

Fifty-four percent of participants have previously received care for their VA from a pediatric specialist. Twenty-six percent continue to be treated by pediatric specialists even after reaching age of maturity.

From the participants receiving care from a pediatric provider, 97% have NO PLAN for when their pediatric specialist can no longer provide care for their VA. Thirty-four percent have given up trying to find a physician willing to provide care. Forty-five percent have no consistent care provider for the VA. Sixty percent are seeing providers who have no special interest or training in VAs.

For those who have consistent care, 18% are seen by hem/onc and 17% by family practice. While 82% have a primary care provider (PCP) and 79% have seen that PCP within the previous year, only 25% report that their PCP usually or always knows important information about the VA. Thirty percent have active or unstable disease and NOT receiving treatment.

**Conclusion:**

Our data supports the need for a generation of hematology-oncology specialists who can manage adult patients with complex vascular malformations. As medical providers for the patients with VAs during infancy and childhood, pediatric hematologists should advocate for continuation of care during adulthood and have an active role in transition programs.

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Poster # 219

**RESPONSE EVALUATION OF SIROLIMUS AND BISPHOSPHONATES FOR THE TREATMENT OF CLA WITH BONE INVOLVEMENT**

**Richard Greiwe, Wendy London, Paige Kao, Ionela Iacobas, Yaser Diab, Karen Fernandez, Kristen Snyder, Sherry Bayliff, Gulraiz Chaudry, Cameron Trenor, Denise Adams**

*Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts, United States*

**Background:**

Generalized lymphatic anomaly (GLA), Gorham Stout disease (GSD) and central conducting lymphatic anomaly (CCLA) can uncompromisingly destroy bone, with significant impact on morbidity, mortality and quality of life. Limited information is published on the effectiveness and safety of the use of sirolimus in combination with bisphosphonates.

**Objectives:**

Based on the addition of mTOR inhibition to bisphosphonate therapy in metastatic cancer therapy, modified regimens have been used for high risk complicated lymphatic anomaly (CLA) patients but limited information is published on the effectiveness and safety of these regimens. Our goal is to apply a newly developed response evaluation definition base of radiologic features in addition to noted symptomatic improvement for the assessment of efficacy for the combination of sirolimus and bisphosphonate therapy in patients with CLA.

**Design/Method:**

An IRB-approved multi-center retrospective review of 25 patients with CLA treated with sirolimus and bisphosphonates was performed at 6 institutions. We evaluated presenting features, treatment and associated side effects, improvement in radiographic abnormalities, symptoms and reported quality of life.

**Results:**

A total of 25 patients were included: 48% GSD (n=12), 36% GLA (n=9) and 16% CCLA (n=4) with an average age of diagnosis of 12.4 months. The most common presenting clinical features consist of pain (n=12), pathologic fracture (n=4), skin lesion (n=4), shortness of breath (n=3), edema (n=2) and leaking/bleeding (n=2). Five patients were asymptomatic but had lesions noted on imaging. Diagnostic imaging modalities used to establish diagnosis and assess response included MRI, CT, Radiography/XR, US and Dexa. Patients received sirolimus and bisphosphonates for an average length of 24.6 months. Average time of response was 9.2 months. Twenty-four patients reported one or more clinical improvements: stable bone mineralization (n=7), stable/decrease size in lymphatic malformation (n=6), stable effusion (n=4), improved pain (n=4), improved imaging (n=4), improved bone mineralization (n=3), improved soft tissue (n=3), improved QOL (n=2), swelling (n=2), leaking/bleeding (n=2) and functionality (n=2). Side effects to sirolimus and bisphosphonates were limited with one Grade III mucositis toxicity. Other reported toxicities included Grade I/II fever (n=8), mucositis (n=3), neutropenia (n=2), acute phase reaction (n=2), hypocalcemia (n=2), lymphopenia (n=1), mouth sores (n=1), nausea (n=1), elevated lipids (n=1), acid reflux (n=1) and arthralgia (n=1).

**Conclusion:**

Sirolimus and bisphosphonates are a safe and effective treatment for CLA with bone lesions. An objective definition of response and improved radiologic classification to describe these disorders is essential. Further study is needed for consensus of treatment dosing and frequency of bisphosphonates.

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Poster # 220

**FREQUENCY OF HEMATOLOGIC AND NON-HEMATOLOGIC COMPLICAITONS  
IN CHILDREN WITH VASCULAR ANOMALIES**

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**Background:**

The frequency of complications in patients with vascular anomalies is not well studied. Identifying the complications and their frequency will be beneficial for a better understanding of the risks and toxicities from various therapies in patients with certain diagnoses. Furthermore, this knowledge will lead to improvement in management, supportive care and clinical practice guidelines.

**Objectives:**

To determine the frequency of hematologic and non-hematologic complications in hospitalized children with vascular anomalies.

**Design/Method:**

With IRB approval, the Pediatric Health Information System (PHIS) database was queried for children < 18 years admitted to pediatric hospitals participating in PHIS between January 2016 and December 2018. The study patients were selected by ICD-10 codes for vascular malformations and tumors based on the International Society of the Study of Vascular Anomalies (ISSVA) classification. Frequency of hematologic complications were determined and compared for patients who did and did not undergo procedures or surgeries. Frequency of non-hematological complications in all patients and those treated with sirolimus were defined. Descriptive statistics were utilized and chi-square tests used for comparisons between two groups.

**Results:**

A total of 641,004 patients were studied with 412,196 patients who underwent a procedure/surgery and 228,808 who did not. The most common hematologic complications in patients who did and did not undergo procedure/surgery were (number in each group): thrombocytopenia (27,387 vs 9,174), iron deficiency anemia (13,662 vs 9,535), epistaxis (5,999 vs 2,531) and melena (6,192 vs 2,846),  $p < 0.001$ . The frequency of complications was significantly higher in patients who had procedures with the highest frequencies in patients with the following diagnoses: complex vascular malformations, lymphatic, venous, arterial and unclassified malformations. The most common non-hematological complications for all patients were (number; percentage): electrolyte imbalance (159,006; 24.81 %), immunocompromised state (50,563; 7.9%), hypotension (42,457; 6.62%), headache (21,695; 3.38%) and seizure (925,009; 3.9%). The highest complication frequencies were observed with the following diagnoses: capillary, arterial and lymphatic malformations and benign, locally aggressive and malignant vascular tumors.

In patients treated with sirolimus ( $n=3,128$ ), the most common complications were: constipation (358), skin changes (332), hypertension (224), hyperlipidemia (92) and hypercholesterolemia (50).

**Conclusion:**

This is the largest study to date of pediatric patients with vascular anomalies investigating complication frequency. We found high frequency of both hematologic and non-hematologic complications. The results will serve as foundation for more extensive research regarding impact of diagnoses, procedures, risk factors and supportive care on rates of complications.

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## **RADIOLOGIC FEATURES OF BONE LESIONS IN COMPLICATED LYMPHATIC ANOMALIES**

**Richard Greiwe, Gulraiz Chaudry, Wendy London, Paige Kao, Ionela Iacobas, Yaser Diab, Karen Fernandez, Kristen Snyder, Sherry Bayliff, Cameron Trenor, Denise Adams**

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### **Background:**

Generalized lymphatic anomaly (GLA), Gorham Stout disease (GSD) and central conducting lymphatic anomaly (CCLA) are complicated lymphatic anomalies (CLA) that uncompromisingly destroy bone, with significant impact on morbidity, mortality and overall quality of life. Classification and diagnosing are challenging due to overlapping clinical, imaging and histologic features. Timely and accurate diagnosis is essential as individuals experience morbidity secondary to numerous complications such as respiratory distress, organ dysfunction, pathologic fractures, infection, functional impairment, disfigurement and even death.

### **Objectives:**

Our goal was to describe the radiologic features of CLA and use the descriptions to improve classification, diagnosis, and evaluation of response. To address this goal, we aimed to create defined radiologic scoring forms (RSF) summarizing the presence or absence of radiographic features for each diagnosis.

### **Design/Method:**

An IRB-approved prospective registry was used to identify 18 patients that had bony CLA and at least two sets of films prior to initiation of treatment with sirolimus and bisphosphonates. Patients needed to be treated for at least 3 months and have post treatment imaging. We hypothesized that using defined radiologic scoring forms for each CLA would improve the accuracy of diagnosis. Two blinded CLA expert radiologists reviewed the imaging and labeled them with a final consensus diagnosis. Using this scoring system, this was expanded to 13 additional patients at 5 other institutions with vascular anomaly centers. Patients with other diagnoses or insufficient data were excluded from the study.

### **Results:**

Initially, 18 pilot patients were radiologically reviewed. One discrepancy was found using the radiologic diagnostic scoring forms. Five patients lacked sufficient records and were lost to follow up. These six patients failed to meet eligibility and were excluded from the study due to a change in diagnosis or insufficient records. Using the RSF to reevaluate the additional 13 patients at 5 outside institutions, no discrepancies in diagnosis were found. The combined 25 patient cohort included 48% GSD (n=12), 36% GLA (n=9) and 16% CCLA (n=4). Diagnostic and/or response imaging included MRI, CT, US, Lymphangiogram, Lymphoscintigraphy and Radiography/XR. Our results support establishing a radiologic classification is needed to accurately diagnose and consequentially evaluate response of CLA with bone lesions.

**Conclusion:**

Using this scoring system for further consensus of diagnosis, improvement in radiologic classification and better definition of response of CLA with bone involvement will be obtained. Further investigation is needed to improve definition of response and radiologic classification to describe CLA with bone involvement.

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Poster # 222

**FIBROADIPOSE VASCULAR ANOMALY PATIENT-REPORTED BASELINE AND POST-TREATMENT QUALITY OF LIFE OUTCOMES**

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**Background:**

Fibroadipose vascular anomaly (FAVA) is a rare, recently-defined painful anomaly with unknown outcomes. A large amount of research has been done looking at clinical presentation of FAVA, but there is minimal evaluation of clinical outcomes and even less assessment of patient-reported outcomes.

**Objectives:**

Our goal is to prospectively follow clinical and subjective patient outcomes by assessing quality of life (QOL) measures at baseline and after medical, surgical or radiologic treatment.

**Design/Method:**

Thirty-four patients in an IRB-approved prospective study were administered PROMIS surveys consisting of various mental, physical and social health constructs appropriate for this group. Patients were surveyed at enrollment, 1 month, 6 months, 1 year and 18 months. If intervention occurred, the survey timeline started over from date of intervention. Patients unable to read the survey in English were excluded from participating in the study.

**Results:**

Among the 34 patients with baseline data, 31 patients had data on T-scores. The mean age at presentation was 19.2 years (SD=8.5, range: 5, 79). Seventy-seven percent (n = 24) were female and 90.33% (n = 28) were white. PROMIS measures are standardized with a score of 50 representing the average US population. Sixteen percent had elevated scores at baseline. Average mobility ( $41.7 \pm 12$ ), pain interference ( $57.1 \pm 9.4$ ), anxiety ( $54.3 \pm 9.1$ ), fatigue ( $53.7 \pm 12.9$ ) and pain behavior ( $51.9 \pm 9.4$ ) were elevated compared to the average population. Lower extremity data was included in the mobility survey. Depression ( $49.7 \pm 9.8$ ) and upper extremity scores ( $50.8 \pm 9.3$ ) were consistent with the population average. Nine patients had data on post-intervention T-scores. Twenty-two percent of patients (n = 2) had elevated scores pre-treatment. Mean pre-treatment T-scores of mobility ( $38.3 \pm 8.3$ ), pain interference ( $58.4 \pm 6.4$ ), fatigue

(55.9 ± 12.1), anxiety (55.7 ± 10.2), upper extremity (53.5 ± 5.5) and pain behavior (53.2 ± 7.0) were elevated. Depression scores (50.7) were fairly consistent with the average population. Our results show statistically significant improvements in anxiety (reduction=6; 95% CI: 0.3, 11.7; p=0.041) and pain interference (reduction=7.9; 95% CI: 0.3, 15.6; p=0.043) six months post-treatment. All other QOL measures improved at six months but didn't reach statistical significance: pain behavior (43.4), mobility (45.0), fatigue (50.5), depression (46.1) and upper extremity (52.8).

**Conclusion:**

FAVA is a complex anomaly that typically presents with pain and dysfunction in an extremity during childhood. Assessment of clinical and patient-reported outcomes of FAVA patients is important to assess treatment response.

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Poster # 223

**IMAGING OF BONY LYMPHATIC DISORDERS**

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**Background:**

Osseous lymphatic disorders are a group of complex lymphatic anomalies that cause a variety of bony and soft tissue lesions. The main lymphatic disorders that affect bone and soft tissue include Gorham Stout disease (GSD), generalized lymphatic anomaly (GLA), central conducting lymphatic anomaly (CCLA), and kaposiform lymphangiomatosis (KLA). These disorders may overlap clinically and radiologically.

**Objectives:**

Early diagnosis of these similar conditions is key as they have long term outcomes ranging from non-progressive to a high risk of mortality. The purpose of the study was to identify radiologic features that best help to differentiate these conditions by analyzing the skeletal and soft tissue changes.

**Design/Method:**

Clinical data and imaging study findings were retrospectively reviewed in patients presenting to our Vascular Anomalies Center with lymphatic anomalies of bone. We proposed to discriminate these entities by analyzing findings on skeletal and soft tissue imaging using radiographs, CT and MRI. Images were independently reviewed by two pediatric radiologists who were blinded to the patient's identifiers and diagnosis. Patients without imaging of lesions were excluded from the study.

**Results:**

Within a cohort of 174 patients with lymphatic involvement and radiological evidence of bony involvement, four distinct phenotypes emerged: GLA (n=78), GSD (n=44), CCLA (n=26) and



KLA (n=26). On average, patients were diagnosed 6.0 years after initial presentation. Peri-osseous soft tissue involvement was found in 73% of GSD, 31% of KLA, 23% of CCLA and 13% of GLA. Homogenous T2 signal was found in 53% of GLA, 44% of CCLA, 24% of GSD and 14% of KLA. Channel appearance was found in 32% of CCLA, 8% of KLA, 3% of GLA and 0% of GSD. Soft tissue involvement of the tracheobronchial tree was seen in 31% of patients with KLA and 0% of the other disorders. Gorham-Stout disease is characterized by confinement to one contiguous anatomical area, destruction of the bony cortex and peri-osseous soft tissue enhancement. Patients with GLA typically had multifocal lytic lesions, but without evidence of dilated central channels or significant peri-osseous soft tissue disease. Bony involvement in CCLA is limited with intraosseous channel-like appearance. KLA was characterized by more significant mediastinal involvement, pericardial effusions and splenic lesions.

**Conclusion:**

Osseous and periosteal manifestations of central conducting lymphatic anomaly, generalized lymphatic anomaly, kaposiform lymphangiomatosis and Gorham Stout disease can be reliably differentiated based on imaging features.

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Poster # 224

**ANC AND ALC DURING SIROLIMUS IN PATIENTS WITH NON-COMPLICATED VASCULAR OR LYMPHATIC ANOMALIES**

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**Background:**

Sirolimus is an immunosuppressive drug that is widely used in solid organ and bone marrow transplantation, and more recently for the treatment of vascular and lymphatic anomalies. Sirolimus has been associated with decreased immunity in the transplant setting in patients that have received other immunosuppressive drugs or were immunosuppressed from previous chemotherapy. The effects of Sirolimus on the immune system in patients with vascular and lymphatic anomalies are not well understood, and there is variability in the approach to fever and PJP prophylaxis.

**Objectives:**

To determine if there is a difference in the ANC and ALC of children with non-complicated vascular or lymphatic anomalies who receive sirolimus and have not received other immunosuppressive agents or chemotherapy.

**Design/Method:**

We conducted a multi-institutional retrospective review from 4 institutions of 40 cases with non-complicated vascular or lymphatic anomalies treated with Sirolimus and analyzed absolute neutrophil count (ANC), absolute lymphocyte count (ALC) prior to and after 1 or 3 months Sirolimus therapy (SIR-1 and SIR-3, respectively). Those with effusions, multiorgan involvement, or history of infections prior to treatment were excluded.

**Results:**

Forty patients with KHE (n=9), GLA=4), CLOVES syndrome (n=1), VM +/- LM (n=23), and other (n=3) were included. Age at initiation of Sirolimus ranged from 0.5–20 years. Male to female ratio was 1:1. Sirolimus was initiated due to extensive disease, lack of response to other therapies, pain, disfigurement, lymphatic drainage, and prevention of ongoing overgrowth. There was no significant change in the ANC and ALC before (SIR-0) or after Sirolimus. The mean ANC at SIR-0, SIR-1 and SIR-3 were: 2585/?L, 2856/?L and 4089/?L. The mean ALC SIR-0, SIR-1 and SIR-3 were: 3050/?L, 3478/?L, 2890/?L. Mean Sirolimus levels at SIR-1 and SIR-3 were 7.8 ng/mL and 7.4 ng/mL respectively. Eleven patients were placed on PJP prophylaxis. Infectious complications while on Sirolimus were not reported at a median follow-up of 30 months. One patient had neutropenia (ANC<500ng/mL) which normalized after discontinuation of PJP prophylaxis.

**Conclusion:**

In this small cohort of patients we found that the ANC and ALC level in patients with non-complicated vascular or lymphatic anomalies at SIR-0 was not different from the SIR-1 or SIR-3. Prospective studies that specifically track ANC, ALC, IgG, and lymphocyte function should be conducted to better understand the effects of Sirolimus in the immune system and to allow for standard recommendations regarding PJP prophylaxis and management of febrile episodes.

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Poster # 225

**A CASE FOR PROPHYLAXIS: CONGENITAL FACTOR VII DEFICIENCY**

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**Background:**

Congenital factor VII deficiency is a rare bleeding disorder inherited in an autosomal recessive pattern and caused by mutations in the F7 gene. Symptoms and severity are highly variable as bleeding propensity does not correlate with the level of Factor VII. We report the initial evaluation, symptoms, and treatment course of a 12-month-old female with a new diagnosis of severe Factor VII deficiency.

**Objectives:**

To present a rare disorder and decision making for prophylactic treatment.

**Design/Method:**

A case report

**Results:**

At 12 months of age, our patient presented for hematology evaluation with mucosal bleeding, palpable bruising, and intermittent periods of refusal to bear weight on her lower extremities. She had recently been treated for presumed pyomyositis of her thigh. She was born by vaginal

delivery and had an uneventful antenatal period. At presentation, her PT was >150s, PTT 29s, INR > 12.6. PT mixing study normalized to 11.6s. Lupus anticoagulant testing was negative. Factors II, IX, X, Protein C and Protein S were normal. Next generation sequencing of the F7 gene revealed homozygosity for sequence variant c. 1272G>A, predicted to result in a premature protein termination and likely pathogenic.

Family deferred prophylaxis with recombinant activated Factor VII until genetic testing was finalized. While awaiting results, she sought care for afebrile meningismus. MRI revealed an early subacute hemorrhage of the cerebellum and widely-extending extra-axial hemorrhage throughout the cerebrum. Extensive subdural hemorrhage involving the entire spinal canal to the S2 vertebral body was found. Recombinant activated Factor VII was initiated (30mcg/kg every 4 hours). Treatment is ongoing.

### **Conclusion:**

We present a case of a 12-month-old with newly diagnosed severe Factor VII deficiency who presented with meningismus due to intracranial and spinal canal hemorrhage. In general, Factor VII deficiency exhibits a poor genotype-phenotype relationship with bleeding symptoms ranging from lethal to asymptomatic. Prophylactic therapy with factor concentrate is a reasonable intervention for those at most risk with severe deficiencies, however, there are no clear dosing guidelines nor criteria for treatment initiation. In our case, our patient had an intracranial and spinal canal hemorrhage while considering prophylactic therapy. Luckily, recombinant factor VII was effective initial treatment for intracranial hemorrhage and she did not require neurosurgical intervention. Despite the disease's clinical heterogeneity, prophylactic treatment with recombinant Factor VII should be considered at initial presentation in patients with severe deficiencies at a young age to avoid intracranial hemorrhage.

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Poster # 226

## **GAME AT YOUR OWN RISK: A SPONTANEOUS UPPER EXTREMITY DVT IN AN AVID VIDEO GAMER**

**Lora Bojilova, Stephanie Segura, Kerice Pinkney**

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### **Background:**

Recent studies show an increasing incidence of childhood venous thromboembolism (VTE). Since childhood VTE is often secondary to the presence of central venous catheter (CVC) use, this rising trend is likely related to increased use of CVCs in chronic complex patients (1). Other factors such as childhood obesity and inactivity also play a role. Unprovoked non-CVC related VTEs are most common in the deep veins of the lower extremities and multiple reports have been published on obese adolescent gamers developing lower extremity deep venous thromboses (DVT) and/or pulmonary embolisms. Primary upper extremity DVTs are rare and usually the product of repetitive activity in the setting of anatomic predisposition. The only published report of upper extremity DVT associated with prolonged video game play occurred in an adult (2). Here we present an unusual case of spontaneous upper extremity DVT in a non-obese adolescent

gamer.

**Objectives:**

Describe a unique case of spontaneous DVT and discuss the importance of screening adolescents for prolonged video game play.

**Design/Method:**

Case report.

**Results:**

A 17-year-old healthy non-obese male presented with a 3-month history of intermittent arm swelling and increase in head and ear pressure with positional changes. Three days prior to presentation he developed intermittent facial swelling and spider-like veins on his chest. He denied chest pain, dyspnea, and lower extremity edema or pain. He reported a sedentary routine, spending upwards of 10 hours at a time playing video games. He denied drug use and family history of coagulopathy. On examination he was hemodynamically stable. He had facial, left upper arm, and left chest edema with scant sternal petechiae. Imaging revealed a left brachiocephalic vein thrombus with involvement of the left internal jugular and subclavian veins. He was started on unfractionated heparin with symptomatic improvement and will complete 6 months of therapy with subsequent reimaging. His hypercoagulability work-up has been negative. On extensive review, the only notable contributing factor for his thrombosis was prolonged gaming.

**Conclusion:**

Video games are a growing part of adolescent life. With gaming often leading to prolonged periods of immobility, extensive video game play must be considered a risk factor for DVT. We recommend that Pediatricians incorporate frequent surveillance of DVT risk factors and provide anticipatory guidance on the risks associated with prolonged video game play and a sedentary lifestyle. References: (1) Boulet SL et al, Pediatrics, 2012. (2) Phipps C, The American Journal of Medicine, 2008.

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Poster # 227

**FIBRYGA FOR MANAGEMENT OF CONGENITAL FIBRINOGEN DEFICIENCY WITH SEVERE BLEEDING COMPLICATIONS**

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**Background:**

Congenital quantitative fibrinogen disorders include afibrinogenemia and hypofibrinogenemia. Congenital afibrinogenemia is the complete absence of serum fibrinogen, usually resulting from homozygous or compound heterozygous loss-of-function (null) mutations in the FGA gene, which codes for the fibrinogen alpha chain. Hypofibrinogenemia is defined as circulating fibrinogen <150 mg/dL and usually results from heterozygous mutations of afibrinogenemia.

Diagnosis is confirmed with demonstration of absent or decreased plasma fibrinogen by both functional assay and immunoassay. Given these disorders are very rare, evidence to guide management is scarce. The main goal is to prevent serious bleeding complications. Treatment includes primary and secondary prophylaxis with fibrinogen concentrates or plasma products as well as management of acute bleeding.

**Objectives:**

Describe a case of an 8-year-old male with congenital quantitative fibrinogen deficiency who presented with an intramuscular hematoma in the newborn period secondary to routine vitamin K injection. Over time he developed breakthrough hemarthroses while on prophylaxis which was effectively managed with scheduled prophylactic FIBRYGA.

**Design/Method:**

Chart review on a patient with hypofibrinogenemia.

**Results:**

The patient is an 8-year-old male who presented at 10 days of life to our institution with worsening intramuscular hematoma of the right thigh following perinatal vitamin K intramuscular injection. Initial laboratory studies revealed PT >120s and PTT >245s, factor V activity 97 UI/dL and factor X activity 105 UI/dL. Serum fibrinogen was < 50 mg/dL. He was initially managed with cryoprecipitate infusions q2wks and aminocaproic acid PRN for acute bleeding. He was transitioned to RiaSTAP 70 mg/kg q2wks at 2 years of age due to skin reactions with cryoprecipitate infusions. He continued to have breakthrough hemarthroses while on RiaSTAP prophylaxis and was switched to FIBRYGA infusions q2wks at 7 years of age. To date, he has had no breakthrough bleeding on his current regimen.

**Conclusion:**

Congenital fibrinogen deficiency disorders are rare. Management varies depending on the severity of bleeding complications. Here we describe the case of an 8-year-old boy with congenital quantitative fibrinogen deficiency and a history of severe bleeding complications effectively managed with scheduled FIBRYGA prophylaxis.

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Poster # 228

**NOVEL PRENATAL DIAGNOSIS OF PROTEIN C DEFICIENCY AND PRIMARY PROPHYLAXIS WITH PROTEIN C CONCENTRATE**

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**Background:**

Severe protein C deficiency (SPCD) is a rare inherited thrombophilia that has high morbidity and mortality. Currently, standard treatment includes protein C concentrate and anticoagulation acutely followed by long-term secondary prophylaxis with chronic anticoagulation.

**Objectives:**

To describe a case series of siblings diagnosed with severe protein C deficiency and the use of primary prophylaxis.

**Design/Method:**

Case series.

**Results:**

A 2 day-old term male presented with progressive apneic episodes that required mechanical ventilation. Brain magnetic resonance imaging (MRI) was performed that showed cerebral edema and limited diffusion consistent with right-sided sub-acute infarct and thromboembolic stroke. Additionally, he had extensive venous thrombosis involving the inferior vena cava on ultrasound. Coagulation labs were remarkable for protein C activity of 12 percent (28-54 percent normal). He was started on long-term anticoagulation with enoxaparin, which was continued at discharge. About six months later, he was found to have persistent low protein C level at 37 percent (60-130 percent normal), so genetic testing was performed. Results demonstrated a compound heterozygous mutation (c.699G>T; c.326\_330dup). Along with these genetic findings, he had a protein C level of 51 percent (60-130 percent normal) at 12 months of age, so he was diagnosed with SPCD. He was continued on chronic anticoagulation. Since then, he has had no further thrombosis or complications. Following his diagnosis, his mother became pregnant and had in utero testing with amniocentesis. Genetic testing showed that he had the same mutation as the first patient, which was concerning for SPCD. Due to this prenatal diagnosis, treatment was initiated immediately after birth to provide primary prophylaxis. Initial labs revealed protein C activity of 6 percent (24-44 percent normal). Protein C concentrate of 66 units per kilogram (goal of 60-80 units per kilogram) was given every twelve hours and titrated to achieve protein C activity trough of 25 percent. He had no thrombosis and had one bleeding complication (hepatic hematoma). He was transitioned to anticoagulation with enoxaparin and discharged to home.

**Conclusion:**

SPCD has proven to be a difficult disease to study due to its scarcity, but it remains clinically significant and devastating to patients. This case series highlights a potentially clinically relevant genetic variant and demonstrates effective primary prophylaxis.

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Poster # 229

**VON WILLEBRAND DISEASE TYPE 2A DUE TO A RARE VON WILLEBRAND FACTOR MISSENSE MUTATION**

**Jennifer Van Helmond, Aarushi Chopra, Jessa Hernandez, Sukrita Mysore, Rafat Ahmed**

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**Background:**

Von Willebrand disease (vWD) is the most common inherited bleeding disorder and is caused by

mutations in the vWF gene resulting in lack or dysfunction of von Willebrand factor (vWF). Most patients present with mild symptoms and few patients are diagnosed. vWD associated severe bleeding occurs in 1 in 10,000 affected individuals. Inheritance can exhibit either an autosomal recessive (Type 2N and 3) or an autosomal dominant (Type 1, 2A, 2B and 2M) pattern. The clinical presentation for patients with Type 2N disease can mimic hemolytic anemia and is therefore commonly misdiagnosed. Platelet-type vWD (also called pseudo-vWD) is due to a mutation in a different gene, GP1BA.

**Objectives:**

To present a case of type 2A vWD in an infant due to a rare missense mutation of the vWF gene.

**Design/Method:**

An 8 month old male presented to the pediatric hematology/oncology clinic for a history of epistaxis. His family history was significant for severe vWD in his paternal aunts and recurrent epistaxis and prolonged bleeding in his father. His initial workup revealed prolonged PTT of 38 sec, low factor VIII activity of 10%, low levels of vWD antigen of 11%, vWD factor activity of 12% and vWD multimer analysis was abnormal with loss of a subset of the high molecular weight multimers, specifically only the very highest molecular weight multimers. This may occur in type 2 vWD, platelet-type vWD, and in certain forms of acquired von Willebrand syndrome. Due to his complex hematologic family history and clinical presentation, a complete vWD genetic panel was ordered to determine if a genetic bleeding disorder was present in this patient.

**Results:**

On the targeted next gene sequencing panel for the complete vWD gene, the patient was found to be heterozygous for missense variant mutation (c.4241T>G, p.Val1414Gly) in exon 28 of the vWF gene. This variant has previously been observed in only one other patient with type 2A vWD to our knowledge. This variant does not have an established minor allele frequency, and is thus very rare.

**Conclusion:**

We identified a rare vWF gene missense mutation in an 8 month old infant presenting with epistaxis and a family history of prolonged bleeding. He was found to have Type 2A vWD, which represents a problem with vWF multimers. Gene sequencing can identify the causative mutation and subtype of vWD, which is important to guide treatment and future care.

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Poster # 230

**MYCOPLASMA PNEUMONIAE INFECTION ASSOCIATED WITH MULTIPLE DEEP VENOUS THROMBI**

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**Background:**

*Mycoplasma pneumoniae* is a common etiology of pneumonia in children and can be associated with cold agglutinins leading to secondary cold agglutinin syndrome (CAS). Thromboembolic events are rare extrapulmonary complications.

**Objectives:**

We describe the case of an adolescent female with a recent *M. pneumoniae* infection who developed deep venous thrombosis (DVT) in multiple extremities.

**Design/Method:**

Case Report

**Results:**

A 16 year-old African-American female developed acute onset left upper arm and right calf pain and swelling. She was discharged four days earlier following a course of azithromycin for lobar pneumonia due to *M. pneumoniae* based on a respiratory biofire test. At presentation, she was hypoxic, tachypneic, and had tenderness and swelling of both involved extremities. Doppler ultrasonography confirmed thrombi in the right lateral posterior tibial vein and left basilic vein extending into the brachial vein. Imaging was negative for pulmonary embolism (PE). Peripheral smear demonstrated RBC agglutination which prevented complete blood count analyses due to clumping. Cold agglutinin titer was elevated at 1:64. Coagulation studies showed a mildly prolonged prothrombin time and elevated fibrinogen level. D-dimers were high at 7.25 mcg. Coomb's test was positive for C3D on a prewarmed serum confirming cold agglutinin disease. C3 complement (205 mg/dL) was elevated while C4 (37 mg/dL) was normal. *Mycoplasma* IgG (3.15 U/L) and IgM (6.67 U/L) levels were elevated. Thrombophilia workup revealed a positive lupus anticoagulant test, heterozygous factor V Leiden gene mutation, elevated beta 2 glycoprotein (>150 SMU), cardiolipin IgG (43 GPL) and IgM (96 MPL). Autoimmune work up was performed due to strong family history of systemic lupus erythematosus (SLE). Her SLE screen was positive for antinuclear antibody but anti-double-stranded IgG DNA, and anti-Smith IgG antibodies were negative. Hepatitis panel, syphilis and HIV screen were negative. The patient received low molecular weight heparin with resolution of DVT by six weeks of anticoagulation.

**Conclusion:**

Etiology of thrombosis following *M. pneumoniae* infection remains unclear. Proposed mechanisms include autoimmune modulations leading to transient antiphospholipid and anticardiolipin antibodies. Few cases of DVT involving cerebral, carotid, mesenteric, and splenic vessels have been described. Cardiac thrombus and PE have also been reported including a single case report of two separate DVT which was associated with PE. In summary, *M. pneumoniae* infection may predispose to thrombosis and transient elevation of antiphospholipid antibodies.

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Poster # 231

**THROMBOSIS SECONDARY TO IDIOPATHIC HYPEREOSINOPHILIC SYNDROME:  
CASE REPORT AND LITERATURE REVIEW**



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**Background:**

Hypereosinophilic syndrome (HES) is characterized by a persistent blood eosinophilia and eosinophil-related end-organ damage, with no identifiable source. It is defined as an absolute eosinophil count (AEC) above 1500. Eosinophil production from the hematopoietic progenitors is regulated mainly by interleukin-5 (IL-5), which plays a role in Eosinophil maturation, differentiation, activation and survival. HES can present as six clinical variants: myeloproliferative HES, lymphocytic variant HES, overlap HES, associated HES, familial HES, and idiopathic HES.

**Objectives:**

To report an adolescent with extensive thrombosis secondary to idiopathic HES, review of existing literature.

**Design/Method:**

Medical record, radiographic imaging, pathology including molecular analyses, and literature were reviewed.

**Results:**

A previously healthy 15-year-old male presented with a new onset macular/petechial rash, fevers and left leg pain. At presentation he had a left femoral deep vein thrombosis, severe thrombocytopenia and hypereosinophilia (HE) with 20% eosinophils and an AEC of 2600. Patient was started on anti-coagulation therapy, he then developed dyspnea and imaging revealed bilateral pulmonary emboli while hypereosinophilia continued to worsen and severe thrombocytopenia persisted. He had an extensive work-up for underlying etiologies of hypereosinophilia including immunoglobulin levels, Echocardiogram, CT of Chest/Abdomen/Pelvis as well as bone marrow biopsy and aspirate including cytogenetics and FISH for FIP1L1/PDGFR, BCR-ABL1, PDGFRB, JAK2, FGFR1, KIT mutations to assess for malignancies such as M-HES, L-HES or lymphoma. In addition, he also had testing to exclude T cell clonality disorders, auto-immune and infectious etiologies. All of these were normal, except for a cytokine panel which revealed an elevated IL-5 level. Once Churg-Strauss and parasitic etiologies were ruled out and he reached an AEC of 5600, he was started on high-dose steroids which led to a prompt reduction of his AEC and correction of his thrombocytopenia. Patient was then bridged over to mepolizumab, which is an IL-5 inhibitor to treat his idiopathic HES and steroids were slowly tapered. He has been stable with monthly infusions of mepolizumab.

**Conclusion:**

Venous thromboembolism (VTE) is an important feature of HES. In our patient, an underlying etiology for hypereosinophilia and VTE was not identified. Idiopathic HES is diagnosis of exclusion, therefore extensive work-up should be performed in search of an underlying etiology. When life-threatening symptoms are present, corticosteroid therapy should be initiated promptly

and steroid-sparing therapies such as IL-5 targeted therapies should be considered to reduce required steroid dose to a minimum.

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Poster # 232

## **MILD HEMOPHILIA A POSING AS VASCULAR LESIONS: CASE REPORT**

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### **Background:**

Hemophilia A, also known as factor VIII (FVIII) deficiency, is an X-linked bleeding disorder of variable severity based on FVIII levels. The hallmark of severe hemophilia A is spontaneous hemarthrosis, while persons with mild hemophilia A typically bleed with trauma and/or surgical challenges. Family history (FH) of hemophilia A aids in diagnosis, however, in up to 30% of cases, there is no FH.

### **Objectives:**

Describe a patient with no FH of bleeding who presented with a persistently bleeding tongue lesion and a forehead “bump” that were suspicious for vascular lesions. Laboratory analysis confirmed mild hemophilia A diagnosis.

### **Design/Method:**

Case report

### **Results:**

A two-year-old boy with no significant past medical history or FH presented to the emergency room for recurrent bleeding from a tongue lesion. The tongue lesion was felt to be a bleeding hemangioma and area was debrided with silver nitrate applied. Hemostasis was achieved, but short-lived. The tongue lesion rebled and he was taken to the operating room (OR) for biopsy of lesion and hemostasis control. Debridement in the OR showed a bleeding laceration which was cauterized. MRI with/without contrast of the face demonstrated a T2 hyperintense enhancing nonspecific (tongue) lesion. Incidentally, he had a forehead “bump” on physical exam for which the same MRI was suspicious for a venous malformation. CT head without contrast supported the same forehead soft tissue nodule was most likely a venous malformation. Prothrombin time (PT) and PTT subsequently resulted with normal PT and elevated PTT. Factors obtained were normal with the exception of FVIII 7%, consistent with mild hemophilia A diagnosis. He received a dose of replacement FVIII and scheduled antifibrinolytics with resolution of bleeding. At follow up, both tongue lesion and forehead “bump” had resolved.

### **Conclusion:**

Persons with mild hemophilia A do not have spontaneous bleeding, are often not diagnosed until later in life, or after trauma or surgical procedures. This patient presented with no FH of bleeding diathesis, no recent trauma or surgical procedures, with a recurrent bleeding tongue lesion and forehead hematoma. Initial exam of tongue lesion and imaging was suspicious for vascular

lesions, but laboratory analysis confirmed diagnosis of mild hemophilia A. This case stresses the importance of consideration of bleeding disorders in the differential diagnosis of persistently bleeding oral lesions despite physical exam and imaging findings suggestive of other diagnosis.

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Poster # 233

## **SIROLIMUS FOR LIFE-THREATENING KAPOSIFORM HEMANGIOENDOTHELIOMA WITH KASABACH-MERRITT PHENOMENON**

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### **Background:**

Kaposiform Hemangioendothelioma (KHE) with the Kasabach-Merritt phenomenon (KMP) is a rare vascular tumor associated with thrombocytopenia and consumptive coagulopathy. KMP which is one of the possible life-threatening complications of KHE has several therapeutic options but the standard therapy for KHE has not set up yet.

Several studies reported recently the effectiveness of Sirolimus, which is a mammalian target of Rapamycin (mTOR) inhibitor has been used extensively in children following solid organ transplantation.

### **Objectives:**

we report a successful therapy using sirolimus for life-threatening KHE complicated with KMP, which failed to respond to multiple interventions.

### **Design/Method:**

We prospectively evaluated a case of patient with complicated KHE and TA treated with sirolimus, mTOR inhibitor, in single-center with multidisciplinary cooperation as Vascular Anomalies Clinic. Dosage of sirolimus was 0.8 mg/BSA per dose twice a day, with adjusting the target drug levels of 10 to 15 ng/mL. The subjective response was checked every 3 months and imaging response using MRI was checked every 6 months.

### **Results:**

A 2-month-old female presented with a tender dusky purplish tumor (6x7cm) on the left upper arm since 1-month-old. The histopathological finding was consistent with KHE in addition to the pathognomonic kaposiform vascular area.

By clinical-laboratory findings, the patient presented anemia (Hb 8.6g/dL), thrombocytopenia (platelet 13k/uL), elevated D-dimer, decreased fibrinogen, necessitating hospitalization. After admission, she was treated with antibiotics IV, propranolol PO, steroid IV, vincristine IV, IVIG during hospitalization for 2 months. The lesion relapsed and aggravated progressively. So Sirolimus (0.1mg/kg/day) was tried showing dramatic clinical improvement. Within 14 days of commencing Sirolimus, the platelet count had risen to normal range (135k/uL). With monitoring of the target drug level, presently she is receiving 0.5 mg/kg/day for 2 years.

Although she has several complications including oral ulcers, diarrhea, pneumonia and diarrhea in early phase, Sirolimus was tolerable, and effective showing nearly complete response and

normal developmental growth.

**Conclusion:**

We report a successful therapy using sirolimus for life-threatening KHE complicated with KMP, which failed to respond to multiple interventions.

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Poster # 234

**A RARE PEDIATRIC CASE OF EPITHELIOID HEMANGIOENDOTHELIOMA**

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**Background:**

Epithelioid hemangioendothelioma (EHE) is an extremely rare tumor of blood vessels. It affects 1:1 million with about 20 new cases diagnosed each year. Although EHE can occur anywhere in the body and at any age, it typically presents in patients aged 30 to 50 and affects the liver, lung, and bones. EHE is generally slow-growing with low-grade malignant potential. The mainstay of treatment is surgical resection, but in cases where it is unresectable, radiation, chemotherapy, immunotherapy or anti-angiogenic agents have been used.

**Objectives:**

To describe a case of a pediatric patient with EHE and review the literature to formulate a plan for follow-up of this patient.

**Design/Method:**

Case Report

**Results:**

The patient is a previously healthy 17-year-old female who presented with a painful mass on her left flank that had been present and slow growing for over a year. Pathology findings that were consistent with EHE included epithelioid, spindle and blister cells, positive stain for CD 31 and CD 34 and the t(1;3)(p36.3;q25) mutation which is associated with EHE. Due to the potential to metastasize, a PET/CT was performed which noted radiotracer uptake in a rounded soft tissue density within the left anterior abdomen, as well as a left inguinal lymph node. She had a surgical resection of the scar around the original lesion, the inguinal lymph node and the left abdominal mass. Pathology of these lesions showed no residual tumor around the scar of the previous excision, but both the lymph node and the abdominal lesion were found to be EHE and were completely excised. In review of the literature, pediatric EHE is extremely rare. Three case reports in the literature describe cutaneous EHE with lymph node metastasis either at diagnosis or found within a few weeks of diagnosis. Because of the metastatic potential described in these cases, as well as the patient depicted here, follow-up is important to detect evidence of recurrence.

**Conclusion:**

EHE is slow growing and is extremely rare in the pediatric population. Though unlikely, it has the potential for metastatic spread. Patients with EHE should undergo metastatic work-up at diagnosis and follow-up scans after their primary lesions have been fully excised. Evaluation should include imaging of the primary site, draining lymph nodes, and abdominal/chest imaging for possible hepatic or pulmonary metastatic disease.

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Poster # 235

## **A RARE CAUSE OF THROMBOSIS: VASCULAR MALFORMATIONS IN THREE ADOLESCENT ATHLETES**

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### **Background:**

Deep vein thrombosis (DVT) is a rare pediatric event with reported incidence of 1 in 10,000 requiring evaluation for risk factors that impact treatment options. Despite appearing in less than 1% of the population, congenital vascular malformations represent a significant cause and independent risk factor for DVT. These thrombotic events are reported in a range of ages but frequently present in young adulthood after an asymptomatic childhood.

### **Objectives:**

We describe three cases of previously healthy adolescent athletes who presented with DVTs secondary to vascular abnormalities. Two patients were diagnosed with Inferior Vena Cava Agenesis (IVCA) and a third patient had Paget Schroetter Syndrome (PSS).

### **Design/Method:**

We review three clinical cases and provide a summary of existing medical literature. Patient 1, a 15-year-old male football player, presented with acute left leg swelling and pain. Doppler US confirmed a DVT treated with 12 months of anticoagulation. Complete IVCA was demonstrated on CT scan obtained when he had a second DVT approximately 1 year off anticoagulation. Patient 2, a previously healthy 17-year-old male basketball player, developed right lower extremity swelling and pain after being admitted for mild diabetic ketoacidosis for new onset type 1 diabetes. He was diagnosed with extensive bilateral DVT and infrarenal IVCA noted on CT scan. Patient 3, a 17-year-old male volleyball player, presented with painless swelling and erythema of his right arm following increased practice. Doppler US confirmed right subclavian and axillary DVT. Diagnosis of PSS was confirmed during surgical resection of his first rib and anterior scalenectomy to reduce compression on subclavian vein.

A PubMed search was conducted using the terms vascular malformations, thrombosis, IVC agenesis, Paget Schroetter.

### **Results:**

IVC anomalies and Paget Schroetter syndrome are rare diagnoses, but with higher incidence among those with DVTs. IVC anomalies are identified in up to 5% of DVT cases, but IVCA

specifically has an incidence of only 0.0005-1% in the general population. In contrast, Paget Schroetter or primary effort thrombosis syndrome describes axillary or subclavian DVTs from compression by the clavicle and first rib. With an incidence of 1-2 in 100,000, PSS is diagnosed more commonly in athletes due to microtrauma from repetitive motions.

**Conclusion:**

Vascular anomalies should be considered in previously healthy pediatric patients presenting with first time unprovoked DVTs. For most patients, lifelong anticoagulation is recommended unless surgical corrective options are available. However, the rarity of these cases makes establishing guidelines difficult.

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Poster # 236

**LYMPHATIC MALFORMATIONS PRESENTING AS LYTIC BONE LESIONS**

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**Background:**

Expansile bone lesions can result from various benign and malignant processes. Common etiologies include polyostotic fibrous dysplasia, Langerhans cell histiocytosis, primary bone tumors, and bony metastases. Non-oncologic conditions such as Fontan palliation leads to a chronically low cardiac output. The resultant increase in systemic venous pressure has multiple downstream effects in the lymphatic system. Increased lymph production and lymphatic congestion due to impaired drainage into the great veins precede subsequent dilatation of the lymphatic channels and eventually result in the formation of new lymphatic collaterals. There are well reported complications associated with these changes, including pericardial or pleural effusions and chylothorax.

**Objectives:**

To describe an uncommon presentation of lymphatic malformations

**Design/Method:**

Description of a case report of a child status post Fontan palliation with expansile lytic rib lesions secondary to abnormal lymphatic flow.

**Results:**

A 7 year old male with autism and history of hypoplastic left heart syndrome status post Fontan palliation presented to the oncology clinic after multiple expansile rib lesions were noted on a routine cardiac CT scan. Review of symptoms were negative for recurrent fevers, weight loss, night sweats, and respiratory symptoms, bone pain, bleeding or bruising. Complete blood count and metabolic panel were unremarkable. Abdominal ultrasound was negative for presence of intra-abdominal malignancy. In consultation with interventional radiologist, MR Lymphangiogram was performed. Occlusion of the thoracic duct and contrast reflux into mediastinal and chest wall lymphatics was demonstrated. Dynamic images showed reflux of

contrast from the thoracic duct directly into intercostal channels filling the bony lesions over time. Management includes optimizing Fontan physiology with cardiac catheterization and initiating bisphosphonate therapy for enhanced bone health. Repeat imaging with MR Lymphangiogram is planned for 6 months from diagnosis to evaluate for possibility of worsening lesions.

**Conclusion:**

While there are multiple known lymphatic complications in palliated single ventricle patients, this is the first documented report of expansile bone lesions developing in the setting of abnormal lymphodynamics.

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Poster # 237

**SUCCESSFUL USE OF SIROLIMUS IN A CASE OF MULTIFOCAL LYPHANGIOENDOTHELIOMATOSIS WITH THROMBOCYTOPENIA**

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**Background:**

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT) is a rare vascular disorder characterized by multifocal cutaneous and gastrointestinal (GI) vascular lesions with thrombocytopenia, although phenotypic variability has been described. Typical cutaneous lesions are described as red-brown to purplish, and range in size. They are most commonly present at birth, increase in number with age, and rarely spontaneously resolve. GI lesions can lead to severe bleeding. Thrombocytopenia is likely due to platelet trapping within vascular lesions. There remains no established therapy, although corticosteroids, sirolimus, aminocaproic acid, propranolol, interferon alpha, and bevacizumab have been reported with varying success.

**Objectives:**

We describe a case of MLT successfully treated with sirolimus.

**Design/Method:**

Case report

**Results:**

A 7 week-old male presented to the emergency department with persistent hematemesis. He was found to be thrombocytopenic (122K/ $\mu$ L) and anemic (8.8g/dL) with scattered purpuric lesions on the extremities, trunk, and scrotum. Infectious etiology was ruled out, bone marrow testing was normal, testing for Wiscott-Aldrich was negative, and a congenital thrombocytopenia panel was negative. He displayed improvement in hemoglobin after red blood cell transfusion and was maintained on iron supplementation. He was treated with a dairy-free diet and omeprazole for presumed milk protein allergy.

He had subsequent recurrence of hematemesis and frankly bloody stools with a hemoglobin of 4.1g/dL and was admitted to the pediatric ICU for red blood cell transfusions and monitoring.

Once stabilized he underwent endoscopy revealing multiple gastric ulcers and arteriovenous malformations. MLT was suggested as a possible diagnosis. At that time, cutaneous lesions had mostly resolved with the exception of his lower extremity and scrotum. Skin biopsy of the scrotal lesion revealed a resection of skin including epidermis, dermis, and subcutaneous tissue incorporating a dermal and subcutaneous vascular lesion, positive for CD31, focally positive for D2-40, and negative for GLUT-1, consistent with a diagnosis of MLT. Given his ongoing GI bleeding and persistent cytopenias he began sirolimus for treatment of MLT. The dose was titrated to achieve a level between 8-12ng/mL. He had subsequent improved platelet count and no further GI bleeding. At most recent follow up his hemoglobin and platelet count were stable at 11.4g/dL and 113K/ $\mu$ L respectively, with an iron saturation of 16%.

**Conclusion:**

There is currently no established therapy for patients with MLT. This case of MLT was successfully managed with sirolimus, as evidenced by improvement in patient hemoglobin and platelet counts, as well as resolution of GI bleeding, in the absence of adverse side effects.

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Poster # 301

**CANINE NK CELL EXPANSION AND NOVEL XENOGRAFT MODEL FOR ADOPTIVE IMMUNOTHERAPY OF OSTEOSARCOMA**

**Mallery Olsen, Monica Cho, Matthew Forsberg, Adeela Ali, Amy Erbe-Gurel, Arika Feils, David Vail, Christian Capitini**

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**Background:**

Osteosarcoma is the most common bone cancer in both canine and human patients, but dogs develop osteosarcomas with an incidence of twenty times that of people; thus dogs are an ideal model for studying therapies for pediatric osteosarcoma treatment. In both species, metastatic and relapsed disease have poor survival with current chemotherapy and surgical treatments. The usage of ex vivo activated natural killer (NK) cells as an adoptive immunotherapy is a promising approach for osteosarcoma treatment, but xenograft models of canine osteosarcoma are not yet available.

**Objectives:**

The objective of this study was to develop a methodology to expand and activate canine NK cells ex vivo, characterize their function against a canine osteosarcoma cell line in vitro, and develop an in vivo xenograft model of canine osteosarcoma using immunodeficient mice.

**Design/Method:**

Peripheral blood from healthy dogs was collected, and peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll. PBMCs were co-cultured with irradiated K562-41BBL-IL15 GFP feeder cells. Human IL-2 and canine IL-21 were added to NK cultures and replenished with fresh media every 2-3 days. Every 7 days, irradiated feeder cells were added. Flow cytometry



was done every 7 days to enumerate CD3-CD5dim canine NK cells. Following 14-21 days of culture, cells were isolated by fluorescence activated cell sorting. The canine osteosarcoma cell line D17 was transduced to express mKate2 (D17 mKate2) and evaluated in an NK cytotoxicity assay using Incucyte. D17 mKate2 cells were also injected subcutaneously as a xenograft into NSG mice, and tumors were followed by digital caliper as well as immunohistochemistry (IHC), IVIS, X-ray, and CT imaging.

**Results:**

While canine NK cells only were expanded up to 8.6 fold using 41BBL/IL15/IL21/IL2 stimulation over 21 days, they showed high cytotoxicity in vitro at 25-50:1 ratios against D17 mKate2 osteosarcoma cells within 24 hours. In vivo, for the first time we show a dose response curve of establishing D17 mKate2 osteosarcoma in NSG mice using  $1 \times 10^6$  –  $10 \times 10^6$  cells. Tumor growth was confirmed by both IVIS and IHC. Metastatic disease was confirmed using x-ray and micro computerized tomography (microCT).

**Conclusion:**

Canine NK cells can be expanded and activated using feeder cells and cytokines that are readily available for human NK cell trials, and show potent cytotoxicity against osteosarcoma in vitro. The canine D17 mKate2 xenograft model recapitulates human osteosarcoma growth locally and metastasizes, making it a viable platform for testing adoptive immunotherapy with NK cells.

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Poster # 302

**LIMITED ENGLISH PROFICIENCY IN PEDIATRIC STEM CELL TRANSPLANT: A RETROSPECTIVE AND QUALITATIVE STUDY**

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**Background:**

More than 25 million Americans (9% of the population) have limited English proficiency (LEP) and are more likely than English-proficient (EP) patients to have poor health literacy, not understand their diagnosis, or experience complications from adverse drug effects.

Hematopoietic stem cell transplantation (HSCT) is a potentially curative procedure for a variety of pediatric malignant and non-malignant diseases. However, HSCT requires prolonged hospitalization and excellent medication adherence to achieve good outcomes. Communication barriers between clinicians and LEP families of pediatric HSCT patients may further complicate this process and affect clinical outcomes.

**Objectives:**

Compare HSCT outcomes of Hispanic pediatric patients and families with LEP to that of EP patients and families. Describe the experiences of Spanish-speaking LEP caregivers of patients that have received HSCT.

**Design/Method:**

We conducted a retrospective review of pediatric patients of Hispanic/Latino descent receiving HSCT at Duke University over a 20 year period. Patients and families were identified as LEP or EP based on clinicians' notes, social work documentation and/or the signature of a Spanish interpreter on treatment consents. Semi-structured interviews were conducted with Spanish-speaking caregivers of pediatric patients that have undergone HSCT at Duke University. Caregivers were eligible if  $\geq 18$  years of age and documented to have a preferred language of Spanish. Interviews were audio-recorded, de-identified, translated and transcribed into English. Interview translations were verified for accuracy by two separate bilingual study team members. The semi-structured interview data were analyzed with the assistance of the NVivo software, to describe recurrent themes in the interviews.

**Results:**

A total of 84 Hispanic/Latino patients were identified, with 53 (63.1%) having LEP. LEP patients were hospitalized on average 13 days longer than EP patients ( $p=0.06$ ). Overall survival was lower in LEP than EP but not statistically significant ( $p=0.206$ ). Multivariable Cox modeling suggested a potentially higher risk of death in LEP vs EP (HR=1.56, 95% CI: 0.38, 6.23). Caregiver interviews ( $n=3$ ) reveal themes involving a preference for Spanish-speaking clinicians, the utility of medical interpreters, and the importance of trust in the medical team. Caregivers expressed fear of poor transplant outcomes and challenges with language barriers. Despite challenges reported during the transplant course for their children, the caregivers expressed gratitude and overall satisfaction with care.

**Conclusion:**

Spanish-speaking patients with LEP undergoing HSCT may be at higher risk for poor clinical outcomes. Qualitative data collection is ongoing, to further describe the barriers for this patient population to reveal opportunities for improvement and intervention to optimize clinical outcomes.

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Poster # 303

**PERIPHERAL BLOOD STEM CELL HARVEST-EFFECTIVE PREDICTORS IN PAEDIATRICS**

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**Background:**

PBSC (peripheral blood stem cells) are used to restore hematopoiesis after high dose chemotherapy in solid tumors by aiding early stem cell recovery and reducing complications associated with prolonged neutropenia. PBSC collection is a time and resource consuming process as rapid appearance of CD34 cells in the circulation need immediate collection to achieve an optimal yield.

**Objectives:**

1> To study the factors affecting the peripheral stem cell collection in children

2> To propose a predictive model for optimal timing of collection

**Design/Method:**

This is a retrospective study, from 2009-2018, collecting demographic, clinical, and laboratory data on autologous stem cell procedures at our centre. Descriptive and statistical analysis of the data was performed

**Results:**

One hundred and eighty apheresis collections were performed on 145 children. Brain tumors (28%) and Neuroblastoma (26.5%) were the most common indications for aphaeresis. Plerixafor was used in 10.5% of the children and GCSF (granulocyte colony stimulating factor) in the remaining. We had 37 poor mobilisers ( $CD34 < 5 \times 10^6 / KG$ ) and 19/37 (51%) of them had infiltrating bone marrow disease ( $p = 0.01$ ). The remaining 18 children had received platinum based therapy prior to aphaeresis ( $p < 0.05$ ). The median days of collection after chemotherapy is 16 in the brain tumour cohort, 15 in neuroblastoma, 13 in lymphoma and 12 in Ewings sarcoma. The mean peripheral CD34 is  $140.66 \times 10^9 / l$  and shows a positive correlation (R score - 0.7454,  $p < 0.0001$ ) to the final product CD34 count. The peripheral monocyte count also showed a positive correlation to peripheral CD34 count (R score - 0.180,  $p = 0.016$ ) in the entire cohort and higher correlation (R-0.233,  $P = 0.007$ ) in the cohort who did not receive cisplatin.

**Conclusion:**

The monocyte count on the day of stem cell collection helps in early detection of peripheral circulating CD34 cells and aids in optimizing progenitor stem cell collection. Other factors including, disease involvement of bone marrow, prior use of platinum therapy significantly influence the final product stem cell yield and result in poor mobilization. Though Plerixafor was used only in children who failed to mobilize on first day of collection, we propose to consider plerixafor/single dose chemotherapy upfront in children at risk for poor mobilization to reduce the need for multiple aphaeresis procedures.

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Poster # 304

**ULTRA-HIGH-DOSE VITAMIN D EFFECTIVELY INCREASES PRE-TRANSPLANT VITAMIN D LEVELS**

**Rusha Bhandari, Paibel Aguayo-Hiraldo, Kimberly Cheng, Sonata Jodele, Etan Orgel**

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**Background:**

Up to 70% of pediatric patients are vitamin D insufficient prior to hematopoietic stem cell transplantation (HSCT). Vitamin D insufficiency is associated with all-cause mortality and may be associated with comorbidities such as graft-versus-host disease (GVHD) and veno-occlusive disease (VOD). Routine, low-dose vitamin D supplementation does not achieve sufficient vitamin D levels ( $> 30 \text{ ng/mL}$ , per Endocrine Society) in most patients during HSCT. Stoss dosing of vitamin D is an alternative approach to replete vitamin D by administering single, oral ultra-high doses of vitamin D3 based on patient weight and starting vitamin D level.

**Objectives:**

To assess whether Stoss dosed vitamin D3 is more effective than routine vitamin D supplementation to achieve sufficient pre-HSCT vitamin D levels.

**Design/Method:**

Patients aged 0-25 years preparing for autologous or allogeneic HSCT with vitamin D level <50ng/mL were eligible for the study. A single oral Stoss dose (7,000-14,000 IU/kg according to baseline vitamin D level, maximum dose 600,000 IU) was administered prior to HSCT. Vitamin D levels were monitored weekly until day +100. We also evaluated the benefit of Stoss dosing on HSCT-related morbidities until day +100.

**Results:**

To date, 28 patients have received Stoss dosing. The median age at time of HSCT was 7 years. In our Stoss cohort, 82% of patients (n=23) received allogeneic HSCT. Sixty-four percent (n=18) received HSCT for malignant diseases. Following Stoss dosing, 96% percent of patients (n=27) had sufficient vitamin D levels. Patients' vitamin D levels increased significantly ( $p < 0.001$ ), from a mean baseline level of 28 ng/mL (standard error [SE]=2.0) to a mean post-Stoss vitamin D level of 72 ng/mL (SE=4.7). Compared to a historical cohort of patients who received routine vitamin D supplementation prior to HSCT, the Stoss cohort had significantly higher mean vitamin D level (36ng/mL [SE=3.0] vs 72ng/mL [SE=4.7],  $p < 0.001$ ). Monitoring for reduction in HSCT-related morbidities is ongoing; to date the Stoss cohort has less GVHD and/or VOD compared to a historical cohort (22% vs 35% respectively,  $p = 0.101$ )

**Conclusion:**

A single oral Stoss dose of vitamin D is potentially effective in achieving vitamin D sufficiency in pediatric patients prior to HSCT. The Stoss cohort achieved significantly higher vitamin D levels than patients who received routine, low-dose vitamin D supplementation. Given the association between vitamin D insufficiency and HSCT-related morbidity and mortality, consideration should be given to larger prospective trials examining the efficacy and potential immunomodulatory benefits from Stoss dosed vitamin D supplementation prior to HSCT.

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Poster # 305

**PREVALENCE OF MUCOSAL BARRIER INJURY LAB-CONFIRMED BLOODSTREAM INFECTIONS IN PEDIATRIC BMT PATIENTS**

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**Background:**

Despite improvements in central line care and rates of central-line associated blood stream infections (CLABSI), blood stream infections (BSI) remain a major life-threatening complication in patients who undergo hematopoietic stem cell transplantation (HSCT). Several complications

have been associated with BSI in HSCT recipients, including prolonged hospitalization, more intensive care admissions, prolonged antibiotic courses, and increased mortality. In 2013 the Centers for Disease Control and Prevention defined a specific class of infection within CLABSI, known as ‘mucosal barrier injury laboratory-confirmed bloodstream infection’ (MBI-LCBI) based on literature review and expert opinion. MBI-LCBIs are thought to be due to bacterial translocation across a damaged mucosal barrier and unlike CLABSI, MBI-LCBIs are not expected to be prevented by improved central line care.

**Objectives:**

To report the incidence of MBI-LCBI in our pediatric bone marrow transplant population and identify risk factors associated with MBI-LCBI.

**Design/Method:**

A retrospective chart review was done of 165 pediatric BMT patients transplanted between January 1st, 2011 and December 31st, 2016 at Phoenix Children's Hospital. Patients with MBI-LCBI were identified using the National Healthcare Safety Network guidelines. Univariate and multivariate analyses were used to compare demographic and transplant-related factors between patients with and without MBI-LCBI.

**Results:**

Median age at transplant was 6 years (range 4 months – 23 years). Most patients (114 patients, 69%) underwent HSCT for a malignant underlying diagnosis. Ninety-four patients developed CLABSI. Of those ninety-four, twenty-four patients (24%, 14% of all patients) met the criteria for MBI-LCBI. Patients who underwent allogenic stem cell transplant had a statistically significant increased incidence of MBI-LCBI (p value 0.05). Among those patients who received allogenic stem cell transplant, those who had a malignant diagnosis (80%) had a statistically significant increased incidence of MBI-LCBI (p value 0.01). Seven patients (30%) with MBI developed shock and required PICU admission. This percentage was significantly higher than the percentage of patients without MBI requiring PICU admission (4%, p value 0.004).

**Conclusion:**

Fourteen percent (23/165) of our BMT patients developed MBI-LCBI. Allogenic HSCT and malignant diagnosis are associated risk factors. More research regarding risk assessment and stratification of patients undergoing HSCT may aid in implementation of early and effective interventions for preventing MBI-LCBI.

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Poster # 306

**OUTCOMES OF TRANSFUSION-RELATED IRON OVERLOAD IN POST-HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS**

**Brandon Lucari, Marika Highberger, Tami John, Trinh Nguyen, Lisa Hensch, I. Vienna Lei, Alexandra Mendoza, Jacquelyn Powers**

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**Background:**

Iron overload (IO) can be a significant problem in chronically transfused patients, resulting in multi-organ toxicity including hepatic cirrhosis as well as cardiac and pancreatic dysfunction. Pediatric oncology and hematopoietic stem cell transplant (HSCT) patients are frequently transfused as part of routine supportive care. However, evidence-based guidelines for evaluation, treatment, and follow-up of IO in post-HSCT oncology patients are lacking.

**Objectives:**

To review the management and outcomes of post-HSCT oncology patients with transfusion-related IO within the Texas Children's Cancer and Hematology Center (TXCH) survivorship clinic.

**Design/Method:**

We conducted a retrospective cohort study of post-HSCT oncology patients followed within the TXCH bone marrow transplant (BMT) long-term survivor clinic from January 1, 2013 through December 31, 2017 with a diagnosis code for IO in the electronic medical record (EMR). Demographic characteristics and clinical information related to HSCT and IO were extracted from the EMR. Data on red blood cell transfusions were obtained via blood bank records. Descriptive analysis was performed. This study was approved by the institutional review board at Baylor College of Medicine.

**Results:**

Twenty-four patients were eligible for study inclusion (79% male [n=19]; 50% White, Hispanic [n=12], 46% White, non-Hispanic [n=11]; median age at time of transplant 13.9 years; primary oncologic diagnoses were acute lymphoblastic leukemia [n=14, 58%], and acute myeloid leukemia [n=5, 21%]). Median (IQR) total red cell transfusions received (n=23) was 37 (29-66). Twenty patients received therapy for IO with either therapeutic phlebotomy (n=18, 75%), chelation therapy (n=1, 4%), or both (n=1, 4%). Prior to treatment initiation, only 11 of 20 patients (n=55%) had magnetic resonance abdominal imaging to assess for iron deposition with median LIC of 6.26 mg Fe/g dry weight. Ten treated patients (50%) had cardiac imaging with median T2\* of 33 ms. In treated patients, pre-therapy median (IQR) ferritin and transferrin saturation values were 1,415 ng/mL (1,005-1,928) and 55% (45-80), respectively. Median (IQR) duration of phlebotomy was 18 months (10-27). Median ferritin, transferrin saturation, and LIC values post-IO therapy were 205 ng/mL, 26% and 1.93 mg Fe/g dry weight, respectively.

**Conclusion:**

In this cohort of post-HSCT oncology patients in long-term follow-up with IO, overall management including laboratory evaluation, imaging, and therapy initiation, was inconsistent. Patients treated for IO had an improvement in iron parameters and decreased iron deposition on follow-up imaging. To improve outcomes moving forward, our center has developed a clinical algorithm for the screening and management of IO in all patients who are one-year post HSCT.

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Poster # 307

**ROLE OF RACE AND ETHNICITY IN OUTCOMES IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION**

**Lily Garcia-Rodriguez, Sana Farooki, Nazia Tabassum, Melissa Jefferson, Mohamed Radhi, Ashley Sherman, Barbara Chignola, Terrie Flatt**

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**Background:**

Hematopoietic Stem Cell Transplantation (HSCT) is a potentially life-saving treatment for patients with both malignant and non-malignant disease processes. Ethnic disparities in HSCT outcomes have been described in both the adult and pediatric literature.

**Objectives:**

To determine the differences in morbidity and mortality in Caucasians, Hispanics, Blacks and other ethnicities receiving HSCT at a single institution.

**Design/Method:**

Retrospective chart review was performed for a cohort of 251 pediatric subjects from 01/01/2000 to 06/30/2019 at Children's Mercy Hospital. We employed descriptive statistics, Kaplan-Meier survival analysis, chi-square test, and Cox proportional hazard regression analysis.

**Results:**

Of the 251 subjects reviewed 172 were Caucasian, 38 were Hispanic, 25 were Black and 16 subjects belonged to other races. Median age at HSCT was 7.8 years (range 3.2 to 13 years). 55.4% underwent HSCT for malignant etiologies and 44.6% for non-malignant diseases. There was a statistically significant difference in the stem cell source with a greater number of patients that were Hispanic, Black and other races receiving cord blood compared to Caucasian patients (31.6 % vs 36.0% vs 43.8% vs 15.1%  $p=0.01$ ). 77% of Caucasian had 100% match compared to only 63% in Hispanic, 52% in Blacks and 63% in patients of other races ( $p=0.03$ ). There was no significant difference in incidence of veno-occlusive-disease and graft-versus-host-disease between the groups. There was a significant difference in mortality among the 4 races ( $p = 0.048$ ); Blacks ( $p = 0.02$ ) and Hispanics ( $p = 0.03$ ) had an inferior outcome compared to the other categorical group (non Caucasian). However after controlling for matching and stem cell source, there was no difference in mortality between races.

**Conclusion:**

Overall, Hispanics and Black had greater mortality compared to subjects belonging to other (non-Caucasian) races. Unknown somatic cytogenetic mutations and germline variants may contribute to inferior outcomes of Blacks and Hispanics compared to subjects of other races. This study demonstrates the continued need to increase donor registries among minority patients.

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Poster # 308

**BONE HEALTH OUTCOMES IN A DIVERSE COHORT OF PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS**

**Anthony Sabulski, Sarah Swauger, Lindsey Hornung, Halley Wasserman, Jonathan Howell, Kasiani Myers**

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**Background:**

Impaired bone mineral density (BMD) leads to fragility fractures and is known to occur in adults following hematopoietic stem cell transplantation (HSCT). Little is known about BMD and fracture risk in pediatric HSCT recipients. Pre-transplant variables that may influence the risk of bone disease include age, underlying diagnosis and pre-transplant steroid exposure. Similarly, post-transplant steroid exposure and GVHD are additional factors that likely impact bone health outcomes.

**Objectives:**

Our study aims to describe the incidence of fragility (low trauma) fractures in a large diverse pediatric HSCT population and to identify risk factors of fracture and impaired BMD.

**Design/Method:**

We included 237 patients (age  $\leq 21$  years at time of transplant) who underwent HSCT at our institution between January 2015 and March 2018. The primary endpoint was incidence of fragility fractures and the secondary endpoint was assessment of BMD on dual-energy X-ray absorptiometry (DXA). We analyzed DXA results at one-year post-HSCT in 72 out of 206 patients alive at 1 year.

**Results:**

A diverse HSCT population was analyzed, encompassing a variety of underlying diseases: malignancy (35%), primary immune deficiency (14%), HLH (12%), genetic conditions (14%), Fanconi anemia (10%) and other diseases (15%). Conditioning regimens were predominantly myeloablative (69%) compared to reduced intensity (30%) or no conditioning (1%). Fragility fractures occurred in 10.5% of patients and were classified as either spine (72%), long bone (20%) or both (8%). Fracture incidence in patients with GVHD (15%) compared to no GVHD (9%) was not statistically different ( $p=0.13$ ). Mortality at one-year was proportionally higher, though not significant ( $p=0.11$ ) in patients who had at least one fragility fracture (24%; 6/25) compared to patients without fragility fracture (12%; 25/212). Vitamin D status at one-year post transplant was sufficient ( $>20\text{ng/mL}$ ) in 94% (160/171) of patients. The median height-for-age adjusted Z-score (HAZ) for spine BMD at one-year post transplant was 0.13 in all patients. The median HAZ spine BMD Z-score in patients with fragility fracture was -1.64, though data was available for only 5 patients.

**Conclusion:**

Pediatric HSCT recipients have a high incidence of fragility fractures and our 1-year DXA data raises concern for abnormal BMD in these patients. As there are likely additional asymptomatic patients with occult fractures not detected in our cohort, this data advocates for establishing bone health screening protocols for pediatric HSCT patients. A detailed steroid exposure analysis of this study population is ongoing and will be constructive for establishing individualized risk for adverse bone health outcomes.



## **CIRCULATING ENDOTHELIAL CELLS IDENTIFY VASCULAR INJURY IN PEDIATRIC STEM CELL TRANSPLANT RECIPIENTS**

**Anthony Sabulski, Benjamin Aunins, Sheyar Abdullah, Nathan Luebbering, Stella Davies**

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### **Background:**

Endothelial damage related to hematopoietic stem cell transplant (HSCT) is multifactorial. Thrombotic microangiopathy (TMA) and hepatic veno-occlusive disease (VOD) are known culprits, while conditioning regimen variations (e.g. myeloablative (MAC) vs reduced intensity (RIC)) and infectious complications also contribute. Circulating endothelial cells (CECs) have been shown to directly reflect vascular injury, making them a potential tool for identifying early evidence of endothelial damage after HSCT.

### **Objectives:**

Our objective is to quantify and characterize CECs in pediatric allogeneic HSCT patients. We aim to identify the timing of peak vascular injury and the relationship between CECs and post-transplant complications.

### **Design/Method:**

CEC analysis was performed prior to and after stem cell infusion using 250uL of whole blood. CECs were isolated using Invitrogen M-450 Tosylactivated Dynabeads coupled to a CD146 antibody. Nuclear staining was done using acridine orange and propidium iodide (AOPI). To be scored as a CEC, cells required: >4 immunomagnetic beads attached, morphology consistent with an intact cell, damaged cell or clump of cells, and immunofluorescence with AOPI staining.

### **Results:**

Over 150 samples were analyzed from 21 pediatric patients with diverse underlying conditions (AML/MDS=6, ALL=5, bone marrow failure=4, immune deficiency=3, hemoglobinopathy=2, myeloproliferative neoplasm=1). From pre-transplant through the first two weeks after HSCT, the maximum CEC value per patient was lower with RIC (n=3, mean=37.3 CECs/mL) compared to MAC (n=18, mean=49.5 CECs/mL). The highest CEC value per patient occurred prior to D+14 in 63% of patients and prior to stem cell infusion in 21% of patients. Two out of three patients whose maximum value occurred after D+30 had concurrent BK viremia with cystitis. Both showed a strong correlation between changes in plasma BK copy number and CEC values. The highest observed CEC values were seen following cardiac arrest (128 CECs/mL) and with symptomatic BK infection (100 CECs/mL). VOD and TMA each occurred in one patient.

### **Conclusion:**

Peak vascular injury occurs prior to D+14 in the majority of HSCT recipients. Conditioning regimens are an important driver of this process and our data suggest RIC results in less endothelial damage. The endothelial injury seen in parallel with rising BK copy number may be

the result of direct endothelial infection by BK virus. Alternatively, the development of BK viremia may occur secondarily to ongoing vascular insult, such as TMA. Additional analysis will be insightful into further applications of CECs in HSCT, as well as the nature of BK-mediated vascular injury.

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Poster # 310

## **IOBAN: ONE MORE STEP TOWARDS GRAFT CONTAMINATION PREVENTION DURING BONE MARROW HARVEST**

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### **Background:**

Lengthy and repeated skin penetration during bone marrow harvests (BMH) increases the potential for contamination and infection of the bone marrow graft. Contamination of the bone marrow graft can lead to additional recipient exposure to antibiotics and increased costs. Iodine impregnated drape, IOBAN, has been shown to decrease wound contamination by providing broad spectrum antimicrobial activity and is widely used in the operating room (OR) for major surgical procedures. However, it has not been widely adopted for BMH.

### **Objectives:**

To assess the quality improvement of graft contamination in BMH following addition of IOBAN

### **Design/Method:**

Assessment of quality improvement in a stepwise manner with retrospective analysis of graft contamination in BMH

### **Results:**

During 2010 through 2015, 4 out of 64 (6%) bone marrow grafts collected at our institution were contaminated with skin organisms noted on sterility cultures. In 2016, 6 out of 15 (40%) bone marrow grafts collected at our institution were contaminated with skin organisms noted on sterility cultures. Root cause analysis was conducted which included negative sterility cultures of heparin solution, negative random cultures of trocar kits, and observation of BMH by infection prevention specialists. Step-wise remedial measures started in 2017 including skin preparation with exclusively ChlorPrep (eliminating betadine as an option), use of IOBAN, donor education and assistance in the pre-op area using CHG wipes, along with continuing education of physicians and OR staff. We noted a reduction in contaminated bone marrow grafts: 2 of 12 (16.7%) in 2017, 3 of 13 (23%) in 2018, and 2 of 12 (16.7%) in 2019. The overall incidence of graft contamination from 2017-2019 was reduced to 7 of 37 (18.9%). Each case involved appropriate notification, investigation, follow-up and reporting per FACT-JACIE standards.

### **Conclusion:**

Multiple interventions were put into place with a subsequent reduction of the graft contamination rate by more than half of previous contamination rates. As bone marrow transplant physicians spend minimal time in the OR, knowledge regarding the efficacy and use of IOBAN may be limited. IOBAN provides a targeted measure to reduce bone marrow graft contamination from skin flora that is easily standardized across institutions.

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Poster # 311

## **LONG-TERM NEUROCOGNITIVE AND QUALITY OF LIFE OUTCOMES IN SURVIVORS OF PEDIATRIC STEM CELL TRANSPLANT**

**Natalie Wu, Kevin Krull, Nicole Ullrich, Nina Kadan-Lottick, Stephanie Lee, Eric Chow**

*Fred Hutchinson Cancer Research Center, Seattle, Washington, United States*

### **Background:**

Patients who undergo hematopoietic stem cell transplant (HSCT) are at risk for neurocognitive impairment due to their underlying diagnoses or treatment-related exposures.

### **Objectives:**

To study long-term self-reported neurocognitive and quality of life outcomes in survivors of pediatric HSCT.

### **Design/Method:**

This was a cross-sectional, single center study. All eligible survivors (HSCT at age <21y and ≥1y post-HSCT) were sent a 60-question survey on cognitive function, quality of life, and other factors predicted to impact cognition. Questions were included from the Neuro-Quality of Life Cognitive Function Short Form (Neuro-QoL), Childhood Cancer Survivor Study Neurocognitive Questionnaire (NCQ), and Patient-Reported Outcomes Measure Information System Sleep Disturbance Short Form. Baseline demographic and transplant characteristics were abstracted from the institutional research database. Analyses included univariate comparisons and multivariable logistic regression.

### **Results:**

Of 626 eligible survivors approached, 199 (50.3% female) responded, at a current mean age of 38.4y (range 18-61) and mean 25.5y (range 1-46) after HSCT. Most survivors underwent transplantation for acute leukemia (53.3%) and received allogeneic transplants (87.9%) with total body irradiation conditioning (66.3%). Survivors reported normal (expected mean=50) overall Neuro-QoL (49.6±0.7) and sleep quality (49.6±0.7) but had impaired (defined as mean>0) scores in all four NCQ domains including emotional regulation (0.3±0.1), task efficiency (0.7±0.1), organization (0.2±0.1), and memory (0.6±0.1), (all p<0.05). Characteristics associated with lower Neuro-QoL scores included: younger age at HSCT (<10y: 47.0±1.2 vs age ≥10y: 50.6±0.8, p=0.01), hearing loss or tinnitus (45.3±1.7 vs 50.6±0.7, p<0.01), history of stroke or seizure (42.5±1.8 vs 50.6±0.7, p<0.01), and self-reported sleep disturbances (T-score≥60: 41.4±2.0 vs T-score<60: 50.8±0.7, p<0.01). In general, these characteristics were also associated with impaired scores in individual NCQ domains except for younger age at HSCT. Patient sex, race/ethnicity,

underlying diagnosis, number of transplants, time since transplant, era of transplant, total body irradiation, or history of chronic graft-versus-host disease were not associated with differences in scores. In patients >25y, lower neurocognitive scores were associated with less educational achievement ( $p<0.01$ ). When adjusted for sex and current age, low Neuro-QoL (T-score <40) was independently associated with hearing issues (OR 4.6, 95% CI 1.8-11.7), history of stroke or seizure (OR 5.1, 95% CI 1.7-15.3), and sleep disturbances (OR 7.5, 95% CI 2.7-20.8).

**Conclusion:**

Pediatric HSCT survivors report average quality of life but worse neurocognitive function compared with the general population. Younger age at transplant, hearing issues, prior stroke or seizure, and sleep disturbances were associated with worse outcomes.

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Poster # 312

**HSCT IN APLASTIC ANEMIA: SIMILAR OUTCOMES WITH MATCHED-SIBLING & MATCHED/MISMATCHED UNRELATED DONORS**

**Katie Greenwood, Swati Naik, Bilal Omer, Meenakshi Hegde, Caridad Martinez, John Craddock, Tami John, Olive Eckstein, Nabil Ahmed, Khalid Yassine, Saleh Bhar, Robert Krance, Ghadir Sasa**

*Baylor College of Medicine, Houston, Texas, United States*

**Background:**

Severe Aplastic Anemia (SAA) is a life-threatening disorder of hematopoiesis. Five-year overall survival (OS) of pediatric SAA patients transplanted from matched-sibling donors (MSD) is 90%. However, only 30% have available donors. Those without MSD undergo immunosuppressive therapy (IST) with cyclosporine and anti-thymocyte globulin (ATG), with reported 64% event-free survival (EFS). Relapse and clonal evolution remain concerns in such patients. This and recent improved outcomes in matched/mismatched-unrelated HSCT has prompted discussion of earlier/upfront alternative donor (AD) transplantation. This study describes our center's experience with MSD and AD transplantation for SAA.

**Objectives:**

Assess OS and EFS of pediatric relapsed/refractory SAA AD transplant patients treated according to institutional SAA Matched-Unrelated Donor (SAA MUD) protocol in comparison to peers that received MSD transplants from 2002-2019.

**Design/Method:**

IRB approval was obtained for retrospective chart review of 72 SAA patients. The 34 MSD transplant patients received cyclophosphamide (200 mg/kg) and ATG conditioning and cyclosporine with mini-methotrexate (MTX) for graft-versus-host-disease (GVHD) prophylaxis. The 38 AD transplant patients (27 matched-unrelated, 12 mismatched-unrelated donors) received cyclophosphamide (200 mg/kg), alemtuzumab, and total body irradiation of 200-400 cGy with tacrolimus and mini-MTX for GVHD prophylaxis. EFS events analyzed included acute GVHD (aGVHD) grade III or IV, extensive chronic GVHD (cGVHD), death, and graft failure (GF). GF

was defined as rejection or poor graft function necessitating further cellular treatment. Cumulative survival and time-to-event Kaplan-Meier curves underwent log-rank analysis.

**Results:**

There is no significant difference in OS between AD (86.8%) and MSD (93.6%) transplant recipients (p=0.3211). No difference was found in EFS (AD 65.7%; MSD 69.3%; p=0.0656). There was no difference in rates of aGVHD grade III or IV (p=0.1007) nor extensive cGVHD (p=0.2918). Rates of GF did not differ (AD 7/28 patients, MSD 3/33 patients; p=0.2683). However, AD patients tended toward GF within months, while MSD patients displayed late GF (0.5-4 years). Additionally, within the AD group, no differences in rates of GVHD (acute or chronic) nor graft failure were seen between MUD and MMUD patients.

**Conclusion:**

Our data suggest MSD and AD transplant recipients display equivalent OS and EFS with similar low rates of severe aGVHD and extensive cGVHD. Rates of GF were similar, although AD transplant patients tended toward earlier graft failure/rejection than MSD transplant patients. Our data supports the current scientific discussion considering earlier AD transplantation for pediatric patients and affirms the low complication rate. Late effects analyses of our cohort including cardiac, pulmonary, renal, and endocrine toxicities remain ongoing.

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Poster # 313

**TISAGENLEUCLEUCEL MANUFACTURING IN PATIENTS < 3 YEARS OF AGE WITH R/R ACUTE LYMPHOBLASTIC LEUKEMIA.**

**Lamis Eldjerou, Christopher Acker, Damien Howick, Lee Clough, Miriam Fuchs, Florence Salmon, Jennifer Willert, Ranjan Tiwari, Mayo Pujols, Matthew Robson**

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**Background:**

Tisagenlecleucel is a CD19-directed autologous chimeric antigen receptor (CAR)-T cell therapy approved for the treatment of patients  $\leq 25$  years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory or in  $\geq$  second relapse. Patients < 3 years of age at screening were excluded from tisagenlecleucel clinical trials (NCT02435849 [registrational ELIANA] and NCT02228096 [ENSIGN]).

**Objectives:**

Report Novartis' experience with commercial manufacturing of tisagenlecleucel for patients < 3 years of age with relapsed/refractory (r/r) ALL.

**Design/Method:**

Patients with r/r ALL were < 3 years of age at time of the request for commercial tisagenlecleucel, and leukapheresis and manufacturing outcome data were obtained after the first FDA approval of tisagenlecleucel (August 30, 2017).

**Results:**

Thirty-one patients with r/r ALL underwent leukapheresis. Median age was 15 months (range, 3-35) and median body weight was 10.2 kg (range, 6.0-15.6; 14 patients < 10 kg and 17 patients ≥ 10 kg). A median of 1 leukapheresis day (range, 1-6) was required to collect sufficient cells, including 2 patients who underwent repeat leukapheresis for second manufacturing attempt. Acceptance criteria for tisagenlecleucel manufacture were met in 29/33 leukapheresis materials; 2/3 that did not meet acceptance criteria were unsuccessful. The first manufacturing attempts were successful in 26/30 (86.7%) patients, and 4/30 experienced manufacturing failure (2 patients < 10 kg and 2 patients ≥ 10 kg). Among the 4 manufacturing failures, 2 successfully underwent repeat leukapheresis and a second manufacturing attempt, and 2 did not undergo a second attempt. The leukapheresis material did not meet acceptance criteria for 2 of the 4 manufacturing failures. The median manufactured cell dose was  $4.0 \times 10^6$  CAR+ viable T cells/kg (range,  $0.37 \times 10^6$ - $4.0 \times 10^6$ ), median percent cell viability was 87.6% (range, 66.7%-95.7%), and median CAR+% expression was 10% (range, 2.7%-25.6%). Successful manufacturing for patients with low weight (< 10 kg) was possible by raising hematocrit to 40% with blood transfusion, using an appropriate size central venous catheter, blood priming of the apheresis instrument, preventing hypothermia during collection, closely monitoring vital signs and electrolytes, performing partial rinse back, and allowing for > 1 leukapheresis day to meet acceptance criteria.

**Conclusion:**

Leukapheresis and tisagenlecleucel manufacturing are feasible in patients with r/r ALL < 3 years of age and with low weight (as young as 3 months and as low as 6 kg) and had manufacturing outcomes comparable with Novartis clinical trial experience in patients ≥ 3 years of age.

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Poster # 314

**HEALTH CARE UTILIZATION FOLLOWING STEM CELL TRANSPLANTATION FOR SICKLE CELL DISEASE**

**Rebecca Chen, Alexander Ngwube, Gregory Guilcher, Dania Monagel, Shalini Shenoy**

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**Background:**

Patients with sickle cell disease (SCD) have multiple morbidities including painful crises and organ dysfunction resulting in lifelong extensive utilization of health care services. Successful hematopoietic stem cell transplantation (HSCT) is curative. The kinetics of improvement depend on patient and transplant characteristics. Our hypothesis was that HSCT stabilized organ function and decreased long-term healthcare utilization at variable pace.

**Objectives:**

The objective of this study was to evaluate the dynamics of end organ recovery and health-care utilization following HSCT in children with SCD.

**Design/Method:**

Following Institutional Review Board approval, data was collected retrospectively at 3 pediatric centers. Patients underwent matched sibling donor (MSD) HSCT following reduced intensity conditioning (RIC) (n= 14) or low dose radiation based non-myeloablative conditioning (NMA) (n=16), or unrelated donor (URD) HSCT following RIC (n=11). Pre- and post-HSCT course was tracked for hospitalizations, renal, cardiac, pulmonary function, CNS events, medication number/duration, and HSCT-related events.

**Results:**

MSD HSCT recipients tapered medications by the end of the first year post-HSCT. Patients undergoing NMA had fewer medications at all timepoints but also had a lower analgesic complexity pre-HSCT. In contrast, URD recipients reached comparable medication taper only at 2-years post-HSCT presumably due to both disease and transplant complexity. Similarly, analgesic use post-HSCT was lower following MSD HSCT despite dependency pre-HSCT. Analgesics were tapered by one-year following MSD and two-years following URD HSCT. The NMA group required no hospitalizations after the first year; one patient required hospitalization in the second year in the MSD RIC group as did 6 in the URD group. No hospitalizations were required in any patient between 2 and 3 years post-HSCT. While cardiac function remained normal in all patients, pulmonary function was stable or improved in all but one from the URD group (FEV1 decreased from 90% to 77% predicted). No MSD recipients but 5 and 4 URD recipients developed transient elevated creatinine levels and microalbuminuria, respectively. Neuroimaging results are under evaluation.

**Conclusion:**

End organ function stabilized post-HSCT. MSD recipients had lower healthcare utilization after one-year post-HSCT. In contrast, URD recipients reached comparable health status at or after two years due to graft-versus-host disease, immune suppression, and medication needs. These results can help design trials to focus on improving outcomes, patient counseling pre-transplant prior to undertaking the procedure, follow -up planning, and determining transplant eligibility from medical and social perspectives. HSCT in the context of clinical trials with extended follow-up is critical to describe the natural history of SCD post-HSCT.

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Poster # 315

**GENE THERAPY KNOWLEDGE AND DECISION MAKING IN TRANSFUSION  
DEPENDENT THALASSEMIA**

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Georgia, United States*

**Background:**

Hematopoietic stem cell transplantation has for decades, been the only treatment option with curative intents for patients with transfusion dependent thalassemia (TDT) but its application is limited by the lack of suitable donors and associated morbidity/mortality. Transplantation of

autologous genetically modified hematopoietic cells, the elimination of graft versus host disease (GVHD) and need for prolonged immunosuppression makes gene therapy (GT) a promising alternative. However, since GT requires prior myeloablative chemotherapy other risks such as infertility remain. Early results of GT studies suggest that not all patients achieve transfusion independence after the procedure, posing a difficult decisional dilemma.

**Objectives:**

The objective of this study was to examine patient knowledge about GT in TDT, evaluate the factors which influence patient/family decisions about TDT, and determine what degree of transfusion dependence would be considered an acceptable outcome of GT.

**Design/Method:**

We designed a qualitative research study using semi-structured interviews for patients/parents with TDT. Using a purposive sampling strategy (to obtain a diverse population), participants were recruited largely from the Cooley's Anemia Conference in Atlanta and the Thalassemia Program. Transcribed interviews were coded and the data were examined for emerging themes (thematic analysis).

**Results:**

17 study participants with mean age of 38Y (17-52Y) have been interviewed. Six adult participants are living with TDT, the other eleven are parents of children with TDT. All participants had heard about GT but had difficulty describing the process. Participants were aware that GT involved use of a patient's own cells, chemotherapy (as with HSCT) and that possible outcomes included transfusion reduction or independence.

Emerging themes for patient/family interest in GT include:(i) curative potential, particularly using a patient's own stem cells, thus no risk for GVHD (ii)abolishing/reducing transfusions, ultimately decreasing iron burden and chelation needs (iii)decreased healthcare utilization and (IV)improved quality of life.

Emerging themes for hesitancy for GT include (i)insufficient knowledge about the process and long-term outcomes (ii) safety (iii) infertility (iv)genetic modification and risk of cancer (v)prolonged hospitalization for GT. Participants expressed hesitancy to pursue a relatively new treatment without long-term proven record of success but generally conveyed a readiness to accept gene therapy in the future as a treatment modality, with reductions in transfusions (at least 50%) and/or moderate degree of anemia as the outcome of therapy.

**Conclusion:**

There is tempered excitement about GT in patients/families with general willingness to accept a reduction in the frequency of transfusions as the outcome.

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Poster # 316

**COMPARISON OF TBI BEFORE AND AFTER CHEMOTHERAPY PRIOR TO STEM CELL TRANSPLANTATION**

**Clayton Habiger, Brandon Triplette, Ying Li**



**Background:**

Hematologic malignancies may require, at one point during their treatment, allogeneic bone marrow transplantation. Preparative regimens prior to transplantation are administered to provide sufficient immunoablation to prevent graft rejection, reduce the tumor burden and empty the host bone marrow for donor marrow cells. Chemotherapy combined with total body irradiation is a common preparative regimen, however evidence of the optimal order remains limited.

**Design/Method:**

A retrospective chart review was performed with information already available in the medical record between the years 1995-2017. Patients were analyzed based on if the patient received chemotherapy followed by total body irradiation (Chemo/TBI), if the patient received TBI before chemotherapy, or if no TBI was administered. Additionally, timing of antithymocyte globulin administration (Distal, Proximal or no ATG) was analyzed as this could represent a significant variable in our results.

**Results:**

The TBI/Chemo group had a 78.9% survival rate, chemo/TBI group had a 55.3% survival rate, and no radiation group had a 65.0% survival rate. Demographics, donor type, status before transplant, diagnosis, and Graft versus Host Disease were roughly the same between the groups. The TBI/Chemotherapy group mostly (92%) occurred in the years 2011-2017 while Chemotherapy/TBI were mostly (58%) in the years 2001-2010. The No ATG group had a 41.3% survival rate, distal ATG group had a 66.7% survival rate, and proximal ATG group had a 72.0% survival rate. The No ATG group was almost entirely comprised of sibling donors and occurred in the 1990s to early 2000s, while the distal and proximal ATG groups were almost entirely matched unrelated donors and occurred in the early 2000s to present. The relapse rate for the TBI/chemotherapy group was much lower than Chemotherapy/TBI and no radiation groups (7.9% versus 31.8% and 30.0%, respectively). Immune reconstitution was roughly equivalent between the TBI groups, but the distal ATG group had quicker CD3 count recovery compared to the other groups (75 days versus 100 and 175 days for proximal ATG and no ATG, respectively).

**Conclusion:**

Our results indicate that administration of total body irradiation prior to chemotherapy in hematopoietic stem cell transplantation preparative regimens are correlated to improved survival and decreased risk of relapse.

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Poster # 317

**EXERCISE IS MEDICINE: A QI INITIATIVE TO IMPROVE MOBILITY IN THE PEDIATRIC STEM CELL TRANSPLANT UNIT**

**Haleigh Schreck, Lydia Robey, Gretchen Eames, Jessica Munger, Brittany Reiling, Ashraf Mohamed**

**Background:**

Patients undergoing stem cell transplant (SCT) endure prolonged hospitalizations with decreased activity level, which quickly evolves into loss of muscle mass and decreased functional strength. The rehabilitation department at a large pediatric facility recognized that these patients have low participation rate (<75%) in planned Physical Therapy (PT) sessions, and many patients become deconditioned by the time of discharge.

**Objectives:**

To increase overall activity level, functional independence, and prevent loss of strength and physical debilitation of patients in SCT unit during prolonged hospital stay.

**Design/Method:**

Exercise is Medicine initiative was developed to provide early education to patients/families on SCT unit emphasizing the importance of regular daily activity, safe participation in exercise, and normalized sleep/wake schedules during hospitalization. Patients/families were empowered to stay active outside of designated PT sessions, thus, shifting session focus toward resistance and endurance exercise rather than basic mobility tasks. Expectations and guidelines were created to promote increased time out of bed during daytime hours. Miles in Motion program was designed to motivate patients by earning prizes for walking laps or riding bikes.

Multiple PDSA cycles (4 cycles over 15 month period) were conducted. Data was collected for the following: success rate of attempted PT sessions before and after roll-out, 1-min sit to stand (STS) scores at admission and discharge, rate of participation in Miles in Motion program, and rate of high frequency skilled therapy needs.

**Results:**

Average admission to SCT unit was 40-45 patients per year with a collective 1,614 admission days/year. Age range included was 0-21 years (7-21 years for Miles in Motion participation). Pre-roll out, 43% of patients had high frequency PT needs ( $\geq 4x/week$ ), which decreased after 1st PDSA cycle to 34% and after the 4th cycle to 14%, indicating significant ( $P<0.5$ ) decline in rates of patient debilitation necessitating frequent PT. By the time of discharge, 71% of patients improved their 1-min STS scores, while the remaining 29% maintained their admission score indicating stable to improved functional strength by discharge. Patients' completion of planned PT sessions increased from 73% to 89% after the 4th PDSA cycle. After the 1st PDSA cycle, 67% of patients participated in Miles in Motion, and 92% participate after the 4th PDSA cycle ( $P<0.5$ ).

**Conclusion:**

With a multidisciplinary approach to enhance and incentivize activity and exercise during prolonged hospitalizations, patients in SCT unit demonstrated increased overall activity levels, successful participation in PT sessions, and retention or improvement of functional strength and endurance.

## **SIGNIFICANCE OF LATE MIXED CHIMERISM IN LEUKEMIA PATIENTS FOLLOWING HEMATOPOIETIC CELL TRANSPLANT**

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### **Background:**

Allogeneic hematopoietic cell transplant (HCT) has played a significant therapeutic role in treating pediatric leukemia patients who present with high risk or relapsed disease. The importance of predominantly donor cells in the short-term following transplant is well understood in order to create a graft-versus-leukemia (GVL) effect and prevent relapse; however, the significance of continued full donor chimerism is not well understood in long-term survivors. It remains unclear whether very late mixed chimerism may be an early sign of impending relapse or bears little clinical significance at a certain time point post-HCT.

### **Objectives:**

We aim to examine the significance of late mixed chimerism as it relates to the risk of relapse or long-term complications in patients post-HCT. We report on two patients at our institution who received HCT as treatment for leukemia (acute lymphocytic leukemia and juvenile myelomonocytic leukemia) and subsequently developed very late mixed chimerism.

### **Design/Method:**

case report

### **Results:**

Our two patients' chimerisms have been tracked yearly following HCT. Patient 1 received a partially T cell depleted allogeneic HCT with a 7/8 HLA-matched female unrelated donor at the age of 2 years 11 months. The earliest documentation of decreasing percentage of donor cells was at twelve years post-transplant. Her variable nucleotide repeat (VNTR) is currently 51.5% donor at 26 years following transplant. Patient 2 received a HCT via 5/6 unrelated female cord blood with a B antigen mismatch donor at the age of 1 year 5 months. The percentage of donor cells started steadily decreasing at seven years post-transplant. His VNTR is currently 83.5% donor at 12 years following transplant. While both patients no longer have a significant proportion of recipient marrow, they have not shown any clinical evidence of impending relapse, graft-versus-host disease, or secondary malignancies. Late effects related to treatment have included hypothyroidism secondary to a thyroidectomy, short stature, osteoporosis, cataracts, focal nodular hyperplasia of the liver, atypical nevi, and renal insufficiency.

### **Conclusion:**

The patients described in this report depict cases of late mixed chimerism that do not appear to correlate with significant clinical consequences. Although studies have shown the importance of

donor chimerism in the early post-HCT period, continued full donor chimerism long-term may not be necessary to achieve continued remission. As the use of cellular therapies (including HCT, donor-lymphocyte infusions, and chimeric antigen receptor T-cells) continues, it will be important to continue to follow donor chimerism to help determine if and when further intervention is necessary if persistence wanes.

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Poster # 319

## **AUTOIMMUNE COMPLICATIONS POST AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION: A CASE STUDY**

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### **Background:**

Autoimmune disorders have been described following autologous and allogeneic hematopoietic stem cell transplantation (HSCT). After HSCT, the innate immune system recovers rapidly whereas the adaptive immune system may take years to fully reconstitute. During this reconstitution of the immune system, patients are at risk for developing graft versus host disease, experiencing graft versus tumor effects, or more recently documented developing autoimmune disorders. Autoimmune disorders have become more reported in up to 5 percent of patients post-transplant.

### **Objectives:**

This report describes an 18-year-old female who developed multiple autoimmune findings following autologous hematopoietic stem cell transplantation for Stage III Neuroblastoma.

### **Design/Method:**

Her initial transplant admission was complicated with severe mucositis, Adenovirus colitis, and severe veno-occlusive disease (VOD) requiring Defibrotide. She was readmitted on transplant day +70 for hematemesis and melena. She developed profuse diarrhea requiring Octreotide, TPN with additional fluids to compensate for insensible losses, and additional supportive care measures. During this time, she developed pancytopenia, indirect hyperbilirubinemia, pleural effusions and atypical pneumonia.

### **Results:**

Testing ruled out VOD, neuroblastoma relapse, and TMA. Between days +70 to +90, she developed the following autoimmune manifestations: autoimmune hemolytic anemia, prolonged aPTT related to an acquired factor inhibitor, positive ANA, thyroglobulin antibodies, autoimmune thrombocytopenia, and autoimmune colitis. IVIG provided brief improvement in her thrombocytopenia, but this was not sustained. She was subsequently started on Mycophenolate Mofetil and Methylprednisolone with improvement in her constellation of symptoms allowing for the weaning of supportive care measures.

**Conclusion:**

She is now six months post-transplant with complete resolution of her symptoms and normalization of all antibodies. She has completed the remainder of her treatment plan, is currently off all immunosuppression for four months, and is cancer free. It is important for clinicians caring for patients post autologous transplant to consider autoimmunity as a post-transplant complication.

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Poster # 320

**THE USE OF BORTEZOMIB FOR TREATING GVHD IN PEDIATRIC HSCT PATIENTS**

**Devangi Shah, Jennifer Douglas, Jumana Ashy, Gregory Suhrheinrich, Edward Dela Ziga, Asha Pillai, Julio Barredo, Warren Alperstein**

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**Background:**

Graft versus Host Disease (GVHD) is a common complication after allogeneic hematopoietic stem cell transplants (HSCT). Corticosteroids are first-line therapy for GVHD, yet consensus is lacking for second-line therapy in patients who experience worsening symptoms when steroid doses are reduced (steroid-dependent) or who progress despite optimum steroid therapy (steroid-refractory).

**Objectives:**

Bortezomib is a first-generation reversible proteasome inhibitor that has shown promise in adult clinical trials; however, there is little data on Bortezomib use for GVHD in children. We hereby report on a single institutional case-series of Bortezomib use for treatment of GVHD in the pediatric population post-HSCT.

**Design/Method:**

A chart review was conducted on four pediatric patients who have been treated for GVHD with Bortezomib in the University of Miami Health System. For each patient, HSCT procedural information, GVHD diagnosis, GVHD flare occurrences, and response to various therapies were recorded.

**Results:**

The first case was a 7-year-old male who presented with gastrointestinal GVHD and skin GVHD post-HSCT. His skin GVHD failed multiple therapies, continued to worsen, and remained steroid-dependent. He then began Bortezomib and received weekly doses (range: 0.5-1.0 mg/m<sup>2</sup>) for 30 weeks. Use of Bortezomib allowed for weaning of steroids and ultimately discontinuation of other immune suppression without additional flares. The second case was a 4-year-old male who presented initially with skin GVHD post-HSCT. His GVHD was steroid-dependent, and Bortezomib was started for another attempt to wean off steroids. After 15 Bortezomib doses (range: 0.4-0.87 mg/m<sup>2</sup>), his skin GVHD resolved, allowing discontinuation of steroids and all immune suppression. However, liver GVHD then developed which was unresponsive to

Bortezomib. The third case was a 1-year-old female who presented with skin GVHD post-HSCT. Her skin GVHD failed multiple therapies and remained steroid-dependent. She then began Bortezomib doses (range: 0.1-1.3 mg/m<sup>2</sup>), to which she showed a partial response but was unable to be completely weaned off steroids. The fourth case was a 19-year-old male with lung GVHD post-HSCT. He received Bortezomib doses (range: 0.2-1.3 mg/m<sup>2</sup>) for 12 weeks with other therapies including steroids, sirolimus, rituximab, and photopheresis. This permitted successful weaning of steroids only. However, he died from progressive pulmonary complications.

**Conclusion:**

We hereby report based on these four cases that Bortezomib is a safe, well-tolerated option for adjuvant GVHD therapy in children post-HSCT, as its addition resulted in successful discontinuation of steroids in two out of four patients. Well-designed studies of GVHD treatment with Bortezomib in pediatrics are necessary to elucidate this initial finding.

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Poster # 321

**HAPLOIDENTICAL BONE MARROW TRANSPLANT IN AN ADOLESCENT WITH SCD AND SEVERE INTRACRANIAL VASCULOPATHY**

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**Background:**

Sickle cell disease(SCD) is an inherited group of disorders due abnormalities in hemoglobin that results in hemolysis and vaso-occlusive phenomena in almost every organ system in the body, including intracranial large-vessel angiopathy also known as Moyamoya vasculopathy. Moyamoya disease is characterized by progressive arterial stenosis of the circle-of-Willis with resultant formation of capillary-sized-collateral vessels. Patients who develop this complication have a high-risk of intraventricular hemorrhage and permanent neurologic deficits.

**Objectives:**

To report the case of an African-American patient with severe homozygous sickle cell anemia complicated by cerebrovascular vasculopathy who successfully underwent a haploidentical hematopoietic stem cell transplant.

**Design/Method:**

Case report

**Results:**

Our patient was diagnosed at birth and migrated to the US with his family when he was at 12 years old. He was referred to our clinic and had established care for the past 8 years. Serial Transcranial-Doppler(TCD) imaging showed elevated left-MCA velocities prompting the initiation of chronic blood transfusions. He however experienced two episodes of right-sided

hemiparesis, numbness, and difficulty pronouncing his name all of which resolved within 24 hours. An MRI brain showed severe stenosis of proximal-MCA with post-stenotic-dilatation and decreased blood flow within the distal-right-PCA. Magnetic resonance angiography(MRA) revealed severe stenosis of the left-MCA and brisk filling of M2-branches consistent with Suzuki-Grade-1-Moyamoya-syndrome. One year later, he presented with an acute ischemic stroke requiring a neuro-ICU admission. A decision was made by neurosurgery not to pursue EC-IC-coil revascularization at that time. Progressive worsening of his vasculopathy led to referral for a hematopoietic stem cell transplant. His only sibling has HbSS and registry search for a matched-unrelated-donor was unsuccessful so his mother was a 7/10 HLA match was selected as donor after work-up. Graft source was peripheral blood stem cells due to concern for poor marrow harvest because of similar patient/donor weight. Pre-transplant work was significant for very high donor-specific-antibody titer which requiring desensitization with plasmapheresis, intravenous immunoglobulin, bortezomib, and rituximab. He again developed a right-sided-hemiparesis while undergoing the desensitization therapy that again resolved within 24 hours. Transplant conditioning regimen involved alemtuzumab/fludarabine/thiotepa, melphalan, tacrolimus, mycophenolate and post-transplant high-dose-cyclophosphamide for graft-versus-host prophylaxis. Results: Engraftment occurred thirteen days post-transplant. Day +30 chimerism was 100% donor, confirming donor engraftment. Patient developed mild graft-versus-host-disease of the skin that has resolved. He is currently ten months post-transplant and asymptomatic. Repeat neuroimaging will be done at 12 months post-transplant.

**Conclusion:**

Haploidentical stem cell transplant for sickle cell disease is a reasonable approach for those with severe complications such as advanced Moyamoya vasculopathy.

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Poster # 322

**HEMATOPOIETIC STEM CELL TRANSPLANT OF AN INFANT WITH  
PRENATALLY DIAGNOSED MYELODYSPLASTIC SYNDROME**

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**Background:**

Myelodysplastic syndromes (MDS) encompass a group of blood disorders in which hematopoietic progenitor cells fail to differentiate appropriately resulting in bone marrow dysplasia and peripheral cytopenias. Abnormal hematopoiesis may occur secondary to inherited or acquired genetic alterations in the hematopoietic stem cell. There is a significantly increased risk of myeloid leukemic transformation among patients with MDS. Pediatric MDS is rare, with an incidence of approximately 1.8-4 cases per million per year including both primary and secondary MDS. Children with MDS have a poor prognosis and require aggressive interventions, with the only curative therapy being hematopoietic stem cell transplant.

**Objectives:**

The authors describe a unique case of pediatric MDS with prenatal diagnosis of hydrops fetalis in the setting of heterozygous mutations of Growth Factor Independence-1b (GFI-1b), a transcriptional regulator gene, and Fanconi Anemia Complementation Group D2 (FANCD2), a protein encoding gene.

**Design/Method:**

Single subject case report and literature review

**Results:**

The patient required intrauterine blood product support and was delivered at 33 weeks gestation. The neonatal course was complicated by severe anemia and thrombocytopenia. At 37 weeks corrected gestational age, a bone marrow evaluation revealed 13% blasts by morphology and 6% CD34+ CD117+ myeloblasts by Fluorescence Activated Cell Sorting (FACS) analysis, suggestive of MDS. The patient remained red blood cell and platelet transfusion dependent. Repeat bone marrow evaluation demonstrated persistent dysplasia. The patient underwent successful matched unrelated donor hematopoietic stem cell transplant at 11 months of age.

**Conclusion:**

This is the first report of pediatric primary MDS occurring secondary to concomitant heterozygous mutations in GFI-1b and FANCD2. GFI-1b functions as a repressor protein in regulating hematopoietic stem cell quiescence. Low levels of GFI-1b result in an increased hematopoietic stem cell population and subsequent AML. The FANCD2 gene functions in DNA repair. FANCD2 mutations have been implicated in both hematopoietic malignancies and solid tumors. Given the patient's initial marrow findings consistent with myelodysplasia, we predicted rapid leukemic transformation warranting early hematopoietic stem cell transplant.

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Poster # 323

**SUCCESSFUL HAPLOIDENTICAL BONE MARROW TRANSPLANTATION OF AN INFANT WITH A NOVEL MUTATION IN SAMD9L**

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**Background:**

SAMD9L, a gene located on chromosome 7, is associated with a clinical spectrum of disorders, including ataxia-pancytopenia syndrome and leukemia with monosomy 7. Few cases have been described, with the majority occurring in an autosomal-dominant inheritance pattern. The role of hematopoietic stem cell transplant (HSCT) in the management of the disease is still being studied.

**Objectives:**

To depict an interesting case of a 2-month-old male with a novel mutation in SAMD9L presenting with bone marrow failure and treated successfully with HSCT.



**Design/Method:**

Case Report

**Results:**

A 2-month-old African-American male presented with respiratory failure secondary to RSV bronchiolitis, subsequently developing persistent pancytopenia. Bone marrow examination revealed aplasia, with normal flow cytometry and cytogenetic evaluations. A comprehensive work up for bone marrow failure and immunodeficiency syndromes was non-diagnostic. The patient was also found to have non-obstructive hydrocephalus, multiple arachnoid cysts, bilateral retinal hemorrhages, and severe developmental delay. He underwent a 4/6 HLA matched unrelated cord HSCT at 5-months-old using non-myeloablative conditioning with fludarabine (150 mg/m<sup>2</sup>). Subsequent graft failure occurred at 2 months post-transplant, as evidenced by absent donor cells by sorted chimerism, persistent pancytopenia, and documented bone marrow aplasia. Following graft failure, exome sequencing showed a heterozygous mutation in the SAMD9L gene (c.2581C>T exon 5, p.Leu861Phe). A NMDP donor search was unsuccessful for an acceptable unrelated donor. Genetic testing in both parents was negative, confirming a spontaneous mutation. At 9 months old, the patient underwent haploidentical related peripheral blood HSCT. A reduced intensity conditioning regimen with rabbit anti-thymocyte globulin (6 mg/kg), busulfan (cumulative AUC 10,400 μMol\*min), and fludarabine (150 mg/m<sup>2</sup>) was used. GVHD prophylaxis included tacrolimus, post-transplant cyclophosphamide, and mycophenolate mofetil. He engrafted on D+14. During the conditioning regimen, he developed recurrent episodes of bradycardia and apnea, requiring ventriculo-peritoneal (VP) shunt placement forty-five days post second HSCT. Currently, the patient remains transfusion independent, without evidence of GVHD. His most recent donor chimerism, on D+90, showed CD3 88.6% and CD33 94.2% donor. He continues to receive comprehensive allied health therapies with progressive improvement in his developmental milestones.

**Conclusion:**

To date, five families and some sporadic cases of SAMD9L mutations have been reported; our patient being one of the few novel mutations described. As recent studies in these patients have shown, HSCT was successful in the resolution of bone marrow failure. Haploidentical HSCT proves to be a viable option for patients with no acceptable unrelated donor, as evidenced by the sustained donor chimerism achieved in this case.

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Poster # 324

**MUSCULOSKELETAL LATE EFFECTS IN A PEDIATRIC ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT POPULATION**

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**Background:**

Survival rates for pediatric patients receiving hematopoietic cell transplantation (HCT) are

nearing 70–80%. Survivors are at risk of therapy-related late effects, including musculoskeletal (MSK)-associated complications. Data on the overall burden of MSK late effects post-HCT is limited, and analysis of such late effects may inform upon post-HCT guidelines.

**Objectives:**

Describe MSK late effects in a pediatric population of allogeneic HCT recipients.

**Design/Method:**

We reviewed MSK outcomes of pediatric allogeneic HCT recipients enrolled on a single institution, prospective, long-term follow-up study between the years 2001 and 2017. Beginning one year post-HCT, annual visits included physical examination, self-reported outcomes and screening diagnostic imaging (bone age: yearly, MRI lower extremity for avascular necrosis (AVN): yearly x3 [or until resolved], and CT bone density and/or DEXA scan: yearly x 2 [or until resolved]). MSK outcomes were categorized into one of seventeen groups. Patient-, disease- and transplant-related characteristics were extracted from a prospectively collected dataset and medical chart review. Descriptive statistics were reported and compared using Fischer’s exact test for categorical variables. Data was analyzed using GraphPad Prism v8.3.

**Results:**

During this time period, a total of 356 patients were enrolled and 294 (82.6 %) developed at least one MSK late-effect. Within the affected population, median age at time of HCT was 10.4 years old (range 0.2–25.2). The average number of annual visits per patient was 7.2 (range 1–15). The majority of affected patients received HCT for a malignant indication (73.1%), using primarily myeloablative conditioning (63.9%). Donor sources included matched-unrelated (42.5%), haploidentical (28.2%), matched-related (26.5%), and cord blood (2.7%). The average number of MSK events per patient was 2.5 (range 0.9–6), with a mean time to first MSK event of 1.7 years (range 1–13) post-HCT. While a wide variety of MSK late-effects were found, the majority included: AVN (n=147, 50%), osteoporosis (n=119, 40.5%), osteopenia (n=102, 34.7%), altered range of motion/chronic bone change (n=81, 27.6%) and short stature (n=54, 18.4%). Most complaints were present at the first annual visit (76.1%), and 91.8% of cases by the third annual visit.

**Conclusion:**

We have found that the burden of MSK disease in pediatric survivors of allogeneic HCT is substantive. The majority of patients developed multiple MSK late effects, most of which were present in the early post-HCT time period. We plan to further evaluate for possible risk factors, with an ultimate goal of improving our monitoring strategy to be able to provide earlier intervention.

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Poster # 401

**EQUITABLE ACCESS TO CAR-T CELL TRIALS: AN ANALYSIS OF PATIENT DEMOGRAPHIC AND SOCIOECONOMIC FACTORS AT A SINGLE INSTITUTION**

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**Background:**

Demographic factors, such as race, ethnicity, and socioeconomic status (SES), have been shown to be associated with inferior outcomes in pediatric acute lymphoblastic leukemia (ALL) patients. Low SES is an independent predictor of relapse and previous studies have shown that patients with low SES are also less likely to enroll on clinical trials. However, these studies have primarily focused on conventional chemotherapy trials, and data regarding trial participation for novel cellular therapies is lacking. Given the limited number of pediatric cellular therapy centers and associated travel-related costs, these therapies may not be equally accessible to all patients.

**Objectives:**

To describe the demographic and socioeconomic characteristics of patients accessing chimeric antigen receptor-T cell (CAR-T) trials for pediatric ALL.

**Design/Method:**

Retrospective chart review was performed on all patients with ALL that enrolled on a CAR-T cell trial at Seattle Children's Hospital from 2012 to 2018. Demographic data (including self-reported race/ethnicity and distance traveled to receive treatment) were collected for each patient and analyzed using descriptive statistics. For patients residing within the United States, ArcGIS NSES Index software was used to assign SES score by census tract (0-100, with 50 as the national average).

**Results:**

Our cohort included 117 patients with 77 males (65.8%). The majority (56.4%) of patients identified as non-Hispanic Whites, while a minority identified as Hispanic (18.8%), Black (4.3%), Asian (6.8%), Hawaiian/Pacific Islander (1.7%), American Indian/Alaskan Native (1.7%), and other (15.4%). Almost one-fourth (24.8%) of patients traveled from outside the United States to receive treatment. The median distance traveled to CAR-T therapy was 1118 miles (IQR: 191, 2802) and 731 miles (IQR: 81.5, 1636) for the entire cohort and domestic patients, respectively. Median SES score was 53.3 (IQR: 46.45, 65.75), with only 2.5% of patients falling in the lowest quartile (SES <25).

**Conclusion:**

Only 2.5% of domestic patients treated at our center were in the lowest SES quartile, suggesting economic barriers to participation in CAR-T cell trials. Patients traveled long distances to participate, likely representing a financial burden which could deter patients with lower SES from enrolling in CAR-T cell trials. We plan to collect similar data from additional institutions to assess whether these findings are consistent across regions.

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Poster # 402

# IMPACT OF PROPHYLAXIS CHOICE ON RISK OF PNEUMOCYSTIS PNEUMONIA: A CASE-CONTROL STUDY

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## **Background:**

Pneumocystis jiroveci pneumonia (PJP) is a life-threatening opportunistic infection that occurs in immunocompromised hosts. Prophylaxis is recommended for pediatric patients with malignancies and trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended first line agent. Despite these recommendations, studies have identified that 30-60% of pediatric oncology patients received second line medication due to myelosuppression or hypersensitivity with TMP-SMX.

## **Objectives:**

To determine the risk of PJP diagnosis in patients receiving TMP-SMX prophylaxis compared to second line medications for prophylaxis.

## **Design/Method:**

We conducted a retrospective, single centre, case-control study of pediatric oncology patients less than 19 years of age treated between 2000-2018 in Toronto, Canada. Cases included children diagnosed with PJP between 2000 and 2018 while being treated for underlying malignancy. Patients diagnosed post hematopoietic stem cell transplant were excluded. All possible controls were identified, matched to cases based on age, oncology diagnosis, treatment protocol, phase of treatment, and oncology diagnosis date (+/-5 years). Data on both cases and controls were collected through chart review. For each case, up to 5 controls were randomly selected. The index date was the date of the PJP diagnosis for cases, and the equivalent dummy date for controls. The odds of receiving TMP-SMX versus other prophylaxis between cases versus controls was calculated. Sensitivity analyses excluding documented non-compliance were conducted.

## **Results:**

Eleven cases with PJP were identified and matched to 50 controls. All patients received TMP-SMX prophylaxis initially. Six (55%) cases and 39 (78%) controls were treated with TMP-SMX for PJP prophylaxis prior to their index date. The remaining patients received pentamidine (inhaled or intravenous), dapsone, and/or atovaquone. Reasons to change to second line were myelosuppression (n=11), nausea/vomiting (n=2), transaminitis (n=1), and rash (n=1). Cases with PJP were less likely to have been taking TMP-SMX as prophylaxis when compared to controls without PJP, though this trend did not reach statistical significance [odds ratio (OR) 0.31, 95% confidence interval (95CI) 0.08 – 1.2, p=0.1]. However, after 4 cases and 1 control with documented concerns of non-adherence to prophylaxis were excluded, the odds of having been on TMP-SMX prophylaxis lowered further and was statistically significant (OR 0.07, 95CI 0.008 – 0.70, p=0.02).

## **Conclusion:**

Receiving TMP-SMX prophylaxis is associated with a lower risk of developing PJP when compared to second line medications. Second line medication for prophylaxis should be warranted and efforts made to rechallenge with TMP-SMX when possible.

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Poster # 403

## **FINANCIAL BURDEN OF PEDIATRIC CANCER ON CAREGIVERS**

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### **Background:**

Childhood cancers typically require extensive treatment at specialized centers. Greater distance to care increases travel time and its associated expense, both direct and indirect. The cost of care to the patient and family, often called the “financial burden” has been studied in adult cancer patients far more than in the pediatric cancer population.

### **Objectives:**

To better characterize the financial burden placed on families of pediatric oncology patients during their child’s treatment at a community-based pediatric cancer center in Northern Minnesota.

### **Design/Method:**

A cross-sectional, self-administered survey was sent to caregivers of pediatric cancer patients, identified through a tumor registry query of patients treated at Essentia Health’s Erick Peter Person Children’s Cancer Center in Duluth, Minnesota for malignant neoplasms, from 01/01/2004 through 12/31/2018. Information surveyed included current household income, primary caregivers’ employment one year before and after cancer treatment, education level of primary caregivers and change in employment. Additionally, open-ended questions about experiences of financial burden during or after the child’s treatment were asked.

### **Results:**

Of the 100 surveys that were mailed, 31 (31%) were returned completed. Sixty-one percent of respondents lived in a rural area at the time of their child’s diagnosis. Based upon the median levels of reported income categories, respondents had an average income of 280% of the federal poverty level (min 30% to max 745%, std. deviation 138%). During the first month after their child’s diagnosis, household caregivers missed an average of 17.8 days of work. During the first six months following the child’s diagnosis, household caregivers missed on average 19.4 days of work per month. Of the 31 respondent households, 41.9% reported that at least one caregiver had to quit work or change jobs as a direct result of their child’s cancer treatment. Caregivers identified additional financial burdens during treatment, including the cost of daycare for siblings, pet care, eating out, hotel accommodations, the cost of gas, vehicle maintenance, and the need to cut back on extracurricular activities for siblings.

### **Conclusion:**

Childhood cancer treatment has tremendous short and long-term financial impact on caregivers, with almost half of families surveyed experiencing job loss within months of their child's diagnosis. The quantitative and qualitative assessment of burden in this population identifies additional ways to ease the burden on caregivers of pediatric cancer patients, particularly for rural residents.

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Poster # 404

## **ARE FERTILITY PRESERVATION DISCUSSIONS OCCURRING IN ADOLESCENT ONCOLOGY PATIENTS?**

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### **Background:**

With an increase in childhood cancer survivors, focus must shift to the prevention of late effects from therapy such as infertility. Currently, there are several options for fertility preservation including cryopreservation of mature oocytes, sperm, and gonadal tissue. Although the above options exist, barriers to fertility preservation remain and discussions regarding fertility options do not occur in a timely manner.

### **Objectives:**

We assessed the frequency of fertility preservation discussions documented for pubertal male and female oncology patients in the EHR. We assessed the number of males offered sperm banking and females referred for reproductive endocrinology at diagnosis from 2014-2018. Results were compared to a previous chart review (2010-2013), after which we implemented a fertility preservation team, increased department-wide education, standardized fertility preservation documentation, and provided patient educational handouts. This information will help us evaluate if these tools improved documentation of reproductive health conversations and rates of those pursuing fertility preservation options.

### **Design/Method:**

We obtained a list of patients from our hospital tumor registry that were diagnosed between 1/1/2014 and 12/31/2018. Charts were screened to further evaluate whether the patient met the inclusion criteria. Data collected included age, gender, tanner stage if male and date of first menstrual cycle if female, diagnosis, whether the patient had a documented reproductive health discussion and pursued fertility preservation.

### **Results:**

There were 123 total subjects (male and female) included in the chart review and 67 (54.5%) had a documented discussion regarding infertility risk prior to treatment initiation. Of the 64 female subjects, 53.1% had a documented discussion while only 17.6% were documented in the fertility preservation note. 3 females froze eggs and 1 froze ovarian tissue. Of the 59 male subjects, 55.9% had a documented discussion, with 45.5% of those discussions documented in the fertility preservation note. 14 males attempted sperm banking. Compared to the previous chart review in

2014, there has been an increase from 35.8% to 54.4% in documented discussions in females. Male discussions are stable from 58.5% to 55.9% currently.

**Conclusion:**

While implementation of a more formal fertility preservation process resulted in an increase in the documentation of reproductive health discussions, particularly in females, there is room for improvement. Future steps include utilization of the EHR to increase the referral rate to the fertility preservation team, obtaining support for a Nurse Navigator to further increase awareness and stream-line the process, and continued education of patients, families and entire health care team.

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Poster # 405

**COMMUNITY AIRBORNE MOLD SPORE COUNTS AND INVASIVE FUNGAL DISEASE RISK IN PEDIATRIC LEUKEMIAS AND SCT**

**Mohammed Almatrafi, Victor Aquino, Tamra Slone, Rong Hang, Michael Sebert**

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**Background:**

Patients with hematological malignancies or who have undergone stem cell transplantation (SCT) are at risk of developing invasive fungal disease (IFD). Exposure to mold spores in the hospital environment due to activities such as construction has been described as a risk factor for these infections. The extent of risk posed by exposure to airborne mold spores in the community however has been less well characterized.

**Objectives:**

We sought to assess whether elevated community airborne mold spore counts were associated with increased risk of IFD in ambulatory pediatric patients with hematological malignancies or after SCT.

**Design/Method:**

A retrospective cohort study was conducted of patients receiving treatment for hematological malignancies or during six months following SCT at a pediatric teaching hospital in Dallas, Texas, from 2014 through 2018. Daily readings of airborne mold spore counts were obtained from a National Allergy Bureau monitoring station in the same metropolitan area. Patients with IFD were identified based on case definitions developed by the EORTC/MSG consensus group. Patients residing outside the Dallas-Fort Worth (DFW) area or with probable hospital onset of infection (defined as symptom onset more than two weeks after admission) were excluded from the primary analysis. Association between community airborne mold spore counts and risk of IFD was tested using zero-inflated Poisson regression.

**Results:**

Sixty cases of proven or probable IFD were identified from 2014 to 2018, of which 47 cases

were classified as having possible ambulatory onset. The overall risk of ambulatory-onset IFD was estimated to be 1.2 cases per 10,000 cohort patient-days (95% confidence interval 0.9 – 1.6). Of these 47 IFD patients, 35 resided within the DFW area at the time of symptom onset. Recurring annual variation was seen in community airborne mold spore counts (365-day lag autocorrelation 0.36, Durbin-Watson statistic  $p < 0.0001$ ), with lowest average levels being observed from December through March (2718 spores/m<sup>3</sup>) and highest average levels measured from June through October (6117 spores/m<sup>3</sup>). A small excess of ambulatory-onset IFD was seen from July through September (12 cases) but did not reach statistical significance ( $p = 0.09$ ). No significant association was found between IFD risk and community mold spore counts when taken as either average or maximum values over intervals from one to six weeks prior to symptom onset.

**Conclusion:**

Among pediatric hematological malignancy or SCT patients in the DFW region, there was not a significant association between ambulatory-onset IFD and airborne mold spore counts.

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Poster # 406

**FOOD INSECURITY AND HOUSEHOLD MATERIAL HARDSHIP IN FAMILIES OF CHILDREN WITH NEWLY DIAGNOSED CANCER**

**Carolyn Rocha, Shilpa Nataraj, Bianca Perdomo, Nassim Durali, Yiran Zhang, Courtney Thornburg, Paula Aristizabal**

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**Background:**

The financial toll of childhood cancer on families can be devastating. Household material hardship (HMH)—which includes food, housing, and energy insecurity—is emerging as a more tangible way to measure and address the financial burden of pediatric cancer treatment. Research on HMH in this population has been limited primarily to non-Hispanic whites, despite reports of increased prevalence of food insecurity among minority households.

**Objectives:**

To assess food insecurity and HMH in a diverse sample of parents of children with newly diagnosed cancer and their associations with health literacy, acculturation, distance to treatment center, and socio-demographics.

**Design/Method:**

We conducted a prospective observational study in parents of children with newly diagnosed cancer (past 6 months) at Rady Children’s Hospital-San Diego aimed at assessing associations between food insecurity and HMH with health literacy, acculturation (if Hispanic), and socio-demographics. Univariate and multivariate analyses were used.

**Results:**

We present preliminary results on 37 participants. Seven (18.9%) reported food insecurity and 17



(45.9%) reported HMH. Compared to married parents, unmarried parents had 34 times higher odds of reporting food insecurity ( $P=0.001$ ) and had 2.18 more points on the HMH scale ( $P<0.001$ ). When controlling for covariates, unmarried marital status remained significantly associated with food insecurity ( $P=0.025$ ) and HMH ( $P=0.010$ ). Parent age was also significantly associated with both measures; compared to parents ages 18-34 years, parents ages 35-64 years had 1.5 less points on HMH scale ( $P=0.001$ ) and were less likely to be food insecure, with odds ratio of 0.104 ( $P=0.018$ ). Lower education was associated with food insecurity ( $P=0.012$ ), whereas public insurance was associated with HMH ( $P=0.010$ ). HMH and food security status were not significantly associated with Hispanic ethnicity, health literacy, acculturation, or distance from treatment center.

### **Conclusion:**

Among families with a child newly diagnosed with cancer, unmarried and younger parents were more likely to report HMH and food insecurity. Despite a significant number of Hispanics in our sample, ethnicity was not associated with increased HMH or food insecurity, likely due to the small sample. These findings underscore the importance of providing financial screening and support to caregivers of children with cancer who may need supplementary resources. Future directions include assessment of HMH and food insecurity in a larger sample, and further studies are required to evaluate how families' financial needs evolve over the course of treatment.

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Poster # 407

## **DESCRIPTION OF CARDIOVASCULAR ALTERATIONS ASSOCIATED TO CHEMOTHERAPEUTIC AGENTS**

**Diana Plazas**

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### **Background:**

Survival of children with cancer has improved over the last decades to almost 80%, resulting in a growing number of childhood cancer survivors (CCSs). In our hospital, survival of acute lymphoblastic leukemia is 73,3% reported in a study from 2016. These survivors are at a risk of (life-threatening) late effects of their cancer treatment, being the most frequent secondary malignant neoplasms and cardiovascular disease

### **Objectives:**

The aim of this study is to describe the prevalence of acute and subacute cardiovascular alterations associated to the use of anticancer drugs in pediatric patients treated for acute leukemias (ALL and AML), Hodgkin lymphoma (HL) and non-Hodgkin lymphomas (NHL)

### **Design/Method:**

This was a descriptive, prospective study, of patients >1y and <18 years, with newly diagnosed acute leukemia (ALL and AML), Hodgkin lymphoma and non-Hodgkin lymphoma recruited between October 2017 and march 2018 and follow-up of this cohort until finishing the proposed evaluations. We studied ECG, echocardiography, Troponin T, BNP and Troponin I at diagnosis

and during the follow up. Exclusion criteria were previous cancer treatment, cardiovascular dysfunction at diagnosis, active cardiopathy before the anticancer treatment and the refusal of parents to participate in the study

**Results:**

We included 141 patients, ALL 94, AML 19, HL 16 and NHL 12. 131 patients were eligible and 101 finished all the proposed evaluations. 0% of patients had acute cardiotoxicity. The prevalence of cardiovascular abnormalities was 42.8%, ECG was abnormal in 28.2% of patients and 20.6% had LVEF <53%; the most affected patients were those diagnosed with high risk ALL (45.4%) and AML (26.3%), who had a cumulative anthracycline dose of 270mg/m<sup>2</sup> and 298mg/m<sup>2</sup> respectively. In the present study, only 17.7% of analyzed patients had abnormal values of BNP through the investigation and 1/131 had elevation of troponin I. We don't find any difference between gender and age, different from the reported on other studies.

**Conclusion:**

The results of the present study confirm the low prevalence of acute cardiotoxicity related to the use of anticancer drugs and reveal a high incidence of subacute cardiovascular abnormalities, most frequently encounter in those neoplasms treated with cumulative anthracycline dose >200mg/m<sup>2</sup>. In our cohort, patients with HL didn't have subacute cardiotoxicity in spite of the concomitant treatment with mediastinal radiotherapy. We did not find correlation between LVEF <53% and elevation of serum biomarkers.

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Poster # 408

**PEDIATRIC CANCERS IN THE TEXAS PANHANDLE: A SINGLE INSTITUTION  
RETROSPECTIVE ANALYSIS**

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**Background:**

Pediatric malignancies are on the rise worldwide. Given the necessity of tailoring treatment strategies to each specific disease, characterization of these various pediatric malignancies is of the utmost importance in improving outcomes. While the epidemiology of pediatric cancers has been studied and reported throughout in the US and across the world, no such epidemiological study has yet been done in the Texas Panhandle region. This epidemiological study attempts to determine specific trends and characteristics of pediatric cancers afflicting the Texas Panhandle region.

**Objectives:**

To explore the rates of childhood malignancy, gender makeup and age at diagnosis of pediatric cancers in the Texas Panhandle

**Design/Method:**

This study utilized retrospective medical record data for 149 patients seen at the Texas Tech University Health Sciences Center (TTUHSC) pediatric oncology clinic from April 2000 - June 2017.

**Results:**

The total number of patients analyzed during this time period was 149. The gender makeup was 81 males (54.4%) and 68 females (45.6%). Ages at diagnosis ranged from 4 days to 19 years. In the Texas panhandle, it was observed that acute lymphoblastic leukemia (ALL) (43%), Wilms's tumor (8.1%), and neuroblastoma (8.1%) were the most prevalent forms of pediatric cancer. The average age of diagnosis within the Texas panhandle region was 6.64 years.

**Conclusion:**

While ALL was the most common childhood cancer encountered both in the Texas panhandle and nationwide, its occurrence was disproportionately more common within the Texas panhandle. Similarly, while both Wilm's tumor and neuroblastoma were 8.1% of observed childhood cancers within the Texas panhandle, their proportions of childhood cancers nationwide were significantly lower at 5% and 6%, respectively. The average age of diagnosis for childhood cancer nationwide is 6 years old, and the average age of diagnosis within the Texas panhandle was similarly found to be 6.64 years.

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Poster # 409

**PILOT STUDY OF APIXABAN IN SECONDARY PROPHYLAXIS OF VENOUS THROMBOEMBOLISM IN PEDIATRIC PATIENTS**

**Ashley Pinchinat, Oya Levendoglu-Tugal, Yara Perez, Neida Otero, Arvind Budhram, Harshini Mahanti, Erin Morris, Adele Brudnicki, Deborah Friedman, Simon Li, Mitchell Cairo**

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**Background:**

Venous thromboembolism (VTE) is a major complication in children and adolescents because of its association with significant morbidity and mortality (Raffini, Pediatrics 2009).

Novel oral anticoagulants, direct factor Xa (FXa) inhibitors, are approved in adults for secondary VTE prophylaxis with established efficacy and safety (Male et al, Thromb Res 2019). Apixaban, a selective inhibitor of FXa, has a rapid onset of action, few drug-drug interactions and a predictable anticoagulant response that enables fixed dosing. It has less variability in pharmacokinetic and pharmacodynamic responses than warfarin, and has a wider therapeutic index (Garcia, J Thromb Haemost 2013). Compared to subcutaneous heparin, no injections are required and no pharmacodynamic monitoring is needed.

**Objectives:**

Evaluate the safety and efficacy of Apixaban (Eliquis®) for the prevention of secondary VTEs in

children and adolescents with a newly diagnosed primary VTE.

**Design/Method:**

Children weighing > 40 kg diagnosed with a primary VTE were eligible for study entry. Consented patients were administered apixaban 10 mg twice daily P.O. for 7 days followed by 5 mg twice daily until day 90, based on the AMPLIFY trial in adults (Agnelli, J Thromb Haemost 2015). Treatment began within 72 hours of diagnosis of VTE and transition from other anticoagulants was permitted. (NCT04041843)

**Results:**

Seventeen patients have been enrolled to date with a median age of 16 yrs (10 – 21 years). Five patients had isolated primary pulmonary emboli, ten with isolated venous thromboembolism, and 2 patients with both PE and VTE. There were no episodes of bleeding, classified as Grade I-V hemorrhage (CTCAE v5.0), or other adverse events and no patients required dose modifications. Of the 15 patients that completed the day 30 evaluations, 40% showed resolution of their primary thrombus, one patient had no change, and the remaining patients showed a decrease in the size of the thrombus. There were no patients that experienced increase of their thrombus or any new VTE, which equates to 100% successful VTE secondary prophylaxis.

**Conclusion:**

Preliminary results suggest that apixaban is safe and well tolerated in children and adolescents for the secondary prophylaxis of patients with a newly diagnosed primary VTE. Additionally, all patients had decrease in the size of their thrombus with 40% experiencing complete resolution as early as 30 days. There was no evidence of apixaban related toxicity. A large cohort trial and follow up is ongoing with plans for future investigations in neonates

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Poster # 410

**THE GUT MICROBIOME AND ASSOCIATED CLOSTRIDIODES DIFFICILE COLONIZATION IN PEDIATRIC CANCER PATIENTS**

**Daniel Willis, Yu Tao, Jingquin Luo, Robert Hayashi, Gregory Storch**

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**Background:**

Clostridioides difficile infections (CDI) are the leading cause of infectious healthcare-associated diarrhea and a growing source of morbidity and mortality in hospitalized patients, including pediatric oncology patients. Interventions such as hand hygiene, isolation and standard room cleaning techniques are utilized to help reduce the infection rate, but despite these efforts, rates of CDI have only increased nationwide over time suggesting that these measures are inadequate. Asymptomatic C. difficile colonized patients contribute to the risk of transmission, however colonization rates in pediatric oncology patients are largely unknown. Recent studies have suggested that abnormalities in gut microbiome composition may predispose a patient to CDI.

**Objectives:**

The objective of this study was to evaluate the gut microbiome in pediatric oncology and hematopoietic stem cell transplant (HSCT) patient and its association with *C. difficile* colonization.

**Design/Method:**

We identified pediatric oncology and stem cell transplant patients with banked stool specimens from two previous studies of the microbiome in this patient population. Bacterial culture was performed on thawed baseline specimens using Cycloserine Cefoxitin Mannitol Broth with Taurocholate and Lysozyme (CCMB-TAL). Broths showing growth were subcultured on sheep blood agar. Morphologically suspicious colonies were confirmed as *C. difficile* using mass spectrometry. Nucleic acid was extracted from each specimen and v4 16S DNA analysis was performed. Using univariate log-binomial modeling, bacterial genera were evaluated as risk factors for associated *C. difficile* colonization. Shannon index was calculated for each sample across genera with the Wilcoxon rank sum test used to evaluate the difference in bacterial diversity between *C. difficile* colonization statuses.

**Results:**

Forty-three patients were identified for analysis. In total, 18 were positive for *C. difficile* by culture of baseline stool samples, including 52% (16/31) of HSCT patients. Bacterial diversity did not differ between non-colonized and colonized patients. Two genera, *Enterococcus* and *Fingoldia* were negatively associated with *C. difficile* colonization (RR 0.16, 95%CI 0.04-0.65 and RR 0.15 95%CI 0.03-0.88, respectively). The presence of *Prevotella* and *Faecalibacterium* were risk factors for colonization (RR 5.4 95%CI 1.42-20.52, and RR 3.88 95%CI 1.06-14.19, respectively).

**Conclusion:**

*C. difficile* colonization was highly prevalent in our pediatric HSCT patients pre-transplant and was also detected in non-transplant oncology patients. Specific co-colonized microbiota appear to be positively or negatively associated with *C. difficile* and may be linked to subsequent CDI. Further investigations into colonization patterns may lead to interventions that could alter the rate of CDI.

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Poster # 411

**DEVELOPMENT OF MOLECULAR TUMOR BOARD: THE NEXT STEP TOWARDS PRECISION MEDICINE**

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**Background:**

As molecular profiling of tumors has become more accessible, there has been increasing interest in tumor sequencing for patients with newly diagnosed and relapsed malignancies. This has left clinicians with highly complex genetic information as well as therapeutic recommendations. Conventional medical training has been inadequate in keeping pace with innovation.

Consequently, several hospitals have established molecular tumor board as a platform to discuss these patients and their results. This is the first of its kind outside of a traditional academic center.

**Objectives:**

To investigate molecular profiles of solid tumors and the targeted approaches to treatment through a multidisciplinary educational approach in order to provide comprehensive care.

**Design/Method:**

At our tertiary care Children's Hospital, we formed a multidisciplinary molecular tumor board in June of 2019 comprising of Hematologist/Oncologist, clinical pharmacist, molecular pathologist, geneticist along with members from clinical research, palliative care and the hospital ethics committee.

**Results:**

This widely attended tumor board is held monthly; a broad spectrum of diseases have been discussed, mostly relapsed and rare solid tumors. Reports issued through commercial platform such as Foundation medicine and those available through research collaboration are discussed. A template for discussion has been followed, described below:

Oncologist: summary of the case and highlights of the driver mutation

Pathologist: compare and contrast the diverse methods of molecular pathology as relevant for the case e.g. FISH versus RT PCR versus NGS

Clinical pharmacist: choice of drug, formulation, molecular pathways

Geneticist/genetic counselors: recommend counseling as appropriate for patient and family members

**Conclusion:**

This tumor board has allowed a formal presentation of complex medical reports in a multidisciplinary format while providing drug recommendation to the primary Oncologist and genetic counseling in relevant cases.

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Poster # 412

**THE ROLE OF GENOMIC BIOMARKERS IN TREATING PEDIATRIC CANCERS**

**Robin Pham, Aubrey Swilling, Tyler Hamby, Anish Ray**

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**Background:**

The outcomes for pediatric oncology patients with advanced stage or recurrent disease have remained poor, despite tremendous advancement in the field over the last several decades. Current efforts have focused on incorporating immunotherapy and related biomarkers to guide therapy options. Tumor mutation burden (TMB) and microsatellite instability (MSI) are two biomarkers that may help predict a patient's response to immunotherapy agents such as programmed death-ligand 1 (PD-L1) inhibitors. The utility of these biomarkers has been

described and validated in adult oncology, but little is known about the use of these biomarkers in the pediatric population.

**Objectives:**

The goal of this study is to describe the tumor mutation burden, microsatellite instability, and PD-L1 status of pediatric neoplasms.

**Design/Method:**

Retrospective chart review was conducted on 82 patients who were treated for cancer and underwent tumor molecular sequencing from 2013 to 2019 at Cook Children's Medical Center. Samples were sent to FoundationOne for remote sequencing. When requested, reports included TMB, MSI, and PD-L1 status. TMB was characterized as low (1-5 mutations/mb), intermediate (6-19 mutations/mb), or high (> 20 mutations/mb); MSI as stable or unstable; and PD-L1 status as positive or negative.

**Results:**

There were 5 patients with CNS tumors, 4 patients with leukemia and lymphoma, 33 patients with neuroblastoma, and 40 patients with other solid tumors. Thirty-four patients were tested for PD-L1 status and 6 (18%) were positive. TMB was determined for 51 patients: 44 (86%) were low burden, 7 (14%) intermediate burden, and 0 (0%) high burden. MSI status was determined for 41 patients and all were determined to be stable. Twenty-six patients had all three of these tests (TMB, MSI, PDL-1 status) performed. Of those positive for PD-L1, only 1 patient received anti-PD-L1 therapy with pembrolizumab. This patient did not experience any drug-related adverse effects but came off the drug because of disease progression.

**Conclusion:**

Biomarkers for immunotherapy are of emerging significance in the treatment of pediatric tumors. This study suggests that biomarker profiles in pediatric malignancies may vary from those in the adult population. More studies are warranted to determine the role of these biomarkers in pediatric cancers.

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Poster # 413

**GENOMIC PROFILING OF PEDIATRIC TUMORS: A SINGLE INSTITUTION EXPERIENCE**

**Aubrey Swilling, Robin Pham, Tyler Hamby, Anish Ray**

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**Background:**

Outcomes for patients with childhood cancer remain poor for relapsed and advanced stage disease, despite intensification of conventional chemotherapeutic agents. In recent years, whole genome sequencing has emerged as a vital tool to identify driver genetic alterations leading to identification of targeted therapies and clinical trials for these patients.

**Objectives:**

The goal of this project is to study the prevalence of potentially actionable oncogenic variants in a sample of pediatric tumors, to identify agents that may target those variants, and to highlight the potential utility of targeted therapies in pediatric cancers.

**Design/Method:**

Retrospective chart review was conducted on 82 patients who were treated for cancer and underwent molecular sequencing from 2013 to 2019 at Cook Children's Medical Center. Tumor samples were sent to Foundation Medicine, Inc. for remote sequencing, which identified genetic variants and available approved or experimental targeted therapies. The druggable recommendations were then stratified by clinical significance supported by current evidence to level 1, 2, and 3. Level 1 variants have the most supported clinical utility as actionable findings. Level 2 variants may have potential clinical utility. Level 3 variants have limited utility or are currently being investigated.

**Results:**

There were 5 patients with central nervous system (CNS) tumors, 4 patients with leukemia and lymphoma, 33 patients with neuroblastoma, and 40 patients with other solid tumors. Thirty-five (43%) patients were initially identified as having genetic alterations with approved or experimental targeted therapy available. In these patients, a total of 42 druggable alterations were identified: 27 (64%) level 1 variants, 10 (24%) level 2 variants, and 5 (12%) level 3 variants. Overall, 13 (16%) patients received targeted therapy based on their identified alterations: 12 (44%) level 1 variants and 1 (10%) level 2 variant were matched to targeted therapy. No level 3 variants were matched to targeted therapy. The most commonly targeted variant was ALK (n=7). Three (23%) matched patients experienced drug-related adverse effects. Only 1 of these patients developed a life-threatening adverse effect.

**Conclusion:**

Remote genomic profiling of pediatric neoplasms provides a feasible option in identifying potential targeted therapies; however, reports require evaluation and interpretation by a multidisciplinary team to provide clinical recommendations. This study highlights that a subset of pediatric tumors harbor targetable genetic alterations, but the use of targeted agents in this population is still not well described and merits further investigation.

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Poster # 414

**COMPREHENSIVE GENOMIC PROFILING OF CELL-FREE CIRCULATING TUMOR DNA IN PEDIATRIC CANCER PATIENTS**

**Andrew Rankin, Alison Roos, Omar Hamdani, Pratheesh Sathyan, Matthew Hiemenz, Eric Severson, Brian Alexander, Shakti Ramkissoon, Prasanth Reddy**

*Foundation Medicine, Cambridge, Massachusetts, United States*

**Background:**

Next generation sequencing (NGS)-based genomic profiling of circulating tumor DNA (ctDNA)



offers the ability to identify potentially targetable and prognostic genomic alterations (GA) non-invasively through liquid biopsy. Additionally, sequencing of ctDNA may reveal intratumoral genomic heterogeneity and the genomic make-up of distant metastases. Pediatric cancer patients often receive no molecular diagnostic testing to inform potential targeted therapy selection and subsequently receive conventional chemotherapy regimens which are associated with poor outcome in many diseases. Genomic profiling with liquid biopsy is non-invasive and may provide a means to identify new treatment options for this underserved patient population.

**Objectives:**

To analyze ctDNA-based genomic profiling results from pediatric patients to determine where liquid biopsy has the potential to inform clinical care.

**Design/Method:**

For genomic profiling of ctDNA from plasma, 20 mL of peripheral whole blood was collected; 20–100 ng cell-free DNA (cfDNA) was extracted from plasma and subjected to genomic profiling, with greater than 30,000× raw coverage, 5,000× unique coverage and approximately 3,000× redundant (i.e., error-corrected) coverage. All testing was performed in a CLIA-certified, CAP-accredited and New York State-accredited laboratory (Foundation Medicine, Cambridge, MA, USA).

**Results:**

Genomic findings were analyzed for 149 pediatric cancer patients (range <1-21 years) who received ctDNA-based genomic profiling. The patient dataset was enriched for neuroblastoma (50%, n=76), but also represented by patients with brain tumors (14%, n=21), osteosarcoma (5%, n=8), and rhabdomyosarcoma (5%, n=8), with the remaining cases consisting of histiocytic neoplasms and a diverse range of solid tumors. Among all cases, at least one GA with predictive and/or prognostic implications was identified in 35% (n=52) of cases. When considering the subset of patients with neuroblastoma, 47% of cases harbored at least one GA in diverse genes including ALK, BRCA1/2, NF1, PIK3CA, NRAS, and BRAF, all potentially druggable with currently-available targeted therapy or that may facilitate clinical trial enrollment.

**Conclusion:**

We describe a population of pediatric patients with targetable gene alterations identified with comprehensive genomic profiling of ctDNA with liquid biopsy, predominantly enriched in neuroblastoma, brain tumors, osteosarcoma, and rhabdomyosarcomas. Emerging clinical evidence suggests liquid biopsy may facilitate treatment decision making in diverse cancer types. This retrospective study adds to this body of data with important clinical implications for pediatric patients with solid tumors. Future investigation into this non-invasive diagnostic approach to identifying druggable genomic biomarkers is strongly warranted.

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Poster # 415

**A MATH MODEL FOR THE PREDICTION OF TUMOR LYSIS SYNDROME: A COLLABORATION WITH CERNER INTELLIGENCE.**

**Nicole Wood, Sasanka Are, David Dellsperger, James Gritter, Kate Vanlandingham, Kinsey Grove, Keith August, Karen Lewing**

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**Background:**

Tumor Lysis Syndrome (TLS) is a life-threatening oncologic emergency. Patients at highest risk for TLS include those with bulky disease, high tumor burden, chemo-sensitive malignancies and pre-existing metabolic derangements. Patients with newly diagnosed and newly relapsed hematologic malignancies, such as leukemia and lymphoma, are at highest risk. Treatment of TLS includes aggressive fluid hydration, allopurinol, and at times rasburicase, a costly medication used to catabolize uric acid.

**Objectives:**

Primary Objective: Develop and adapt a TLS math model for pediatric oncology.

Secondary Objectives: Utilize the math model to identify patients at high risk (HR) for TLS and minimize rasburicase usage in patients at moderate risk (MR) and low risk (LR) for TLS.

**Design/Method:**

The original TLS math model developed by Cerner Intelligence was adapted for use in pediatrics and applied retrospectively to children with leukemia or lymphoma from January 1, 2009 to November 11, 2019 and prospectively from April 1, 2019 to October 1, 2019 in Cerner for investigators only.

**Results:**

The TLS model categorized patients as LR, MR or HR for TLS based on white blood cell count (WBC), serum uric acid (SUA), serum creatinine (SCr) and serum lactate dehydrogenase (LDH).

Retrospective application of the TLS model to 805 patients over a 10-year period classified 576 (71%) patients as LR, 183 (23%) MR and 46 (6%) HR. Of the HR patients, 11 (24%) received allopurinol only, 5 (11%) received rasburicase only, 26 (57%) received both medications and 4 (8%) received neither. Of the MR patients, 120 (66%) received allopurinol only, 5 (3%) received rasburicase only, 26 (14%) received both medications and 32 (17%) received neither. Of the LR patients, 234 (40%) patients received allopurinol only, none received rasburicase, 10 (2%) received both medications and 332 (58%) received neither.

Prospective review identified 23 patients with newly diagnosed leukemia or lymphoma over a 6-month period. 4 (17%) patients were classified as HR, 3 (13%) as MR and 16 (70%) as LR. All HR patients received both allopurinol and rasburicase. 1 MR patient received rasburicase and all 3 received allopurinol. No LR patients received rasburicase and 12 of the LR patients (75%) received allopurinol only.

**Conclusion:**

Our collaboration with Cerner Intelligence led to a validated model for predicting TLS in pediatric patients and may be used to detect undiagnosed patients at HR for TLS, accurately trend TLS risk and aid physicians in determining the need for rasburicase in HR TLS.

## LANDSCAPE OF POTENTIALLY ACTIONABLE FUSIONS IDENTIFIED BY GENOMIC PROFILING OF PEDIATRIC TUMORS

Andrew Rankin, Alison Roos, Omar Hamdani, Pratheesh Sathyan, Matthew Hiemenz, Eric Severson, Brian Alexander, Shakti Ramkissoon, Prasanth Reddy

*Foundation Medicine, Cambridge, Massachusetts, United States*

### **Background:**

Pediatric cancers are generally characterized to be genomically quiet; however, recent studies have identified actionable genomic alterations (GA) that may help guide treatment decisions or clinical trial selection. Genomic fusions involving NTRK1/2/3, ROS1, or ALK genes act as drivers in some pediatric tumors and have targeted therapy options. However, pediatric cancer patients often receive no molecular diagnostic testing and subsequently receive conventional chemotherapy regimens which are associated with poor outcome in many diseases. Comprehensive genomic profiling (CGP) may provide a means to identify new treatment options and improve clinical outcomes for this underserved patient population.

### **Objectives:**

To conduct a retrospective analysis of targetable genomic fusions identified from 6990 pediatric cancer patients (range <1-21 years) who received genomic testing during the course of routine clinical care and determine the frequency of patients with additional potential therapeutic options based on genomic profiling.

### **Design/Method:**

CGP was performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified, CAP (College of American Pathologists)-accredited laboratory (Foundation Medicine Inc., Cambridge, MA, USA). Hybrid capture was performed for all coding exons from 287 (version 1) to 315 (version 2) cancer-related genes plus select introns from 19 (version 1) to 28 (version 2) genes. Various samples were similarly assayed but performed in DNA on 406 genes and selected introns of 31 genes involved in rearrangements, and in RNA on 265 genes.

### **Results:**

Potentially targetable fusions were identified in 423 solid tumors and 70 hematologic malignancies, representing ~7% of pediatric cancers in the Foundation Medicine pediatric database (n=6990). Pediatric cancer patients with pilocytic astrocytoma (n=111), unspecified glioma (n=33), inflammatory myofibroblastic tumors (IMT) (n=30), papillary thyroid carcinoma (PTC) (n=26), soft tissue sarcoma (n=22), or anaplastic large cell lymphoma (n=17) demonstrated the highest frequency of targetable fusions investigated. Of pediatric patients with lung cancer (n=15), 47% (n=7) had a targetable fusion involving ALK, RET, or ROS. NTRK fusions were enriched in patients with soft tissue fibrosarcoma (n=11), PTC (n=6), malignant peripheral nerve sheath tumors (n=3), and glioblastoma multiforme (n=4). FGFR fusions were identified in patients with ganglioglioma (n=5), oligodendroglioma (n=4), unspecified glioma

(n=6), and bladder urothelial carcinoma (n=2), among other tumor types. RET fusions were enriched in patients with PTC (n=15), while ROS fusions were enriched in patients with brain tumors (n=15) and IMT (n=6).

**Conclusion:**

Our results suggest that CGP in pediatric cancer patients can identify targetable genomic fusions across diverse pediatric cancer types which may not be identified with standard of care molecular diagnostic testing.

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Poster # 417

**EVALUATION OF SYMPTOMS AND NASAL FINDINGS IN INDIVIDUALS WITH A PATHOGENIC GERMLINE DICER1 VARIANT**

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**Background:**

Nasal chondromesenchymal hamartoma (NCMH) is a rare, typically benign, nasal tumor that commonly presents in young children and has a reported association with DICER1 pathogenic germline variations. NCMH can be locally destructive and recurrent if not discovered early and fully resected.

**Objectives:**

We sought to determine differences in sinonasal signs and symptoms between DICER1-carriers and controls, determine likelihood of development of NCMH in our cohort, and expand the published literature with six new cases of NCMH.

**Design/Method:**

Medical charts were reviewed from DICER1-carriers (individuals with pathogenic germline DICER1 variations) and controls enrolled in the DICER1 Natural History Study at the National Cancer Institute (NCI) to quantify and compare rhinological symptoms experienced between cohorts. Both the NCI DICER1 study and the International Pleuropulmonary Blastoma/DICER1 Registry were queried for unpublished cases of NCMH. Lastly, a systematic literature review was conducted.

**Results:**

There were no clinical differences in rhinological symptoms experienced by the DICER1-carriers and controls seen in the ENT clinic as part of the DICER1 Natural History Study. However, two patients went on to develop chronic sinonasal symptoms and were both found to have NCMH. Additionally, we identified six unpublished NCMH cases in the NCI study and International PPB/DICER1 Registry. A review of the literature identified twelve published cases since the last review in 2015. Of these published and unpublished cases, 38% had at least one

additional DICER1-associated tumor and 24% of the NCMH were found in the ethmoid sinus over other areas. The incidence of NCMH in DICER1-carriers in this cohort, including both Field and Clinical Center cases, is 2 cases in 555 person-years of observation.

**Conclusion:**

We quantified the risk of developing NCMH in our cohort of 236 DICER1-carriers, report six unpublished cases, and provide an updated review of the literature. As NCMH can be damaging to surrounding structures and recurrent, we advocate for a low threshold for evaluation and referral of any patient with pathogenic germline DICER1 variations with chronic sinonasal symptoms. Symptoms can include, but are not limited to, chronic rhinorrhea, nasal congestion or recurrent sinusitis (especially unilateral), snoring, nasal masses, proptosis of the eye or nasomaxillary pain.

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Poster # 418

**MEDICAL MANAGEMENT OF ALK-POSITIVE PEDIATRIC IMT: A SINGLE INSTITUTION EXPERIENCE**

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**Background:**

Inflammatory myofibroblastic tumors (IMT) are rare soft tissue neoplasms with These can occur anywhere in the body, although rarely metastasize. Surgery is considered standard of care; however, there are instances where these tumors are inoperable or cannot be fully resected. Most IMTs harbor alterations in the ALK tyrosine kinase, resulting in an oncogenic addiction that renders them sensitive to targeted ALK inhibition. In this report, we share our institutional experience with the pharmacologic treatment of pediatric IMTs.

**Objectives:**

To document the use of the ALK inhibitor crizotinib for the medical management of pediatric IMT

**Design/Method:**

Between 2010 and 2019, six patients were diagnosed with ALK – positive IMT and treated with the first generation ALK inhibitor, crizotinib. Tissue biopsy was obtained for each patient and ALK status confirmed by various methods including immunohistochemistry, FISH/cytogenetics, or next generation sequencing. Patients were treated by the standard dosing guidelines and monitored for response and toxicities. Charts were reviewed from date of presentation to present.

**Results:**

Between 2010 and 2019, six patients ages 6 months to 14 years with IMT harbored ALK fusion proteins and were treated with crizotinib. We observed a 100% response rate, and all patients had a complete or nearly (>90%) complete response per RECIST criteria. Toxicities were manageable (grade 1-2 nausea, transaminitis, and peripheral edema), with only 1 of 6 sustaining

a dose limiting (Grade 3-4) adverse effect. Treatment duration ranged from 20 to 42 months. Importantly, in 5 of 6 patients, crizotinib was discontinued after receiving at least 20 months of treatment with no evidence of disease at the time of cessation. There has been no evidence of recurrence in these patients with a maximum duration off therapy of 5.75 years. Furthermore, after a brief (3 month) trial off therapy due to adverse effects followed by local disease progression, one patient was re-challenged with crizotinib and demonstrated a repeat complete response.

**Conclusion:**

Crizotinib is an effective and well tolerated therapy for ALK-positive IMT that can be safely discontinued in patients with IMTs. Additional investigation is critical to better understand the optimal length of pharmacotherapy needed to treat IMTs without surgery.

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Poster # 419

**CHARACTERIZATION OF SKELETAL ABNORMALITIES IN PATIENTS WITH MEN2B**

**Iris Li, Iris Hartley, Jaydira Del Rivero, Joanna Klubo-Gwiezdzinska, James Reynolds, Srivandana Akshintala, Michael Collins, John Glod**

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**Background:**

Multiple endocrine neoplasia type 2B (MEN2B) is a rare genetic syndrome that is caused by mutations in the RET proto-oncogene (M918T in 95% of cases). The disorder is inherited in an autosomal dominant fashion and is characterized by both endocrine and nonendocrine features. 100% of patients develop medullary thyroid cancer (MTC) and are also at risk for pheochromocytoma. Patients also typically exhibit ganglioneuromatosis of the gastrointestinal tract, ophthalmological abnormalities, and mucosal neuromas. Often present but understudied are skeletal abnormalities.

**Objectives:**

To both better care for these patients and to also understand the role of increased RET signaling in skeletal biology, we studied an NIH cohort to determine the spectrum of the phenotype of skeletal findings in MEN2B.

**Design/Method:**

A retrospective chart review was conducted on patients enrolled in the Longitudinal Assessment and Natural History Study of Children and Young Adults with MEN2B with or without MTC at the National Institutes of Health. Forty-seven patients with MEN2B were included in this study.

**Results:**

Forty-seven patients were evaluated. Age range was 5-36 years with a median of 19 years; 23/47 (49%) patients were female. 15/47 (32%) of all patients were found to have foot-related

abnormalities that included the following: talipes equinovarus, pes cavus, foot asymmetry, metatarsus adductus, and foot malalignment. 22/47 (47%) had a history of scoliosis. 20/47 (43%) experienced at least 1 fracture. No major differences were found between sexes in the incidence of foot-related abnormalities, scoliosis, or fractures ( $p>0.14$  for each). All of these findings are significantly more prevalent than would be expected in an unselected, age- and sex-matched cohort.

**Conclusion:**

In our cohort of patients with MEN2B, clinically significant skeletal abnormalities were common. These findings suggest a direct role of RET in bone biology and call for further investigation of skeletal abnormalities in MEN2B.

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Poster # 420

**INCIDENCE OF PROTEINURIA IN NF2 PATIENTS RECEIVING AVASTIN**

**Sana Mohiuddin, USMAN BAIG, YUSHA SUN, Amber Gibson, RITA SWINFORD, John Slopis, Wafik Zaky**

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**Background:**

Neurofibromatosis 2 is a rare autosomal dominant disorder where patients are prone to growth of noncancerous tumors like vestibular schwannomas, meningiomas and ependymomas. Vestibular schwannomas (VS) are the most common tumors in NF2 syndrome occurring in almost all patients. Multiple drugs have been used in the past for the treatment of VS including Avastin (Bevacizumab), a VEGF inhibitor. Avastin has shown in clinical trials to reduce tumor size and improve hearing in patients with VS.

**Objectives:**

Although proteinuria is a known side effect of Avastin, incidence of proteinuria seems to be higher in patients with NF2 when compared with other patient populations. We studied our patient population with NF2 who received Avastin as part of their therapy, and compared the incidence of proteinuria in these patients with historical controls (non NF patients) who received Avastin as part of their therapy.

**Design/Method:**

A retrospective chart review of NF2 patients with VS who were treated at MD Anderson with Avastin was done. We collected data for all adverse effects noted during Avastin therapy.

**Results:**

From our population of NF2 patients, six received Avastin at our institution. All patients received Avastin for a duration of 8-12 cycles at a standard dose of 10mg/kg every 2-3 weeks. Three of the six patients had Avastin as single agent therapy, and the other three had Avastin in combination with temsirolimus. Four out of the six patients (66%) had proteinuria during therapy with avastin. For one patient, therapy was stopped due to toxicity with progressive proteinuria.

This patient underwent renal biopsy which showed minimal glomerular changes, IgA nephropathy with normal cellularity and segmental cellular inter-positioning without global glomerulosclerosis or interstitial fibrosis.

**Conclusion:**

Proteinuria is a known complication of Avastin with an incidence of 3-10% in patients receiving Avastin. When looking at other trials that have used avastin as part of their therapy, incidence of proteinuria was reported to be 2.4% and 7.7% in Children Oncology Group protocols in medulloblastoma and glioma respectively. In our study, we had higher incidence of proteinuria, at 66%, which may point towards the underlying germline NF2 mutations as a contributing factor. Although NF2 patients are not reported to have a renal vascular disease, they are definitely at a higher risk of renal complications with Avastin, and more research is warranted to understand the reason for this risk and to better manage the related side effects.

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Poster # 421

**ENHANCING CARE TRANSITIONS: IMPROVING THE PLANNED CHEMOTHERAPY ADMISSION PROCESS**

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**Background:**

The direct admissions process is an intricate patient care model that is affected by gaps in communication as well as unforeseen deviations that have the potential to negatively impact patient safety as well as decrease patient/family and provider satisfaction. This is especially true when dealing with a high-risk pediatric oncology population. In order to optimize this aspect of transition of care, we sought to establish and sustain a system to restructure our workflow for planned inpatient chemotherapy admissions.

**Objectives:**

Our smart aim was to streamline the admission process to decrease the rate of unplanned chemotherapy admissions from the pre-intervention baseline of 32.5% to 15% within 3 months. This was based on our global aim of improving logistics as well as stakeholder satisfaction with the planned admissions process for scheduled chemotherapy.

**Design/Method:**

Key stakeholders in the process were administered brief 5 question surveys to identify the key drivers in the current planned admissions process. Using Plan-Do-Study-Act (PDSA) quality improvement methodology, we identified areas of potential intervention. Our first PDSA cycle included education on the planned admission process, discussion of planned admissions at our weekly, multi-disciplinary, divisional sign-out meeting and implementation of a calendar to document admissions in advance along with the chemotherapy to be administered. This new workflow replaced our previous email-based admission notification system. A short survey was again administered at the end of the PDSA cycle to assess stakeholder satisfaction and identify



other areas for improvement.

**Results:**

Within the last 3 months, our rate of unplanned admissions has decreased below our anticipated goal to a level of 8%. Analyzing the post-intervention surveys, providers were satisfied with the new workflow, but still noted deficiencies in the multidisciplinary communication when pertaining to admitting patients. While this rate will likely never decline down to zero due to the constant presence of unforeseen clinical circumstances and changes in patients' status, we hypothesize that a lower rate of unexpected events will improve patient safety and satisfaction.

**Conclusion:**

We hope to be able to continue this reduction of unplanned admissions through maintaining this standardized process. Future PDSA cycles will focus on improving communication about admissions and the establishment of a standardized admission checklist.

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Poster # 422

**FIRST LOOK: SENSITIVITY AND SPECIFICITY OF STIR MRI FOR THE DETECTION OF PEDIATRIC MALIGNANCY**

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**Background:**

Classically, pediatric leukemia is diagnosed through abnormalities in a complete blood count (CBC) with subsequent bone marrow assessment. In cases of other malignancies, diagnosis is based on pathological examination of tissue. However, in cases where no abnormalities in the CBC exist, the diagnosis may be protracted. Case series have shown the importance of magnetic resonance imaging (MRI) in establishing a malignancy diagnosis when laboratory studies show no abnormalities. There is currently a dearth of literature quantifying the sensitivity and specificity of short T1 inversion sequence (STIR) MRI in diagnosing pediatric malignancy.

**Objectives:**

To quantify the sensitivity and specificity of STIR MRI in diagnosing pediatric malignancy including the calculation of positive and negative predictive values.

**Design/Method:**

A retrospective analysis of all pediatric STIR MRI studies conducted at Children's Hospital and Medical Center from 2013 to 2018 were reviewed including patient characteristics, presenting diagnosis/symptom, final diagnosis, STIR MRI findings with radiologist interpretation, final bone marrow or tissue pathology, and whether a new diagnosis of cancer was made based on these results. Kappa statistic was used to evaluate the diagnostic agreement between STIR MRI results concerning for malignancy and the gold standard diagnostic study of the respective final diagnosis. Sensitivity, specificity, false positive, and false negative estimates were provided with

joint 90% confidence regions for sensitivity and specificity.

**Results:**

142 patients received a STIR MRI during the study period. Four patients were excluded for having prior STIR MRI studies. There were 21 cases with STIR MRI findings concerning for malignancy. Of those with concerning MRI findings, 13 were determined to have a final diagnosis of malignancy. Additionally, of the 117 with MRI findings not suggestive of malignancy, only 1 case had a final diagnosis of malignancy. The Kappa coefficient for agreement between STIR MRI and final diagnosis was 0.71 indicating good agreement. The sensitivity of STIR MRI in detecting malignancy was found to be 92.9% [95% CI: 66.1-99.8%] with a specificity of 93.5% [95% CI: 87.7-97.2%]. The positive predictive values was determined to be 61.9% [95% CI: 38.4-81.9%] and the negative predictive value was 99.1% [95% CI: 95.3-100%].

**Conclusion:**

To our knowledge, this is the first and largest retrospective study to report sensitivity, specificity, and predictive value of STIR MRI as a diagnostic tool for pediatric malignancy. The sensitivity and specificity determined by this study suggests that STIR MRI may be of value in initial diagnostic approaches. Larger multi-center collaboration will be needed to further support these data.

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Poster # 423

**EVALUATION OF EMPIRIC VANCOMYCIN FOR FEVERS DURING HIGH-DOSE CYTARABINE ADMINISTRATION**

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**Background:**

Cytarabine (cytosine arabinoside, Ara-C) is a nucleoside analog used in multi-drug chemotherapy regimens for the treatment of AML, ALL, and non-Hodgkin lymphomas. One of the known adverse effects of cytarabine, particularly in patients receiving high-dose cytarabine (HDAC), is drug-induced fever. The reported incidence of fever with HDAC ranges anywhere from 43% to 81%. Multiple studies have demonstrated an increased risk of viridans group streptococcal bacteremia in patients who have received HDAC therapy with reported mortality around 10%. For this reason, our institution and several other institutions across the country routinely include vancomycin as empiric coverage for patients who develop fever during HDAC, due to concern for resistance to cephalosporin monotherapy.

**Objectives:**

This retrospective chart review aims to describe the occurrence and characteristics of fever during HDAC administration. Using this information, we can attempt to establish the most appropriate empiric antibiotic regimen for patients during HDAC administration.

**Design/Method:**

Information including sex, diagnosis, age at diagnosis, dates of cytarabine infusion(s), G-CSF administration, onset and duration of neutropenia and lymphopenia, and presence of fever were collected by electronic chart review for each HDAC infusion from 2007 to August 2018.

HDAC-related fever was defined as a temperature  $>38.0^{\circ}\text{C}$  occurring anytime from the start of cytarabine until 24 hours after the end of cytarabine. If fever was documented, additional information was collected, including number of blood cultures obtained during febrile episode, other infectious studies obtained, number of positive blood cultures and organism(s), other identified sources of infection(s), and presence of abnormal vital signs as documented by nursing staff in the electronic record (according to PALS guidelines).

**Results:**

Of 208 administrations documented, patients developed fevers during or within 24 hours of the end of HDAC administration on 82 occasions (39.4%). A total of 375 blood cultures were obtained from time of fever onset during HDAC administration through  $>24$  hours afebrile, with a median of 3 cultures per febrile period. One blood culture was positive for an oral flora organism determined by the microbiology lab report to be a likely contaminant. This patient was not neutropenic at the time of fever, and this organism was sensitive to cephalosporins. There were no other positive blood cultures in non-neutropenic or neutropenic patients.

**Conclusion:**

Fever due to HDAC is relatively common but appears to frequently lack association with bacteremia during the time of HDAC administration. Broad-spectrum empiric antibiotic regimens including vancomycin may be unnecessary for these patients, particularly before they become neutropenic.

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Poster # 424

**CLINICAL DECISION MODEL TO OBTAIN PERIPHERAL BLOOD CULTURES IN FEBRILE PEDIATRIC ONCOLOGY PATIENTS**

**Lev Gorfinkel, Caitlin Hansen, Veronika Shabanova, Stephanie Prozora, Rozalyn Rodwin, Umar Qadri, Tomas Manghi, Beth Emerson, Antonio Riera**

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**Background:**

The utility of peripheral blood cultures in pediatric oncology patients presenting with fever is controversial. The latest guidelines provide a weak recommendation based on moderate-quality evidence to obtain concurrent peripheral and central venous line (CVL) blood cultures. A recent systemic review showed that about 1 in 40 bloodstream infections (BSIs) would be missed if only CVL cultures are obtained.

**Objectives:**

To derive a clinical decision rule for obtaining peripheral blood cultures in pediatric oncology

patients presenting to a pediatric emergency department (ED) with fever and a CVL.

**Design/Method:**

A retrospective chart review was performed on all pediatric oncology patients under the age of 21 from February 2013 to February 2018 who were referred to the Yale-New Haven Children's Hospital ED for evaluation of fever while on active therapy. Cases were included for review if both CVL and peripheral blood cultures were obtained during the ED evaluation. Our multidisciplinary researchers created an a priori list of possible clinical predictors of BSI. Logistic regression with a random intercept was used to determine independent predictors of BSI and generate a prediction model for obtaining peripheral blood cultures. Associations were summarized as odds ratios (ORs) with 95% Confidence Intervals (95% CIs). Bootstrapping analysis was performed for internal validation.

**Results:**

Among 509 encounters that met inclusion/exclusion criteria, there were 48 instances of BSI for an overall prevalence rate of 9.4%. Of the 48 cases with BSI, 23 patients had positive-central/positive-peripheral cultures, 21 patients had positive-central/negative-peripheral cultures, and 4 patients had negative-central/positive-peripheral cultures. Clinical predictors that were statistically significant and independently associated with positive peripheral blood cultures included the following variables: Vasopressor support (OR 57.9, 95% CI 13.7-243.9), capillary refill time > 3 seconds (OR 15.2, 95% CI 3.6-64.6), a peripherally-inserted central catheter (OR 6.0, 95% CI 1.4-24.9) or a Broviac-type CVL (OR 5.0, 95% CI 2.0-12.6), maximum temperature in ED > 39°C (OR 4.6, 95% CI 2.1-10.3), and mucositis on exam (OR 3.1, 95% CI 1.1-9.1). The area under the curve (AUC) for this model was 0.80 (95% CI 0.71-0.88) in the derivation cohort and 0.80 (95% CI 0.69-0.91) after the internal validation.

**Conclusion:**

We derived a clinical prediction model that may be useful in deciding when to obtain peripheral blood cultures in febrile oncology patients with CVLs and actively receiving chemotherapy. Future studies should focus on prospective and external validation of this diagnostic prediction tool.

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Poster # 425

**UTILIZATION OF AN OBSERVATION UNIT TO IMPROVE ANTIBIOTIC ADMINISTRATION IN IMMUNOCOMPROMISED PATIENTS**

**Terri Vaccarelli, Ann Stratton**

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**Background:**

Fever in an immunocompromised patient is an emergency that requires immediate evaluation and treatment. Studies have demonstrated delay in antibiotic administration prolongs hospital stay and increases risk for complications. Guidelines set by oncology and infectious disease organizations recommend antibiotics within 60 minutes of fever. Here we review the utilization

of pathways and an Observation Unit to improve the time to antibiotic delivery in immunocompromised patients.

**Objectives:**

1. Review data on antibiotic administration times with the establishment of an Observation Unit for immunocompromised patients with fever
2. Identify areas needing improvement in antibiotic administration time
3. Identify keys to success for staff to allow for improved antibiotic administration

**Design/Method:**

This is a retrospective review of data collected from time of arrival to antibiotic administration in the Emergency Department, Hematology/Oncology Outpatient Clinic and the Observation Unit from 2013-2018. The Observation Unit was established in 2010 for evaluation of Hematology/Oncology patients with fever. With the initiation of the Observation Unit, protocols of treatment were established for the Observation Unit and the clinic, and staff, patients and families were educated. Initially the nursing staff was reliant upon pharmacy for antibiotics, which was found to cause a delay in time to administration. Standardized dosing (weight based) was implemented and antibiotics became available as floor stock. A standard workflow was implemented for nursing to prepare for and deliver the care to a febrile patient. Educational handouts and leaflets were made available regarding the Observation Unit in all Hematology/Oncology patient care areas. In the Emergency Department, staff was reeducated on treatment goals and order sets implemented.

**Results:**

Initial data showed that less than half of immunocompromised patients presenting to the emergency department received broad-spectrum antibiotics within one hour of arrival. With additional training and implementation of order sets the percentage of time to antibiotic administration improved in the Emergency Department from 48% in 2013 to 69% in 2018. Both the Observation Unit and Outpatient Clinic areas saw an improvement in the number of patients that were receiving antibiotics within 1 hour and continue at 97% or greater.

**Conclusion:**

1. With ongoing education and implementation of high risk fever order sets, the percentage of immunocompromised patients receiving empiric broad-spectrum antibiotics within one hour of arrival to the emergency department has significantly increased
2. Utilization of an Observation Unit for immunocompromised patients with fever decreases the time until antibiotics are administered in this high-risk population.

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Poster # 426

**REDUCTION OF TIME-TO-ANTIBIOTICS FOR PEDIATRIC ONCOLOGY PATIENTS WITH FEVER AND NEUTROPENIA IN AN ED**

**David Kram, Sarah Martin, William Pearsall, Thomas Russell, Michael Mitchell, Chad McCalla**

**Background:**

There is a high risk for life-threatening infections in neutropenic pediatric oncology patients who present with fever, and timely administration of antibiotics can mitigate this risk. However, fever may be the only symptom of an underlying infection at presentation and the absolute neutrophil count (ANC) is typically unknown at presentation. Complex algorithms aimed at predicting neutropenic status are often unsustainable. Therefore, rapid administration of antibiotics for all children with cancer with a central line who have fever is critical.

**Objectives:**

We conducted a quality improvement (QI) initiative aimed at delivering antibiotics within 60 minutes to at least 95% of pediatric oncology patients with a central line who present with fever to an academic pediatric emergency department (ED), regardless of their ultimate ANC. This aimed to sustainably achieve the benchmark goal of time-to-antibiotics within 60 minutes for pediatric cancer patients with fever and neutropenia.

**Design/Method:**

Based on a one-year baseline period showing a need for improvement in time-to-antibiotics in the ED to deliver antibiotics within the generally accepted benchmark of 60 minutes, a multidisciplinary QI team identified several key drivers which were suspected to contribute to the overall prolonged time to antibiotics, and coordinated interventions and assessments per QI methodology. Among others, a key intervention was to administer ceftriaxone, a third generation cephalosporin that does not cover pseudomonas species, to all pediatric oncology patients with fever, before ANC value resulted.

**Results:**

Over the two year period between 7/1/2017 – 6/30/2019, 325 episodes of pediatric oncology patients presenting to the ED with fever occurred. The percentage of all febrile pediatric oncology patients receiving antibiotics within 60 minutes rose from 39% to 97%. Mean time-to-antibiotics fell from 96.4 minutes to 29.8 minutes. Of those episodes, there were 20 positive blood cultures, 2 of which were infections that were insensitive to ceftriaxone but sensitive to a pseudomonas-covering antibiotic. Both of those patients were admitted to the hospital after they were found to be neutropenic, where they empirically received a pseudomonas-covering cephalosporin even prior to culture positivity per standard of care.

**Conclusion:**

Our initiative achieved our goal of antibiotic delivery within 60 minutes during a sustained period to greater than 95% of pediatric oncology patients with fever. This included a novel approach of delivering ceftriaxone up-front to all pediatric oncology patients in the ED with fever and suspected neutropenia, and this approach seems to be safe on preliminary assessment.

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Poster # 427

# **HOSPITAL PHYSICIANS IN PEDIATRIC ONCOLOGY/STEM CELL TRANSPLANT: SUCCESSES AND OPPORTUNITIES**

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## **Background:**

With increasing census, complexity of care, and changing resident structure, subspecialty hospital physicians (hospitalists) are becoming more prevalent in pediatric units. Hospitalists are increasingly employed as front-line clinicians in inpatient settings. The oncology hospitalist program at our academic center has developed to meet growing demands of the oncology and stem cell transplant (SCT) program. As hospitalist medicine has become a defined career, opportunities in this program have expanded to include academics, mentoring, research, and education. This program is unusual, and there are limited studies describing such a pediatric oncology hospital physician model; there is little information about hospitalists' perception of their clinical duties, work-life balance, job satisfaction, and academic opportunities.

## **Objectives:**

This survey project aimed to assess the pediatric oncology hospitalist role at our institution, and describe hospitalists' perception of clinical duties, work-life balance, job satisfaction, and academic opportunities available within the model.

## **Design/Method:**

Two anonymous surveys were created and sent to oncology hospital physicians who were employed in the Division of Oncology at the Children's Hospital of Philadelphia from 2017-2019 (n=26). Survey A focused on assessment of nonclinical roles (academics, teaching, research, administrative duties). Survey B focused on assessing satisfaction with job hours, autonomy, relationships, wellness, and support using a five-point Likert scale as well as open ended questions allowing for free-text responses.

## **Results:**

Twenty-two (85%) hospitalists completed the surveys. All respondents felt the work-life balance, hours, and flexibility are attractive and that oncology/SCT is intellectually stimulating. Of the respondents, 91% agreed they had excellent relationships with oncology staff, and 95% felt supported by supervisors. Most respondents (86.4%) agreed there were significant opportunities for research, education, and teaching. Many respondents (91%) felt this job would be valuable toward career and personal goals; 95% were happy they took this job. Areas for improvement include transitions of care and wellness support, as only 77.3% felt there were smooth transitions in handoff given shiftwork, and 45.5% felt the job can be emotionally draining.

## **Conclusion:**

The pediatric oncology hospital physician is a viable, versatile career path that provides freedom for pursuit of a wide range of academic opportunities, both clinical and non-clinical. This work demonstrates that hospital physicians are overall satisfied with this job. Expansion of such a model within our institutions and other centers should be well received. Future directions will

involve addressing areas of improvement including wellness and patient care transitions, as well as assessing career trajectories and academic successes of our hospitalists.

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Poster # 428

## **IMPROVING KNOWLEDGE AND COMFORT OF ONCOFERTILITY: AN INSTITUTIONAL QUALITY IMPROVEMENT PROJECT**

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### **Background:**

Discussions about fertility risks and referral to an oncofertility specialist are now recommended as integral steps in the management of newly diagnosed pediatric cancer patients. Despite increased awareness of these needs, provider knowledge, comfort, and practice regarding fertility preservation varies widely and many survivors continue to receive sub-optimal counseling.

### **Objectives:**

Our objective and smart aim was to increase knowledge and comfort of pediatric solid tumor providers regarding fertility preservation in newly diagnosed patients 50% from baseline by developing and implementing educational materials on fertility risks and preservation options.

### **Design/Method:**

Solid tumor providers completed a survey to assess baseline knowledge and comfort regarding oncofertility. Provider knowledge was assessed via five free-response questions and comfort was self-assessed on a 10-point scale. A brief didactic educational session was presented followed by a question-and-answer session. Descriptive statistics were produced for group aggregate and intra-individual scores at baseline and after the educational session.

### **Results:**

Twelve solid tumor providers completed the survey with 10 pre-test scores, 10 post-test scores, and 8 pairs of pre/post-test scores in the same individual. There was an increase from baseline for all knowledge questions, with the following pre- and post-test scores: minimum cumulative cyclophosphamide dose considered high risk (25% pre, 100% post); name of a gonadotoxic medication other than cyclophosphamide (92% pre, 100% post); minimum abdominal-pelvic radiation dose considered high risk in post-pubertal females (33% pre, 100% post); risk of infertility of childhood cancer patients compared to healthy sibling controls (25% pre, 80% post); and timing for oocyte or embryo cryopreservation (33% pre, 100% post). Provider comfort scores also increased from baseline. Providers had a pre-test median comfort score (MCS) of 6.5 [inter-quartile range (IQR): 5.75-8] and post-test MCS of 9 (IQR: 8.75-9) regarding discussion of infertility risk due to chemotherapy, with similar increases seen in MCS for discussion of infertility risk due to radiation, infertility risk for pre- and post-pubertal patients, and fertility-preservation options.

### **Conclusion:**



Solid tumor provider knowledge and comfort regarding oncofertility can be improved by brief, targeted education. Next steps include the development and dissemination of a supplemental resource with high yield oncofertility reference material as well as 2-month and 6-month follow-up surveys to assess knowledge retention.

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Poster # 429

## **IMPLEMENTING TRANSITION OFF-THERAPY(TOT) SERVICES IN A MID-SIZE PEDIATRIC ONCOLOGY PROGRAM**

**Brinda Mehta, Komal Rai**

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### **Background:**

Completing pediatric cancer therapy is a milestone in the life of a patient and family but it can be fraught with issues such as anxiety, dealing with side effects of therapy as well as reintegration back into the community. There is recent emergence of interest to provide early transition support to cancer survivors soon after they complete therapy.

### **Objectives:**

Implement transition off-therapy (TOT) services in pediatric cancer survivors treated at our mid-size oncology program, assess patient/parent feedback and primary care physician feedback regarding our new process. Provide TOT services to at least 80% of patient/families who are within 0-6 month's off-therapy over the next 12 months.

### **Design/Method:**

The Plan-Do-Study-Act (PDSA) method was implemented for this new process. Primary oncologist team along with the psycho-social team met with each patient/parent for comprehensive evaluation during TOT visit. A '10-point transition goals' checklist was created to address critical aspects of cancer survivorship. A survey was given to the patient/parent at the end of this visit for their feedback as well as a short survey sent to PCP along with end of treatment correspondence materials.

### **Results:**

Within the first 2.5 months of implementing TOT program, a total of 24 patients were eligible for TOT visits of which 22 (91.5%) received TOT services. Average number of days to set-up a TOT visit was 92 days (range:14-189 days). Rate of treatment summary completion at time of TOT visit was 83.3% (20/24). Only 25% (6/24) had complete '10-point transition goals' checklist completed with single TOT visit. Patient/parents reported overall satisfaction with the visit as well as materials provided. Patient/parents prefer this information to be provided within the first 3 months of completing therapy. Transition information sent to PCP was sub-optimal (58%) but their feedback regarding our new process was favorable.

### **Conclusion:**

Providing TOT services is feasible in our mid-size pediatric oncology program with overall

favorable satisfaction among patient/parents. Preparation of treatment summary and coordination of visit with several other team members impacted completion of '10-point transition goals' checklist. In the next phase of the PDSA cycle we will assess the reasons for lack of treatment summary completion, improve communication with the patient's PCP as well as assess for sustainability of the new process.

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Poster # 430

## **INCREASING PALLIATIVE CARE TEAM INVOLVEMENT IN PEDIATRIC ONCOLOGY PATIENTS**

**Oluwaseun Olaiva, Sana Farooki, Lisa Tarbell, Nicholas Clark, Karen Lewing**

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### **Background:**

Palliative Care Team (PaCT) involvement with pediatric oncology patients improves quality of life and increases likelihood of receiving end-of-life care consistent with patient and family wishes. Barriers to early integration of PaCT exist. The U.S News & World Report benchmark is that >75% of patients with refractory cancer receive PaCT consult >30 days prior to death, with our institution reporting 62% in 2018. Patients with cancer diagnoses having a 5-year event free survival (EFS) of < 50% were identified between January 1, 2017 and December 31, 2018. 34 patients with these diagnoses died during this timeframe, and 50% had PaCT consult note placed >30 days prior to death. During the same timeframe, 29 patients were newly diagnosed and 27% (n=8) had a PaCT note placed within 30 days of diagnosis.

### **Objectives:**

Our SMART aim was to improve the percent of patients with a PaCT consult note placed > 30 days prior to death from 50% to 60% for patients with the target diagnoses between March 1, 2019 to December 31, 2019 at our institution. Our secondary aim was to improve the percent of patients with a PaCT note placed within 30 days of new diagnosis from 27% to 47% during this period.

### **Design/Method:**

Our PDSA cycle ramps included a division-wide survey of oncology provider identified barriers to consulting PaCT and an agreed list of oncologic diseases with 5-year EFS < 50% for which consultation was recommended at the time of diagnosis (Infant acute lymphoblastic leukemia, infant acute myeloid leukemia, diffuse intrinsic pontine glioma, high risk glioma, glioblastoma, atypical teratoid rhabdoid, metastatic ewing sarcoma, metastatic osteosarcoma, high risk neuroblastoma, desmoplastic small round cell tumor, alveolar high risk rhabdomyosarcoma). A template for documenting discussion regarding PaCT team involvement was designed and information dissemination sessions were held (Intervention 1). We emailed monthly reminders about the template and criteria for when PaCT consult was recommended (Intervention 2). Reminders were emailed to primary teams within two weeks of new diagnosis (Intervention 3).

### **Results:**

Between March 1, 2019 to December 31, 2019, 18 patients meeting criteria died and 61% (n=11) had PaCT consult note placed > 30 days prior to death. There were 14 patients with new diagnosis meeting criteria and 71% (n=10) had PaCT consult placed within 30 days of diagnosis.

**Conclusion:**

We demonstrated improvement in PaCT involvement in pediatric oncology patients with 5 year EFS < 50% both at diagnosis and > 30 days prior to death.

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Poster # 431

**A MULTIDISCIPLINARY QI PROJECT OF MANAGING ASPARAGINASE REACTIONS IN THE ERA OF ERWINIA SHORTAGES**

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**Background:**

Asparaginase is an important component of therapy for acute lymphoblastic leukemia (ALL). The clinical challenge in managing asparaginase reactions is being able to distinguish between infusion versus allergic reactions. Due to an Erwinia shortage, we developed a quality improvement (QI) project to help providers manage and interpret these reactions.

**Objectives:**

The QI project aimed to standardize our methodology in the assessment and documentation of reactions in patients receiving asparaginase. An asparaginase reaction algorithm was adapted and implemented to offer a systematic approach to differentiate between infusion and hypersensitivity reactions, therefore switching patients to Erwinia only when truly indicated and re-challenging patients previously labelled incorrectly as intolerant to pegasparaginase.

**Design/Method:**

Reviewing the literature, we identified key components to differentiating pegasparaginase reactions and adopted an algorithm. A reaction note was created with an EPIC smart block which provides a consistent approach to documenting asparaginase reactions and a convenient method to retrieve data from our EMR. Baseline data was collected retrospectively and through the implementation of the QI project, several Plan-Do-Study-Act (PDSA) cycles were followed to assess documentation and utilization of the algorithm through its evolution.

**Results:**

In our pilot phase, we successfully re-challenged patients with pegasparaginase that had been previously switched to Erwinia. The standardized reaction note documented the assessment by the provider and our goal was for 80% agreement between the provider and the QI team. In the first PDSA cycle the agreement rate was 78% and reached 100% in the second cycle. The retrospective data showed that 40% of the patients labelled with asparaginase allergy were switched to Erwinia. Data analysis is ongoing, but early results show that the rate remained 40% for patients who were documented with an asparaginase reaction during the first PDSA cycle but

increased to 70% in our second cycle. During this same period the incidence of moderate reactions increased correlating with the higher incidence of patients switched to Erwinia in the second PDSA cycle.

**Conclusion:**

This QI project has allowed us to re-challenge patients with pegasparaginase previously labelled as intolerant. It has improved our comfort in the assessment and management of these reactions. The success of this project has relied on the continued commitment and collaboration between our provider, nursing and pharmacy colleagues. Given our newfound experience, the QI project has further evolved due to the ongoing Erwinia shortage to include use of pre-medications with alternative infusion rates and therapeutic drug monitoring for all infusions.

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Poster # 432

**COMPARING NITROUS OXIDE VERSUS PROPOFOL-ASSISTED SEDATION FOR LUMBAR PUNCTURES IN CHILDHOOD ALL**

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**Background:**

Childhood acute lymphoblastic leukemia (ALL) treatment incorporates many lumbar punctures (LPs) with intrathecal (IT) methotrexate (MTX) administration in order to prevent and treat central nervous system leukemia. Propofol is often successfully used as a sedation agent for such procedures, although its use incurs some inconvenience, cost, and time constraints. At our institution, LPs frequently incorporate inhaled nitrous oxide (N<sub>2</sub>O) as a sedation agent.

**Objectives:**

To compare the effectiveness and safety of nitrous oxide versus propofol sedation for lumbar punctures in childhood ALL patients.

**Design/Method:**

Retrospective cohort study of all patients aged 0-25 years with ALL treated between 1/1/2013-12/31/2018 treated at the Children's Minnesota Cancer and Blood Disorders Center, including all LPs performed in the clinic setting under either propofol or N<sub>2</sub>O sedation. Comparisons between propofol and N<sub>2</sub>O procedures were made using two-sample T-tests,  $\chi^2$  tests, and Fischer's exact tests where appropriate.

**Results:**

Among 307 pediatric patients with ALL, 3171 clinic LPs were undertaken with 47.6% (n = 1509) under propofol sedation and 52.4% (n = 1662) under N<sub>2</sub>O sedation. Patients with lower BMI (18.8 vs 20.0 m<sup>2</sup>, p < .001) and younger age (8.1 vs 8.8 years, p = .005) were more likely to be selected for N<sub>2</sub>O sedation. Successful IT chemotherapy delivery (96.5% vs 95.4%, p = .122) and procedure complications (3.4% vs 4.4%, p = .142) were equivalent among propofol and N<sub>2</sub>O procedures, respectively. Traumatic LPs (RBC  $\geq$  10 cells/ $\mu$ L) were less frequent in N<sub>2</sub>O

procedures (26.3% vs 31.4%,  $p = .002$ ). Respiratory complications occurred in 1.5% ( $n = 47$ ) of propofol LPs, 74.5% of which ( $n = 35$ ) required additional interventions. There were no documented respiratory complications among the N2O LPs. Patient discomfort was noted during 1.7% ( $n = 29$ ) of N2O cases.

**Conclusion:**

For a large proportion of children with ALL, LPs with IT chemotherapy were performed effectively and safely under N2O sedation, suggesting a select group of patients for whom N2O can effectively replace propofol during this procedure. Future efforts should focus on procedure cost analyses and developing a predictive model for selecting N2O-assisted sedation candidates.

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Poster # 433

**IMPROVING EFFICIENCY FOR SEDATED PROCEDURES IN A PEDIATRIC ONCOLOGY CLINIC**

**Joel Kaplan, Adrienne Hersey, Alyson Galek, Cali Matchunis, Sarah Thornton, Krystina Banas, Emita Clark, Kelly Wohler, Samantha Johnson, Meghan Beverley**

*Atrium Health/Levine Children's, Charlotte, North Carolina, United States*

**Background:**

Lumbar punctures with instillation of chemotherapy and bone marrow evaluations are vital components of leukemia treatment. Given the invasiveness of these procedures many pediatric oncology programs perform them under sedation. Long wait times from patient arrival at clinic to the start of procedures was a major dissatisfier for our patients and families. Many steps are required for these procedures, including nurse evaluation and port/line access, laboratory evaluation, physician visit, anesthesia availability, and patient recovery. This complexity required a formalized quality improvement (QI) plan.

**Objectives:**

This QI project aimed to improve the efficiency of patient throughput in the pediatric oncology clinic for patients requiring lumbar punctures and bone marrow aspirate/biopsies. The outcome goal was to decrease the mean time from patient arrival to in-procedure room time from 111 minutes to 86 minutes by June 2019.

**Design/Method:**

A multidisciplinary QI team managed the project using the Model for Improvement QI framework. A smart aim, key driver diagram, failure modes and effects analysis, run, and control charts were developed. Change ideas tested through multiple PDSA cycles included priority rooming, determining standard work for different roles, optimizing the procedure appointment template, weekly pre-visit planning, communication board for tracking status, and anesthesia priority and communication. Weekly annotated run charts and control charts were used to evaluate improvement.

**Results:**

XbarS Shewhart charts were used to analyze the time from patient arrival to in-procedure room time. Baseline data revealed a mean patient arrival to in-procedure time of 111 minutes with lower control limit (LCL) of 62 minutes and upper control limit (UCL) of 151 minutes. After testing change ideas, there was special cause resulting in the mean decreasing to 89 minutes with LCL at 51 minutes and UCL at 128 minutes. After further testing, a second episode of special cause was identified with reduction of patient arrival to in-procedure room time to a mean of 76 min with LCL of 54 min and UCL of 99 min. The success of this project has been sustained through December 2019.

**Conclusion:**

By meeting the project goal, patients were less likely to have a delay in essential treatments and high value providers and resources were more optimally utilized. Applying QI tools, we were able to identify important change ideas critical to improving our sedated procedure throughput and efficiency. This project illustrates that the efficiency of care delivery to our patients can be improved utilizing QI methodology.

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Poster # 434

**JUVENILE XANTHOGRANULOMA HARBOURING NOVEL SOMATIC MRC1-PDGFRB THAT EXHIBITS DASATINIB SENSITIVITY**

**Candelaria Deimundo Roura, Abigail Cruz, Marcela Popescu, Michael Clay, Shaimaa Eissa, Kim Nichols, Lu Wang, Patrick Campbell**

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**Background:**

Juvenile Xanthogranuloma (JXG) is a benign proliferative disorder of childhood and the most common of the non-Langerhans cell histiocytoses. Incidence is unknown, and in most cases JXG resolves spontaneously.

Platelet-derived growth factor receptor beta (PDGFRB) is a receptor tyrosine kinase that binds to PDGF family members. A variety of myeloproliferative disorders and hematologic cancers have been linked to mutations in the gene encoding PDGFRB. For example, the Early B Cell Factor 1 - PDGFRB (EBF1-PDGFRB) gene fusion of B-cell precursor in acute lymphoblastic leukemia (ALL), within the Philadelphia-like ALL subtype, has been reported in patients who are refractory to chemotherapy. However, they have achieved response with tyrosine kinase inhibitors such as imatinib. JXG has not previously been associated with PDGFRB fusions.

**Objectives:**

Report to describe a case of JXG with a somatic MRC1-PDGFRB fusion.

**Design/Method:**

Data were gathered via chart review and direct patient care.

**Results:**

A 4-month-old female presented with an enlarging chest wall mass. PET/CT revealed an FDG-

avid 5 x 2.9 x 2.6 cm mass centered over the left fourth/fifth ribs with anterior rib destruction, multiple areas of nodular pleural thickening in the left hemithorax, and enlarged left hilar and mediastinal lymph nodes.

A core needle biopsy revealed a “dense histiocytic infiltrate that permeates background skeletal muscle and is associated with dense fibrosis and scattered inflammatory cells.”

Immunohistochemical staining supported a diagnosis of JXG. Molecular testing performed on the tumor revealed wildtype BRAF V600. Subsequent whole exome and transcriptome sequencing revealed a novel Mannose Receptor C-Type 1 (MRC1)-PDGFRB fusion. The patient was initially treated with prednisone and vinblastine, however there was no appreciable response on PET/CT after 6 weeks. Due to promising results in other hematologic disorders, we then initiated therapy with Dasatinib resulting in a considerable reduction in the size of the thoracic mass and resolution of the pleural tumors.

### **Conclusion:**

This is the first report of a patient with JXG containing a somatic PDGFRB translocation. Evaluation of targetable kinases may be of upmost importance in the management of patients with systemic JXG. Consideration of tyrosine kinase inhibitors is warranted for patients harboring these mutations who fail conventional therapies, such as vinblastine and prednisone.

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Poster # 435

## **CUTANEOUS MUCORMYCOSIS IN THE SETTING OF B-CELL ACUTE LYMPHOCYTIC LEUKEMIA: A CASE REPORT**

**Uju Momah, Viven Solomon, Tatiana Lara-Ospina, Eilleen Gillan**

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### **Background:**

Mucormycosis is an opportunistic fungal infection found in immunocompromised patients, including those with human-immunodeficiency virus, diabetes, renal insufficiency, organ transplant, long-term immunosuppressive and corticosteroid therapy, as well as leukemia and lymphoma. Following candidiasis and aspergillosis, infection by Mucormycosis is the third most common angioinvasive fungal infection. Infection begins in the paranasal sinuses and nose, rapidly progressing after inhalation of fungal spores and disseminating throughout the body if left untreated. Early diagnosis is crucial in providing adequate treatment for this life-threatening condition.

### **Objectives:**

In this case report we discuss the novel clinical scenario in which mucormycosis infection should be suspected in a patient with B-cell acute lymphoblastic leukemia (ALL) and double-negative T cells. At the time of detection, our patient presented atypically with a 1.5-2 cm eschar with an erythematous surrounding on her right lateral forearm found after induction. Further work-up revealed extensive dissemination including lung and nasal nodules. Given the poor prognosis of infection and rapidity with which it can spread, mucormycosis is a serious condition that requires early detection and initiation of treatment.

**Design/Method:**

A case study was done while the patient was admitted to the inpatient service at a pediatric hospital. Her entire history was reviewed, her course followed, and updates regarding her case monitored even after discharge. This case report discusses her acute presentation and diagnosis of B-cell ALL, as well as related mucormycosis infection.

**Results:**

This case report discusses the diagnosis and therapy provided to a B-cell patient with a related mucormycosis infection. It presented atypically with a skin lesion after induction, with additional work-up revealing dissemination with multiple lung nodules. We highlight the importance of early detection and treatment options, as seen in this patient who was diagnosed via skin lesion observed on her forearm that was suspicious for mucormycosis, with subsequent work-up revealing dissemination into the lungs. A treatment regimen of amphotericin and posaconazole B were emergently started, and a lung wedge resection, debridement of her left forearm, and nasal polyp removal were performed.

**Conclusion:**

Mucormycosis is an invasive, aggressive fungal infection that can occur in patients with compromised immunity in the form of HIV, malignancy and long-term immunosuppressive therapy, among other means. While cutaneous infection can remain localized to the skin, it can rapidly undergo hematogenous dissemination to other organ systems throughout the body. The mortality rate is high, particularly in patients in an immunocompromised state, making urgent identification and treatment critical in disease management.

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Poster # 436

**SYMPTOMS MIMICKING A NEUROENDOCRINE TUMOR: EVALUATION OF AN ADOLESCENT WITH E-CIGARETTE USE**

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**Background:**

The growing prevalence of e-cigarette use (vaping) and vaping-related lung injuries necessitates the documentation of unique symptoms. We report a case of hyperhidrosis, diarrhea, and hypertension in a 17-year patient, which improved with cessation of e-cigarette use, which has not previously been reported in the literature.

**Objectives:**

The purpose of this case study is to document an unusual presentation of possible vaping-related symptoms, mimicking symptoms of a neuroendocrine tumor.

**Design/Method:**

Data gathered by chart review.



**Results:**

A 17-year-old male was referred for oncology evaluation due to several weeks of drenching sweats, which occurred throughout the day. His sweating was significant enough that he eventually quit school and returned to live at home, where he isolated himself with limited activities.

At presentation, he denied fever, weight loss, recent travel history, or use of new medications. He had a history of smoking with e-cigarettes with synthetic cannabinoid oil daily, with increased use over the 2 months prior to presentation, believing it would reduce his sweating. Review of systems was also significant for abdominal pain, 2 episodes of non-bloody diarrhea daily, and decreased appetite. He also endorsed new onset of blisters on his fingers bilaterally, with an erythematous rash on his left palm.

Vital signs significant for elevated blood pressure of 141/88. On physical exam, his pertinent findings included diaphoresis of the upper body and blisters of the distal fingers bilaterally. Infectious disease evaluation was negative for Rickettsia, Babesia, Ehrlichia, and Lyme, and TB. Endocrinology evaluation revealed normal thyroid function.

Further work up was performed to rule out neuroendocrine tumor. CXR and abdominal MRI were normal; lab work including CBC, LDH, uric acid, ESR, serotonin, and a 24 hour cortisol, metanephrine, and catecholamine urine collection was all within normal limits. 5h1aa urine testing resulted as mildly elevated (11.6) and then normal on repeat sent after cessation of vaping. Urine toxicology was only positive for tetrahydrocannabinol.

At follow up, he reported discontinuation of vaping and endorsed that the episodes of sweating were less intense and less frequent. The rash and diarrhea resolved. He was referred to rheumatology, and psychiatry for further evaluation, and diagnosed with general anxiety disorder.

**Conclusion:**

Neuroendocrine tumors can present similarly with facial flushing, diarrhea, fluctuations in blood pressure, sweating, and skin rash due to hormone release secondary to carcinoid syndrome. Cessation of vaping reduced the frequency and intensity of his symptoms, suggesting that vaping THC oil may have contributed to/or exacerbated his symptoms.

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Poster # 437

**A NOVEL CASE OF PROLONGED IFOSFAMIDE ENCEPHALOPATHY AND LONG-TERM TREATMENT WITH METHYLENE BLUE**

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**Background:**

We present the case of an 11-year-old female with autistic spectrum disorder and recurrent episodes of severe somnolence for five months following Ifosfamide-containing chemotherapy for her Non-Germinomatous Germ Cell Tumor. Periods of somnolence occurred prior to

receiving cranial radiotherapy. Administration of methylene blue gave immediate but limited response, with resolution of somnolence lasting 1-2 days between administrations. The somnolence could not be explained by neuroimaging or laboratory evaluation, but EEG indicated persistent encephalopathy. Side effects of Ifosfamide include encephalopathy, delirium and confusion. CNS Toxicity often presents within twelve hours of drug initiation and subsequently resolves following drug discontinuation (1-2 weeks). Ifosfamide is metabolized in the liver giving rise to multiple metabolites including chloroacetaldehyde, a potentially neurotoxic metabolite theorized to cause encephalopathy. Current guidelines for neurotoxicity-treatment are to stop Ifosfamide and provide supportive care. Methylene blue acts to inhibit chloroacetaldehyde formation and has been described as a therapy and prophylaxis for Ifosfamide-induced neurotoxicity. It is effective within 30 minutes and lasts up to 3 days. Prolonged treatment is not described in the literature.

**Objectives:**

Our objective is to describe a novel case of extremely prolonged encephalopathy following Ifosfamide treatment cessation and requirement of long-term repeated treatment with methylene blue.

**Design/Method:**

We will describe our case, review the background of Ifosfamide and Methylene blue and summarize the literature on Ifosfamide-induced encephalopathy, concluding with a hypothesis of a mechanism.

**Results:**

A literature review determines that neurotoxicity is a side effect of Ifosfamide, but this effect has not been described persisting longer than 30 days. Our case continued to require treatment with methylene blue for 5 months following cessation of therapy. The literature indicates that Methylene Blue is moderately effective in treating Ifosfamide-induced encephalopathy but no cases have been noted that describe such a prolonged course of recurrence. One case notes an adult oncologic patient, who presented with neurologic dysfunction following Ifosfamide persisting for more than ten years, however this was associated with an ongoing complex course of chemotherapy care.

**Conclusion:**

Ifosfamide-induced encephalopathy is well described, but there are no reported cases of such prolonged encephalopathy responsive to methylene blue. We hypothesize that there could be a genetic/metabolic component relating to her reaction to Ifosfamide with her pre-existing autism. This possible association is also noted in a case study describing mental status changes in an autistic child receiving Ifosfamide. We aim to investigate this further via genetic and metabolic screening.

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Poster # 438

**ROTHIA BACTEREMIA, PNEUMONIA, MENINGITIS IN AN ADOLESCENT DURING AML CHEMOTHERAPY CAUSING MORBIDITY**

**Rachel Robertson, Arun Ranjan Panigrahi, Rita Cheema**

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**Background:**

*Rothia Mucilaginosa* (RM) is one of the most abundant phylotypes representing >0.5% of healthy oral microbiome however it can also become an aggressive opportunistic pathogen. It is rarely documented in immunocompromised patients with pediatric blood cancers including Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML) or those undergoing bone marrow transplant (BMT) and standardized treatment regimen is lacking.

**Objectives:**

That others may gain needed treatment insight into multi-organ RM infection and its potential aggressive nature in neutropenic patients and consider Penicillin-G if Cefepime efficacy is lacking.

**Design/Method:**

Single subject case report.

**Results:**

A 17yo M with AML diagnosed 3 months prior presented with febrile neutropenia secondary to RM bacteremia leading to significant complications and multi-organ involvement including sepsis, pneumonia and meningitis leading to diffuse cerebritis and coma with substantial morbidity. This was within the context of days prior receiving chemotherapy which included intrathecal Cytarabine, systemic Etoposide and Cytarabine. His admission blood culture was positive for *Rothia Mucilaginosa* in 1 lumen of his double-lumen central-line. Despite Cefepime and Vancomycin, he remained febrile even with follow-up negative blood cultures. A further infectious disease work-up was performed and concern for fungal infection arose. He was found on CT to have disseminated lung nodules with cavitation yet lung biopsy was negative; remaining febrile despite antibiotics. Brain MRI then revealed a ring-enhancing lesion with multiple punctate foci with edema, ventriculitis and diffuse cerebritis with a RM positive lumbar puncture. He continued to worsen and was emergently intubated and remained encephalopathic for several months requiring tracheostomy.

**Conclusion:**

His admitting RM bacteremia likely seeded his brain tissue and despite ongoing treatment with Cefepime and Vancomycin the infection persisted in his brain tissue because of ineffective penetration. Both Penicillin-G and Cephalosporins are  $\beta$ -lactam antibiotics; he was initially treated with Cefepime which is a typical choice in febrile neutropenia. Both are bacteriocidal however penetrate CSF differently. Antibiotic penetration is not only dependent on the intrinsic property of the drug but also the status of the blood-brain barrier. In our patient he clearly had meningeal inflammation which causes separation of intercellular tight junctions thereby allowing more robust antibiotic penetration. The change to Penicillin-G also coincided with count recovery which may have aided maximal therapeutic antibiotic concentration to penetrate the CSF. It is hoped that by sharing this, others may gain needed treatment insight into multi-organ RM infection in neutropenic patients and strongly consider that RM may not be a contaminant.

## **DINUTUXIMAB DESENSITIZATION: A PROTOCOL FOR CHILDREN WITH SEVERE INFUSION REACTIONS**

**Jenna Allison, Jill Beck, Tara Blesh-Boren**

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### **Background:**

The use of ch 14.18 anti-GD2 antibody has been well documented to improve event free survival in high risk neuroblastoma; however, the side effect profile can limit effective medication delivery. Infusion reactions such as cough and fever are likely with antibody administration, while bronchospasm, angioedema, and anaphylaxis are less likely but have more serious implications on completion of therapy. Patients who experience severe or life-threatening adverse events are not able to receive antibody and therefore are at higher risk for progressive or relapsed disease. We present a patient who was unable to receive full dose antibody therapy per Children's Oncology Group protocol ANBL0032 due to adverse events during three separate infusions. Although antibody therapy was discontinued, the patient completed isotretinoin therapy. End of therapy imaging demonstrated relapsed disease. We developed a desensitization protocol to deliver ch 14.18 anti-GD2 antibody as a part of salvage therapy.

### **Objectives:**

Following significant infusion related reactions, we present a patient who was not able to receive full dose ch 14.18 anti-GD2 antibody per front-line therapy and subsequently developed relapsed disease at the end of therapy. Our goal was to safely and effectively deliver full dose ch 14.18 anti-GD2 antibody as a part of salvage therapy.

### **Design/Method:**

We designed a ch 14.18 anti-GD2 antibody desensitization protocol in order to safely infuse full dose ch 14.18 anti-GD2 antibody. Antibody was delivered via a three bag, diluted concentration system over 20 hours in conjunction with pre-medications for allergic reactions.

### **Results:**

The patient has successfully received two cycles of full dose ch 14.18 anti-GD2 antibody per our desensitization protocol with minimal side effects and no significant adverse events.

### **Conclusion:**

There currently is no published literature regarding safe delivery of ch 14.18 anti-GD2 antibody in patients who have previously been unable to receive this medication due to adverse events during initial exposure. We present a case in which the patient experienced multiple, significant infusion related reactions resulting in discontinuing the intended course of ch 14.18 anti-GD2 antibody during front-line therapy, potentially resulting in relapsed disease. We have successfully delivered this medication as part of salvage therapy. It is unclear at this time

whether this will have an impact on event free survival following completion of relapsed therapy.

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Poster # 440

## **REVIEW OF PEDIATRIC CANCER RELAPSES >5 YEARS FROM DIAGNOSIS IN ADOLESCENT/YOUNG ADULT (AYA) PATIENTS**

**Mary Dang, Rebecca McFall, Linda Rivard, Marie-Ellen Sarvida, Ricarchito Manera, Jason Canner**

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### **Background:**

Advances in curative chemotherapy have improved long-term survival in patients with de novo pediatric cancers, leading to a population at increased risk of late effects secondary to their treatment. Children's Oncology Group (COG) responded by developing late effect studies, guidelines, and dedicated survivorship clinics. As more intensive therapies have prolonged initial disease control and extended survival beyond 5 years, these patients face an increased risk of late recurrence of their primary malignancy and mortality. Data from Surveillance, Epidemiology, and End Results (SEER) shows relapse of primary disease as the most common cause of death in long-term survivors, and therapeutic studies have recommended relapse surveillance for those >5 years post-therapy. However, COG late effect guidelines currently have no recommendations for relapse surveillance. Of these survivors, the AYA population is an especially vulnerable group due to variable transition programs and life changes. We describe four AYA cases with late relapse, identifying the need for improved survivorship guidelines relating to primary disease recurrence.

### **Objectives:**

To highlight the importance of surveillance in pediatric patients >5 years from diagnosis for late primary disease relapse.

### **Design/Method:**

Case series of four AYA patients with late relapses.

### **Results:**

Patient 1 is a 22-year-old with Ewing sarcoma, treated per AEWS0031 with surgery and compressed therapy, noted to have a pulmonary mass confirmed to be Ewing sarcoma. Patient 2 is a 20-year-old diagnosed with AML at age 5 treated per AAML0531 with Gemtuzimab, no transplant, who presented with a peritonsillar abscess and myeloblasts on his CBC. Patient 3 is a 22-year-old diagnosed with metastatic Wilms tumor treated with chemoradiotherapy, found to have recurrent pneumonia and lung mass determined to be Wilms. Patient 4 is a 15-year-old girl with history of preB ALL at age 3, who presented with a one-year history of fatigue and headaches. CBC confirmed pancytopenia, subsequently showing bone marrow and CSF relapse.

### **Conclusion:**

Improved cancer outcomes have led to a comprehensive approach to survivorship. Despite the knowledge that relapse disease continues to be the most common cause of death in 5-year survivors, there are currently no guidelines addressing recurrence of initial disease.

Project:EveryChild will collect data for 10 years from initial registration, improving our understanding of late effects and guiding future practice; however, guidance on extended monitoring for relapse disease is lacking. We propose that surveillance practices among pediatric and AYA programs be reviewed with the goal of organizing a task force to explore the need for relapse surveillance guidelines.

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Poster # 441

## **DELAYED METHOTREXATE EXCRETION DUE TO SEQUESTRATION IN A THYMIC CYST**

**Heather Deville, Kenneth Heym, Tyler Hamby, Ashraf Mohamed**

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### **Background:**

High-Dose Methotrexate (HD-MTX) is extremely effective in childhood cancers; yet, it has many side effects due to its toxic potential. For this reason, it is important that HD-MTX levels are continuously monitored while administering this medication. The normal timeframe for HD-MTX clearance is 2-3 days. In most patients, the levels should decline as the kidneys filter the medicine from the blood; however, in rare cases, prolonged excretion can result from HD-MTX accumulating in "third spaces", for example pleural effusions or ascites. In scarcer instances, HD-MTX has been reported to be sequestered within cysts in the ovaries and in the liver, which led to very prolonged time to excretion with high potential for severe systemic toxicity.

### **Objectives:**

The purpose of this study is the importance of recognition and investigation of persistent prolonged Methotrexate excretion.

### **Design/Method:**

A 16-year-old female patient was admitted for HD-MTX for osteosarcoma in 2019. Her renal function tests were within normal limits. During her first cycle of HD-MTX, she experienced delayed clearance of MTX taking approximately 7.00 days to clear, requiring prolonged hospitalization for drug level monitoring as well as monitoring for renal and other organ toxicity. Over the next two months, her clearance for HD-MTX cycles remained prolonged at 5.95 days and 7.08 days.

Six weeks later, the patient then presented to the clinic with chest pain. Upon evaluation, a CT angiogram revealed an elongated cystic structure in the superior mediastinum, consistent with a thymic cyst.

### **Results:**

Because of increase in the cyst size as well as pressure symptoms, the cyst was surgically removed. The pathology report of the cyst showed that there was inflammation, including

cholesterol clefts found, but it was not neoplastic.

The patient cleared her next two scheduled HD-MTX treatments for osteosarcoma 10 and 11 weeks post-diagnosis, without delay in 2.66 and 2.93 days, respectively.

**Conclusion:**

This case study brings to light a very rare occurrence of MTX sequestration within a pre-existing benign thymic cyst, leading to prolonged time to MTX clearance and hence prolonged hospitalization requiring extended leucovorin rescue. It would be prudent to consider imaging patients with persistent delayed MTX excretion, looking for unusual areas where 3rd spacing may occur, like the thymic cyst in our case.

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Poster # 442

**REMISSION OF UNRESECTABLE SUBMANDIBULAR UNICENTRIC CASTLEMAN DISEASE WITH RITUXIMAB THERAPY**

**Leighton Elliott, Jagadeesh Ramdas**

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**Background:**

Angiofollicular lymph node hyperplasia, also known as Castleman Disease (CD) is a rare lymphoproliferative disorder discovered by Benjamin Castleman in 1956. The disease definition has changed over time with further discovery into its histopathologic features. CD is now divided into three subtypes: unicentric (UCD), idiopathic multicentric (IMCD), and HHV-8 associated multicentric disease according to the most recent literature. International consensus treatment guidelines were established in 2018 for IMCD using anti-IL-6 agents, rituximab, or chemotherapy. Resection is the gold standard for UCD which confers cure nearing 100%. Neoadjuvant rituximab and radiotherapy have been suggested. One other case report has been published where remission was achieved of a thoracic UCD with rituximab.

**Objectives:**

Discuss the case of a child with head and neck UCD that was difficult to diagnose and who achieved remission with rituximab

**Design/Method:**

Case Report and Literature Review

**Results:**

An 8 year old male presented to his pediatrician for right neck mass. He was diagnosed with cervical adenitis and repeatedly treated with antibiotics with moderate response and recurrence. He underwent fine needle aspiration and subsequently excisional core biopsy, which showed reactive lymphadenopathy. Incidentally, the patient suffered from chronic osteomyelitis of his foot with *Achromobacter* species and was treated with IV ceftazidime for 9 weeks; during that time, the submandibular mass was controlled. After stopping ceftazidime, the mass recurred. Parotidectomy was performed, however residual tumor remained wrapped around his facial

nerve and not amenable to resection. Pathology reported Castleman-like features. HHV-8, HIV, and hepatitis panel were negative; IL-6 was not elevated. CT chest/abdomen/pelvis was negative for other lymphadenopathy or mass and the patient was diagnosed with UCD. The patient had waxing and waning mass size with associated symptoms of pain, eye-twitching, tinnitus, and ear infections. Five years post-parotidectomy, the tumor grew rapidly to 7 cm x 7cm within a month and rituximab was started. Tumor size clinically decreased within a week and about 50% based on repeat CT scan 6 weeks later. He received 2 maintenance doses of rituximab separated by 3 months. Nine months later, the mass was 1 cm x 2 cm on exam and the patient had no recurrence.

**Conclusion:**

UCD can usually be treated by surgical resection. In the cases where surgery is not preferred due to anatomy or comorbid disease, rituximab should be considered. Further research is needed regarding outcomes with rituximab therapy.

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Poster # 443

**IMPORTANCE OF FUNCTIONAL ASSAY IN A PATIENT WITH LEUKOCYTOSIS AND LEUKOCYTE ADHESION DEFICIENCY-1**

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**Background:**

Leukocyte adhesion deficiency, type 1 (LAD-1) is an autosomal recessive primary immunodeficiency characterized by impaired adhesion to vasculature causing defective neutrophil migration to sites of infection. This is caused by a quantitative and/or a qualitative defect in the CD11/CD18 receptor on the cell surface. LAD-1 is caused by mutations in the ITGB2 gene which encodes CD18. LAD-1 diagnosis relies on the measurement of CD18 expression. LAD-1 presents clinically in the newborn with leukocytosis, delayed separation of the umbilical cord and serious life threatening infections. Treatment for patients with severe clinical disease is allogeneic stem cell transplantation.

**Objectives:**

We report a three month male infant with LAD-1 presenting with severe leukocytosis and unusual severe clinical phenotype and point out the difficulty of diagnosis especially in those patients with a qualitative defect in CD18.

**Design/Method:**

Case Report/Literature review

**Results:**

A three month old male of nonconsanguineous parents, presented with a WBC of 93,000-126,900. He did not have delayed umbilical cord separation, or history of any skin or pulmonary infections. Infectious, immunological and rheumatological workups were negative. A bone



marrow examination was normal. Workup for LAD-1 at Lab 1 revealed normal CD18 expression. At Lab 2, a specialized immunologic lab, revealed CD18 6,984 (normal >8,245), CD11a 1,122 (normal >1,451). A third lab, a international reference lab, revealed, CD18 30%, and CD11a 3.3%, CD11b 3.3%. There is a discrepancy/variability in all three labs, yet Labs 2 and 3 show a decrease in CD18 and CD11a expression. Further confirmation was done with neutrophil chemotaxis assay which was absent (with normal appropriate controls). The patient had a protein losing enteropathy and failure to thrive based on poor weight gain. Endoscopy and colonoscopy revealed esophagitis, stomach ulcerations and an ulcer in the transverse colon. Whole exome sequencing (WES) showed a compound heterozygote mutation with c.817G>A(p.G273R) and c.412T>C(p.S138P). The same genetic mutation was described by Hogg et al. and resulted in a severe clinical phenotype requiring bone marrow transplantation.

### **Conclusion:**

This case illustrates the difficulty in diagnosis of LAD-1, the need for high level of suspicion, the variability of CD18 testing, importance of WES analysis and functional testing. Our patient although having the same genetic mutation was phenotypically dissimilar to the patient reported. Perhaps, functional testing can predict disease severity and can be used for decision making and need for transplant. (Hogg, J Clin Inv,1999), (Levy-Mendelovich,Imm, 2016)

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Poster # 444

## **CASTLEMAN’S DISEASE AND NEPHROTIC SYNDROME: A PEDIATRIC CASE REPORT**

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### **Background:**

Castleman’s disease (CD) is an uncommon and poorly understood disorder of lymph node hyperplasia of unknown etiology. It belongs to the atypical lymphoproliferative disorders, a heterogeneous group of diseases characterized by a hyperplastic reactive process involving the immune system. CD is classified into two clinical subtypes: localized and multicentric. CD may occur anywhere along the lymphatic chain; most commonly in the mediastinum. Extrathoracic sites include the neck, axilla and retroperitoneum. Renal manifestations are not uncommon in CD; however, nephrotic syndrome (NS) is rare.

### **Objectives:**

To discuss the presentation, workup, and treatment of a patient with Castleman’s disease and nephrotic syndrome.

### **Design/Method:**

Case Report

### **Results:**

Case Presentation: A 7-year-old African-American female presented with a 3-day history of periorbital and lower extremity edema. Urinalysis revealed nephrotic-range proteinuria. Urine protein: urine creatinine >2. Laboratory investigations demonstrated hypoalbuminemia and hypercholesterolemia, concerning for NS. Imaging workup for complaints of abdominal pain were significant for bulky mesenteric adenopathy, prominent inguinal femoral lymph nodes, and bilateral pleural effusions.

Diagnostic workup for secondary etiologies of NS were negative. Oncologic workup investigating for causes of bulky adenopathy were not suggestive of malignancy. Peripheral blood smear was unremarkable. PET/CT findings were suggestive of lymphoproliferative vs infectious process – revealing diffuse hypermetabolic lymphadenopathy with increased uptake in the tonsils, cervical lymph nodes, and ileocecal region. Pathological examination of bilateral tonsillectomy, excision cervical node biopsy, and colonoscopy suggested reactive follicular hyperplasia and germinal center B-cells. These findings were inconclusive for malignancy or infectious process.

Corticosteroid therapy for NS was deferred given the uncertain etiology and the risks involved with initiating immunosuppressive therapy in the context of potential infection or malignancy. She improved clinically with fluid restriction, diuretic therapy and was discharged with close follow up of renal function, fluid balance and lymphadenopathy progression. She represented one month later with worsening swelling and weight gain concerning for untreated nephrotic syndrome. This was managed with a 6-week course of corticosteroids and diuretics until ideal dry weight was obtained. Currently, she has been off corticosteroids for two months without symptom recurrence.

### **Conclusion:**

This case report presents an example of successful treatment of nephrotic syndrome in the setting of multicentric Castleman’s disease. The treatment of CD and the possible reversal of nephrotic syndrome is a controversial issue as current approaches are based essentially on case reports, including high-dose corticosteroids and in some cases the addition of colchicine, since clinical studies are lacking due to the rarity of this disease.

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Poster # 445

## **USE OF RITUXIMAB AND PREDNISONE TO TREAT CHILD WITH IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE**

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### **Background:**

HHV8-negative/idiopathic Multicentric Castleman Disease (iMCD) is a rare lymphoproliferative disorder, particularly in children. Diagnosis based on international consensus criteria of idiopathic MCD (iMCD) requires multicentric lymphadenopathy with defined histopathology,  $\geq$  2 clinical/laboratory changes, and exclusion of other mimics. Although the exact etiology of iMCD is unknown, excessive production of IL-6 is linked to development of disease, and anti-

IL-6 therapy is currently recommended for the treatment of iMCD in adults. However, lower median IL-6 levels have been reported in treatment non-responders in at least one randomized controlled trial of anti-IL-6 therapy for iMCD. It may be prudent to consider other initial treatments in cases of iMCD and normal serum IL-6.

**Objectives:**

We describe the successful treatment of a pediatric patient with iMCD and normal serum IL-6 using rituximab and prednisone to achieve a sustained complete response.

**Design/Method:**

An 11 year old male with no previous medical history presented with one week of fever, dyspnea, diffuse lymphadenopathy, and anasarca. Laboratory testing was significant for microcytic anemia with normal platelet count, hypoalbuminemia, elevated inflammatory markers (CRP 17.4 mg/dL, ESR 99 mm/hr, fibrinogen 616 mg/dL), elevated D-dimer with mild coagulopathy, isolated IgG hypergammaglobulinemia (2,040 mg/dL), negative HIV serology and HHV-8 PCR, and normal serum IL-6 (5 pg/mL). PET/CT revealed diffuse mildly hypermetabolic lymphadenopathy of neck, thoracic, and abdominal/pelvic regions (SUV range 3.3 to 10.8). Excisional lymph node biopsy revealed HHV8-negative, mixed-type variant Castleman disease. Bone marrow biopsy showed mildly increased reticulin fibrosis and mild plasmacytosis. Our patient met the diagnostic criteria for iMCD.

**Results:**

The patient received treatment with rituximab (375mg/m<sup>2</sup>) weekly for four doses along with prednisone (20mg/m<sup>2</sup>/dose) twice daily for one week followed by a subsequent one-week taper. Within 72 hours of starting treatment, his symptoms markedly improved with decreased edema and resolution of fever and respiratory symptoms. Additionally, the patient's anemia, hypoalbuminemia, elevated inflammatory markers, and coagulopathy all resolved after two weeks of treatment. After approximately one month of treatment he remained asymptomatic and repeat PET/CT showed near complete resolution of hypermetabolic lymphadenopathy. He remains asymptomatic with normal laboratory markers at most recent follow up, approximately 21 months post-treatment.

**Conclusion:**

There are few published reports on the successful treatment of iMCD in children. Our single patient experience suggests that the use of rituximab with steroids may be a reasonable initial strategy for the treatment of children with iMCD, particularly in the setting of normal serum IL-6 levels.

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Poster # 446

**THE EFFECT OF PROLONGED ANTENATAL IVIG TREATMENT IN PREVENTING GESTATIONAL ALLOIMMUNE LIVER DISEASE**

**Faraz Afridi, Janine Gomes, Sukrita Mysore, Alla Kushnir, Rafat Ahmed, Linda Slater-Myer**

**Background:**

Gestational Alloimmune Liver Disease (GALD), previously known as neonatal hemochromatosis, is a rare disease typically characterized by subacute fetal liver injury and often accompanied by hepatic and extrahepatic iron deposition. Findings include hypoglycemia, coagulopathy, hypoalbuminemia, elevated serum ferritin, elevated alpha-fetoprotein, and ascites. Extrahepatic hemosiderin deposition is often seen in salivary glands. Typically, the mortality rate was close to 80% with all patients needing liver transplantation. With maternal IVIG treatment and changes in neonatal treatment, the prognosis has greatly improved to less than 20% mortality with infrequent need for liver transplantation. Diagnosis of GALD is typically done on a postmortem analysis.

**Objectives:**

To describe a term female infant whose mother received IVIG during pregnancy due to a diagnosis of GALD in a prior child.

**Design/Method:**

Single study case report

**Results:**

A term female infant was born via scheduled c-section to a 32 year old G2P1000 mother who had been receiving weekly IVIG during this pregnancy due to the death of her first child at 4 days of life. Autopsy of that female baby demonstrated extensive neuropathological changes, liver steatosis, iron depletion, and ascites, consistent with GALD. Following delivery of our current patient, there was an elevated alpha-fetoprotein (greater than 80,000) and coagulopathy with peak international normalized ratio of 1.6. The patient received fresh frozen plasma and IVIG on day of life 1 with improvement of these levels and of fibrinogen which was initially low. Complete blood count, liver function tests, and ammonia were within normal limits. Ferritin level was difficult to interpret with a lack of neonatal normative levels. An MRI of the liver demonstrated normal size, morphology, and normal iron levels based on T2 relaxometry. A buccal biopsy did not demonstrate extrahepatic iron deposition. MRI of the brain showed significant stenosis of the right transverse and sigmoid sinus relating to dural venous sinus thrombosis. There was no evidence of parenchymal infarction and no evidence of iron deposition. At this time, enoxaparin was initiated. The patient was discharged home on day of life nine on enoxaparin therapy.

**Conclusion:**

There are few reported cases of patients with GALD, especially after maternal IVIG treatment. This case report exemplifies the effect of antenatal IVIG infusions during subsequent pregnancies in women with a history of GALD in prior children. This effect is protective, evidenced by lack of liver injury noted in this patient. This supports the use of immunotherapy during pregnancy to prevent recurrence of alloimmune injury.

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## **NOT THE MEDICATION, IT'S THE TUBING SYSTEM: A CASE OF ANAPHYLAXIS TO MEDICINE DELIVERY TUBING SYSTEM**

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### **Background:**

Hypersensitivity to chemotherapeutic agents and latex is not an uncommon phenomenon in cancer patients and sometimes can be life threatening. Hospitals now use precautions in using latex for patients with latex allergy. We present a unique case of a child who developed an allergic reaction to the IV tubing system that was used to administer chemotherapy.

### **Objectives:**

To highlight a rare case of IV tubing related anaphylaxis and the importance of a thorough work up for anaphylactic reactions.

### **Design/Method:**

Case report study of an incidence of allergic reaction while receiving infusion at our ambulatory infusion center at our institution.

### **Results:**

A four year old female with a diagnosis of Primitive neuroectodermal tumor grade IV of the parietal lobe was receiving chemotherapy with vincristine in the ambulatory clinic at our hospital. Approximately 3 minutes after the infusion started the patient developed facial redness and coughing. The infusion was stopped, and the patient developed swollen lip and erythema of bilateral cheeks. Oxygen saturation dropped to 87% on room air. The patient was given a dose of 1mg/kg of Diphenhydramine and 2mg/kg of Hydrocortisone. The patients' symptoms gradually resolved over a period of 20 minutes.

Work up for the allergic reaction was initiated which include evaluation for hereditary angioedema and autoimmune diseases since anaphylaxis to vincristine is rare. Vincristine was held. Subsequently, the patient had further allergic reactions while receiving pentamidine, saline flush and hydrocortisone. The work up was broadened since no one medication seemed to be the cause. The studies for hereditary angioedema and rheumatologic diseases were negative. The work up yielded negative results for normal saline, normal saline flushes and chlorhexidine wipes. Finally, she was found to be allergic to the low sorbing tubing system which triggered the anaphylaxis. With this conclusion, her chemotherapy was resumed without premedication and was tolerated well.

### **Conclusion:**

Low sorb tubing systems are polyethylene lined with a PVC free fluid path, that helps prevent absorption of drugs into the matrix of tubing. This is a unique case of tubing related anaphylaxis in a child. To our knowledge this is the first reported case of this type of anaphylaxis. This case

highlights the importance of root cause analysis and that low sorbing tubing system can cause allergic reaction in patients.

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Poster # 501

## **CHEMOTHERAPY INDUCED THROMBOCYTOPENIA IN PEDIATR SOLID TUMOR PATIENTS**

**Katherine Armstrong, Michael Ortiz, Stephen Roberts, Ira Dunkel, Cheryl Goss, Slotkin Emily, Gerald Soff**

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### **Background:**

Pediatric solid tumor chemotherapy regimens often lead to significant myelosuppression, including chemotherapy-induced thrombocytopenia (CIT), causing delays and/or dose modifications of subsequent cycles. The consequences of CIT in pediatric oncology has not been well established.

### **Objectives:**

To evaluate the incidence and impact of CIT in intensive pediatric solid tumor regimens.

### **Design/Method:**

We define CIT as platelets  $< 75,000/\text{mcL}$ . We evaluated CIT resulting from the N8 and EFT regimens, two commonly utilized myelosuppressive regimens used to treat high-risk neuroblastoma and Ewing sarcoma, respectively. N8 and EFT consist of 5 and 7 cycles, respectively, of high-dose cyclophosphamide, doxorubicin, vincristine, etoposide, and either cisplatin (N8) or ifosfamide (EFT). Patients  $\leq 25$  years old with high-risk neuroblastoma or localized Ewing sarcoma treated with N8 or EFT at MSKCC from 2013-2018 were reviewed to determine the frequency and etiology of platelet transfusions and chemotherapy dose reductions/delays. A dose reduction was defined as  $\geq 20\%$  reduction in intended chemotherapy dose and a treatment delay was defined as the chemotherapy start date  $\geq 25$  days from start of prior cycle.

### **Results:**

Forty-nine patients (N8 N=25, EFT N=24) were treated during the study period. Platelet transfusion requirements increased with cycle number. With N8, there was a median of 1.5 (range 1-7) transfusions in cycle 1, which increased to 3.0 (range 1-15) in Cycle 5. With EFT, there was a median of 0.0 (range 0-2) transfusions in cycle 1, which increased to 2.0 (range 0-8) in Cycle 7. The total platelet transfusions per full regimen were a median of 11.0 (range 7-35) for N8 and 9.0 (range 2-23) for EFT.

Chemotherapy dose reductions and delays due to CIT similarly increased over the course of therapy. With N8, 5.0% of patients had a reduction and/or delay at cycle 2 due to isolated CIT, which increased to 45.5% by cycle 5. And with EFT, at cycle 2, no patient had a chemotherapy reduction and/or delay due to CIT, however by the last cycle, 39.1% experienced reduction

and/or delay of treatment due to isolated CIT.

**Conclusion:**

CIT is a common and serious sequela of pediatric solid tumor regimens resulting in frequent platelet transfusions and chemotherapy modifications which worsen as treatment progresses. Further research is needed to identify ways to minimize CIT. We are planning a clinical trial of a thrombopoiesis stimulating agent in pediatric solid tumor patients undergoing myelosuppressive chemotherapy with the goal of minimizing platelet transfusions and chemotherapy modifications.

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Poster # 502

**CLR 131 IN PATIENTS WITH RELAPSED OR REFRACTORY PEDIATRIC MALIGNANCIES**

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**Background:**

CLR 131 is a novel targeted radiotherapeutic that exploits the selective uptake and retention of phospholipid ethers by malignant cells. CLR 131 selectively delivers radiation to malignant tumor cells, thus minimizing radiation exposure to normal tissues. The mechanistic basis for the cancer-cell selective uptake involves interaction with lipid raft regions of the plasma membrane. Therapeutic efficacy has been demonstrated in various pediatric and adult-type cancer xenograft models, confirming the ability of CLR 131 and its isosteres to almost universally target tumors, regardless of histopathological origin.

**Objectives:**

Based on initial preclinical experience in pediatric cancers and clinical data in adult malignancies, CLR 131 is being examined in a Phase 1 trial, CLOVER-2 (NCT03478462) to determine the safety, tolerability, and initial efficacy of CLR 131 in children and adolescents with relapsed/ refractory malignant solid tumors/lymphoma and recurrent/refractory malignant brain tumors.

**Design/Method:**

Eligibility criteria include pediatric solid tumor or malignant brain tumors that are clinically or radiographically suspected to be relapsed or refractory, for which there are no standard treatment options with curative potential. Subjects must be between ages 2 and 21 with no limit to the number of prior therapies. Subjects must have a measurable lesion and appropriate bone marrow and organ function. CLR 131 is administered as a single infusion in escalating doses beginning at 15 mCi/m<sup>2</sup>. Adverse events (AEs) are graded by NCI-CTCAE v5. Responses are determined using established criteria associated with the specific pediatric indication as determined by the investigator.

**Results:**

As of 15Dec2019, three subjects with brain tumors have received CLR 131; one at 15 mCi/m<sup>2</sup> and two at 30 mCi/m<sup>2</sup>. Diagnoses included DIPG and glioblastoma with a median age of 12 years (range 10-15) and a median of 1 prior therapy (range 1 to 2). Treatment emergent AEs (TEAEs) at the 15 mCi/m<sup>2</sup> dose level included Grade 1 nausea, vomiting, and fatigue, all of which were attributed to disease progression. There were no TEAEs determined to be related to CLR 131 by the investigator. Assessment of the 30 mCi/m<sup>2</sup> dose level is ongoing.

**Conclusion:**

CLR 131 is a unique, first in class targeted radiotherapeutic for pediatric malignancies. Preliminary data for CLR 131 administered as a single dose shows an acceptable and expected safety profile in this patient population. Dose escalation to determine the highest tolerated dose for both solid tumors/lymphomas and brain malignancies is ongoing.

Support provided by CellerBio, Inc.

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Poster # 503

**ROLE OF TYROSINE KINASE INHIBITORS IN CHILDREN WITH MEN2 ASSOCIATED MEDULLARY THYROID CARCINOMA**

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**Background:**

Vandetanib and cabozantinib are approved for adults with symptomatic or progressive advanced medullary thyroid cancer (MTC), and trials with novel RET-targeting agents are ongoing. Pediatric MTC is typically seen in association with multiple endocrine neoplasia 2 (MEN 2) syndrome, either MEN2A or MEN2B. The optimal time to initiate tyrosine kinase inhibitors (TKIs) in pediatric patients with MEN2-associated MTC is unclear.

**Objectives:**

To describe the longitudinal evaluation of pediatric patients with MEN2-associated MTC followed on a natural history study (NCT01660984) at the National Cancer Institute (NCI).

**Design/Method:**

Clinical and imaging data were extracted from medical records and disease course of patients on TKIs and not on TKIs, was analyzed. Medians (interquartile range) are reported.

**Results:**

Between 7/13/07-12/17/19, 56 patients (29 male/27 female; 12 MEN2A/44 MEN2B; age 13.5 years (10.7, 16.4)) were followed. Eleven had undergone prophylactic thyroidectomy (9 MEN2A, 2 MEN2B), of whom 10 had no biochemical or imaging evidence of disease



subsequently. In 45 patients, age at MTC diagnosis was 10.7 years (8.6, 13.0) and 43/45 had thyroidectomy with or without lymph-node dissection prior to presentation at NCI. Twenty (18 with stage 3/4 disease at diagnosis) initiated TKI therapy at 2.5 years (0.7, 4.1) from diagnosis. At start of TKI, calcitonin was 13072 pg/ml (3946, 26266); 19 had metastatic and 1 had locally recurrent disease. At follow-up of 6.3 years (5.5, 8.2), 5 were deceased secondary to disease progression, 11 continue on TKI therapy (2 with disease progression), and 4 are monitored off treatment. Twenty-six patients (20 with stage 3/4 disease at diagnosis) never received TKI therapy with follow-up of 4.4 years (2.4, 7.1) from diagnosis. At initial presentation to NCI, disease burden was generally lower (calcitonin 150 pg/ml (52, 742)). One had normal biomarkers, 12 biochemical persistence without positive imaging, 5 locoregional disease, and 8 had distant metastatic disease. Follow-up data was available in 18/26 patients. At a follow-up of 3.1 years (2.0-4.5) from initial presentation, 7 have stable biomarkers and the other 11 have rising biomarkers (4 without radiographic progression or worsening symptoms and 7 with some concern for radiographic progression). At most recent follow-up, the median calcitonin was 523 pg/ml (120, 1854).

**Conclusion:**

Long-term TKI therapy is well tolerated in patients with progressive/symptomatic disease. Pediatric MTC patients with indolent disease, even with distant metastasis, can be monitored without TKIs for extended periods. The impact of TKI initiation on survival or development of resistance is unknown.

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Poster # 504

**MOLECULAR MECHANISM(S) OF RESISTANCE TO VANDETANIB IN MEDULLARY THYROID CARCINOMA**

**Brittany Glassberg, Sophia Khan, Alex Pemov, Bob Hawley, Brigitte Widemann, Javed Khan, John Glod**

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**Background:**

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor arising from parafollicular C cells of the thyroid. Pediatric cases of this cancer are associated with the diagnosis of multiple endocrine neoplasia, which is caused by a mutation in the rearranged during transfection (RET) gene. Vandetanib, an oral receptor tyrosine kinase inhibitor, is approved for the treatment of patients with progressive MTC. While there is a response rate of 50% the majority of patients will eventually develop resistant disease.

**Objectives:**

The goal of this work is to understand genetic and epigenetic underpinnings of sensitivity and resistance to vandetanib and develop novel synergistic combination therapies in medullary thyroid carcinoma.

**Design/Method:**

The TT cell line (RET mutation p.C634W) was cultured in increasing concentrations of vandetanib over 5 months to generate a vandetanib resistant cell line. Both vandetanib-sensitive and -resistant lines were evaluated by exome-, RNA-sequencing, and methylation array analysis. In parallel we performed Genome-wide CRISPR knock-out and CRISPR activation of both sensitive and resistant cell lines using the TKO Version 3 Library, consisting of 71,090 gRNAs targeting 18,000 genes, and the Calabrese P65-HSF activation Library, using 113,328 guides for 18,885 genes.

**Results:**

Both whole exome and RNA sequencing demonstrated increased variant allele fraction (VAF) with LOH of the RET C634W variant in the resistant cell line. Gene set enrichment analysis showed increase in cell cycle and increase in expression of several genes including multidrug-resistance- 1 (ABCB1) which confers drug resistance in other cancers and autotaxin (ENPP2) which catalyzes production of lysophosphatidic acid (LPA) that evokes growth factor-like responses including stimulation of cell proliferation and chemotaxis. Autotaxin also has been reported to stimulate motility and angiogenesis and is overexpressed in several carcinomas. Genome-wide CRISPR inactivation of drug-treated cells showed significant enrichment of guide RNAs associated with resistance to vandetanib, including MAP3K15, an intermediate of the MAP Kinase pathway. Gene set enrichment analysis of the CRISPR inactivation data showed enrichment of the proteasome pathway as a potential candidate of growth suppression by vandetanib.

**Conclusion:**

We have identified several potential mechanisms of resistance to Vandetanib which are currently being validated. Combinations of Vandetanib with other small molecule inhibitors including Bortezomib are being tested for synergy and prevention of resistance. Positive hits will be tested in patients through clinical trials.

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Poster # 505

**EARLY EXPERIENCES WITH TRIPLE IMMUNOCHEMOTHERAPY IN AYAS WITH FIBROLAMELLAR CARCINOMA**

**Ariel Gliksberg, Paul Kent, Claire O'grady**

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**Background:**

Fibrolamellar Carcinoma (FLC) is a rare liver malignancy affecting adolescents and young adults (AYA) without underlying liver disease. Surgery is the only consensus treatment. Even after complete resection, recurrence is common. Currently there are no established systemic treatments, especially for high risk disease (unresectable, relapse, disease progression on systemic therapy, or metastatic disease). Research suggests that FLC may be a good target for immunotherapy. We share our experience using systemic “triple immunotherapy” (TT): 2 week cycles of: 7 days continuous infusion 5FU or oral capecitabine, interferon alpha-2b on days 1,3,5,7 or PEG-Interferon and nivolumab on day 1.

**Objectives:**

To evaluate the tolerability and early efficacy of TT in AYAs with high-risk FLC.

**Design/Method:**

Data from all patients who received TT from 5/2018 to 1/2020 was reviewed to assess tolerability, survival and toxicity.

**Results:**

Eighteen patients were treated with TT of which 10 (8F,2M with a median age of 20) were evaluable based on follow up scans with a median number of 13 cycles of TT (6-31). At the time of analysis, the median PFS on TT was 6 months, 22% longer than the best PFS prior to TT, with 80% of patients (8) stable or improving, one progression and one who died 2 months after initiating TT. For the 4 patients who achieved surgical remission before or during therapy, none have relapsed (PFS 9 months). Overall objective response (CR+PR) and tumor control rate (CR+PR+SD) were 60% and 80%, respectively. There were no withdrawals from treatment due to side effects, though 2 had dose adjustments. All experienced mild adverse effects, most commonly fever and headache, but only 2 patients with grade 3 toxicity.

**Conclusion:**

Our early results of TT for high-risk FLC are promising, with good tolerability and treatment response, particularly in patients who have achieved surgical CR. Further longitudinal data is needed to confirm outcomes, especially in patients still early in their treatment.

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Poster # 506

**DISPARITIES IN ANTINEOPLASTIC IMMUNOTHERAPY USE FOR PEDIATRIC MALIGNANT ADRENAL TUMORS**

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**Background:**

Therapies in pediatric oncology are becoming increasingly targeted, individualized, and costly. Children of certain racial, ethnic, and sociodemographic groups are at risk of inequitable receipt of these novel therapies.

**Objectives:**

To examine the distribution of antineoplastic immunotherapy in patients with neuroblastoma in 2016, the year after Federal Drug and Food Administration (FDA) approval of dinutuximab for high-risk disease, incorporating it in the standard of care.

**Design/Method:**

The AHRQ 2016 KID pediatric inpatient care database accounts for discharges from 4,200 hospitals across 47 states, representing a random sample of 6,266,285 pediatric discharges within

the calendar year of pediatric patients aged = 20 years at admission from all community non-rehabilitation hospitals in states participating in the Healthcare Costs and Utilization Project (HCUP). All elective discharges were included if they had an International Classification of Diseases, Clinical Modification, Version 10 (ICD-10) diagnosis code of C74 in any position in the record. These correspond to malignant neoplasms of the adrenal gland and were used as a surrogate for neuroblastoma. Dinutuximab is the only immunotherapy administered to children with neuroblastoma, and therefore the ICD-10 procedure code Z51.12, coding the administration of antineoplastic immunotherapy was used as a proxy for administration. The KID contains discharge-level records, not patient-level records, and as such individual patients who are hospitalized multiple times in one year may be present in the KID multiple times. The key demographic variables used in this study were age, sex, race, median household income for patient's ZIP Code, hospital region, hospital type, and expected primary payer.

### **Results:**

Of the 4,566 discharges for pediatric adrenal cancers in 2016, 2,499 (54.7%) were elective admissions and 495 (24.7%) of these included administration of antineoplastic immunotherapy. Immunotherapy administrations was more common in older children (OR 1.07,  $p < 0.01$ ), who are more likely to have high-risk disease. When adjusting for age, children of black race and those of the lowest ZIP code income quartile were significantly less like to receive antineoplastic immunotherapy. On multivariable modeling, the association between black race and the lowest income quartile remained significant and these impacts were quantitatively meaningful (OR 0.62,  $p < 0.05$ ; OR 0.74,  $p < 0.01$  respectively). Hospital region was found to be a significant determinant with hospital in the Midwest and North Central having fewer discharges containing coding for antineoplastic immunotherapy as compared to the Northeast (OR 0.49,  $p < 0.001$ ).

### **Conclusion:**

Racial and sociodemographic disparities were found in the use of antineoplastic immunotherapy in pediatric patients with malignant adrenal tumors.

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Poster # 507

## **INHIBITION OF USP7 SUPPRESSES NEUROBLASTOMA TUMOR GROWTH**

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### **Background:**

The ubiquitin proteasome system plays an essential role in post-translational modification to maintain proteostasis in our cells. Ubiquitination of a target protein is coordinated by four different enzymes which add and link ubiquitin in specific ways that determine the fate of the protein. Ubiquitination is further regulated by deubiquitinases which remove ubiquitin molecules from target proteins and rescue them from being degraded. Dysregulation of this ubiquitin proteasome system has been linked many human diseases, including cancer. Ubiquitin-specific protease 7 (USP7) is a deubiquitinase that plays a critical role in viral replication, immune

response, tumor suppression and DNA repair, and overexpression of USP7 has been associated with tumor aggressiveness in a variety of tumors, including in neuroblastoma. Therefore, USP7 is a potential therapeutic target in neuroblastoma. AD04 is a highly potent and selective small molecule inhibitor of USP7 that has demonstrated significant antitumor activity in preclinical models of adult cancer. We hypothesized that AD04 would be effective against neuroblastoma cells.

**Objectives:**

To evaluate the efficacy of USP7 inhibition with AD04 against neuroblastoma tumor growth.

**Design/Method:**

Neuroblastoma cell lines were treated with increasing concentrations of AD04. Cell proliferation was measured using continuous live cell imaging. Relative cellular viability was measured using AlamarBlue assays. Changes in protein expression of MYCN and p53 were measured by Western blotting.

**Results:**

Treatment of most neuroblastoma cell lines with AD04 resulted in significant decreases in cell growth and cell viability in vitro, whereas AD04 had little effect in a subset of neuroblastoma cell lines. The sensitive neuroblastoma cell lines were P53 wild-type, whereas resistant neuroblastoma cell lines had P53 gene mutations. There was no correlation seen between MYCN amplification status and the response to AD04. Treatment with AD04 led to increased protein expression of p53 in all sensitive cell lines tested and increased protein expression of MYCN in MYCN-amplified cell lines. Work is ongoing to evaluate the modulation of ubiquitination through USP7 inhibition to further characterize the mechanism of efficacy.

**Conclusion:**

Our data suggests that AD04 may be a promising therapeutic option for neuroblastoma.

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Poster # 508

**MSI2 IS A NOVEL ONCOGENIC DRIVER IN NEUROBLASTOMA**

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**Background:**

Neuroblastoma (NB) is the most common extracranial solid tumor of childhood and in the high-risk subset, less than 50% of patients survive 5 years after diagnosis. Given the relative paucity of targetable somatic mutations in NB and the long-term negative effects of the currently employed treatment modalities, we seek to develop innovative targeted therapies. We hypothesize that altered regulation of transcription and translation are major mechanisms of neuroblastoma oncogenesis. We have shown that one such regulator, the RNA-binding protein (RBP), LIN28B, promotes neuroblastoma aggression, highlighting the role of RBPs in

modulating NB tumorigenesis. As there are approximately 1500 RBPs, we hypothesized that subsets of RBPs may serve as drivers of neuroblastoma aggression. Using a candidate-based approach, we identified MSI2.

**Objectives:**

In an effort to ultimately more effectively treat neuroblastoma, we seek to determine the role of RBPs in NB pathogenesis.

**Design/Method:**

We genetically depleted MSI2 in human NB cell lines using short hairpin RNA (shRNA) and small interfering RNA (siRNA) and examined the impact on proliferation, survival, and expression of downstream target genes.

**Results:**

We interrogated clinically annotated neuroblastoma gene expression datasets and found that increased expression of MSI2 is associated with worse prognosis, higher stage and reduced survival in high-risk NB. Additionally, we observed decreased colony formation in clonogenic assays, increased apoptosis and decreased proliferation in vitro and in vivo of NB cells with reduced MSI2 levels. We then used unbiased proteomics approaches to identify MSI2-influenced proteins and identified networks implicated in metabolism, translation, and the regulation of oxidative stress. We further explored the role of one such target, eIF4E in NB tumorigenesis. Genetic depletion of eIF4E also results in reduced proliferation of human NB cell lines.

**Conclusion:**

Here we have shown for the first time that higher MSI2 expression is associated with higher stage and worse prognosis in NB. In addition, our in vitro and in vivo results support a role of MSI2 in mediating multiple hallmarks of cancer. Proteomics analysis revealed that many metabolic pathways and networks known to lead to clinical aggression of tumors are downstream of MSI2. These results are indicative that MSI2 and many of its targets including eIF4E are important in NB tumorigenesis. We will continue to validate these targets with the rationale that this provides a basis for better understanding tumorigenesis and RNA biology in NB; thus, unveiling novel therapeutic vulnerabilities in this disease.

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Poster # 509

**ACTIVATION OF INKT CELLS USING GLYCOLIPID ANTIGENS AND CD1D-ANTI-GD2-SCFV FUSION PROTEINS**

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**Background:**

Neuroblastoma (NB) is the most common childhood extracranial solid tumor and confers a 5-year overall survival of approximately 50% in the high risk form. Interestingly, the frequency of intratumoral invariant natural killer T-cells (iNKTs) correlates positively with survival in NB

patients. iNKTs kill immunosuppressive tumor associated macrophages and myeloid derived suppressor cells, recruit and activate immune effectors such as T and NK cells, and secrete pro-inflammatory cytokines to remodel the tumor microenvironment (TME). However, sustained activation of iNKTs in the TME remains difficult to induce due to the development of anergy (diminished responsiveness to stimulation). iNKTs are activated by glycolipid antigens (GAg) presented by a MHC-1-like protein called CD1d. Phenylated GAg have previously been shown to promote sustained activation of iNKT cells, as has incorporation of GAg into a soluble form of CD1d. Therefore, proteins that can target the the NB-associated antigen GD2, and also activate iNKTs with phenylated GAg-loaded CD1d hold potential for the induction of sustained iNKT-mediated, NB-specific cytotoxicity.

### **Objectives:**

Our objectives are to demonstrate the effects of phenylated and non-phenylated GAg exposure on iNKTs, prove the capacity for novel CD1d-anti-GD2 single chain variable fragment (scFv) fusion proteins to promote iNKT-mediated NB-specific cytotoxicity, and explore the effects of varying GD2 binding affinity on iNKT-mediated cytotoxicity.

### **Design/Method:**

We compare iNKT cytokine release following exposure to the GAg alpha-GalactosylCeramide (aGC) and the phenylated C34 in chronic (days 1, 3, and 7) vs acute (day 7 only) stimulation experiments. Briefly, C57Bl/6 mice were injected i.p. with indicated GAg. 4 hours following the last injection, hepatic iNKTs were isolated and intracellular interferon-gamma expression was measured by flow cytometry. CD1d-anti-GD2-scFv recombinant DNA was generated using cloning methods and then used to produce 3 novel CD1d-anti-GD2-scFv fusion proteins of varying GD2 affinities. Chromium release killing assays were used to study the NB-specific, iNKT-mediated lysis induced by these fusion proteins.

### **Results:**

Unlike aGC, C34 promotes a robust response of iNKT interferon-gamma release in the acute and the chronic setting without inducing significant anergy. Killing assays using anti-GD2-CD1d proteins demonstrate specific iNKT-mediated cytotoxicity of high-GD2-expressing NB cell lines, but not low-GD2-expressing NB cell lines.

### **Conclusion:**

C34 induces iNKT stimulation to the same extent as aGC, without inducing anergy. Further, novel fusion proteins between CD1d and anti-GD2 scFvs can be used to induce cytotoxicity of neuroblastoma cells. These results hold promise for the therapeutic potential of off-the-shelf fusion proteins to activate iNKTs for NB treatment.

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Poster # 510

## **A SUBSET OF HIGH-RISK NEUROBLASTOMA DISPLAYS REDUCED SENSITIVITY TO MEVALONATE PATHWAY INHIBITION**

**Michelle Green, Raymond Hohl, Jeffrey Neighbors**

**Background:**

Neuroblastoma (NB) is one of the deadliest childhood cancers, involving tumors arising from neural crest cells. At diagnosis over 50% of patients present with high-risk (HR) disease that has very poor prognosis and five-year survival rates of only 40%. Despite intensive treatment regimens for patients with HR NB approximately 15% will not respond and about 50% will relapse. Thus, this subset of patients, termed ultra-high-risk (UHR), are in desperate need of novel therapeutics. The mevalonate (MVA) pathway is a potential therapeutic target for UHR NB as it produces key biomolecules including cholesterol and isoprenoids, which are required for cancer cell growth and proliferation.

**Objectives:**

The goal of this study is to test the potential therapeutic benefit of MVA pathway inhibition with statins, bisphosphonate, and isoprenoid transferase inhibitors in UHR NB models.

**Design/Method:**

In vitro assays were done with cell lines that have ultra-high-risk NB characteristics, SK-N-AS and SK-N-BE(2)-C, and the high-risk SH-SY5Y cell line. The effect of MVA inhibitor treatment on NB cell viability was analyzed by MTT assays and subsequent crystal violet staining, which measure metabolic activity and membrane staining respectively. Treatment induced apoptosis and differentiation was analyzed by microscopy, western blot, and flow cytometry. Neurosphere formation assays are ongoing to investigate the MVA inhibitor effect on differentiation.

**Results:**

We found that UHR NB cell lines appear less sensitive to treatment with statins than the HR cell line in MTT assays and crystal violet staining. We also found that the UHR cell lines appear to have a slight increase in metabolic activity and crystal violet staining with bisphosphonate treatment. Morphological changes including cell body rounding and neurite outgrowths, are seen in the HR cell line with 24- and 48-hour statin treatments. The SK-N-AS UHR cell line displays some cell body rounding and neurite outgrowths with 24-hour statin treatment, however these are not seen with 48-hour treatment.

**Conclusion:**

Inhibition of the MVA pathway does not appear to be a viable therapeutic option for UHR NB. This is evident by the observed increase in cell viability with some inhibitor treatments and the lack of persistent morphological changes or protein expression consistent with differentiation. The concentration of statins required to reduce cell viability in vitro is also significantly higher than achievable serum levels in patients. These findings also suggest that there are unique signaling pathway(s) that enable ultra-high-risk NB survival with MVA pathway inhibition that are not active in high-risk NB.



# JUST BECAUSE YOU CAN DOES NOT MEAN YOU DO: TREATING INTERMEDIATE-RISK NEUROBLASTOMA WITHOUT SURGERY

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## **Background:**

Neuroblastoma is the most common extracranial solid tumor in children. It has a wide spectrum of clinical behavior and treatment approaches vary from observation alone to a combination of surgery, chemotherapy, radiotherapy, autologous stem cell transplant, and immunotherapy. The presence of image-defined risk factors in neuroblastoma is associated with an increase in surgical complications. The overall surgical goal in intermediate-risk patients with neuroblastoma is to achieve the most complete tumor resection consistent with preservation of full organ and neurologic function. However, this may necessitate leaving residual disease adherent to these anatomical structures.

## **Objectives:**

Describe clinical findings, treatments and outcomes of pediatric patients diagnosed at NCH from 03/2014-12/2019 with neuroblastoma INRG stages L2 or greater who were treated with chemotherapy alone.

## **Design/Method:**

A retrospective analysis of patients diagnosed at NCH from 03/2014-12/2019 with neuroblastoma INRG stages L2 or greater treated with chemotherapy alone due to large masses, deemed resectable but with increased morbidity, was conducted to describe outcomes.

## **Results:**

Six were identified on the retrospective analysis of patients diagnosed at NCH from 03/2014-12/2019 with neuroblastoma INRG stages L2 or greater treated with chemotherapy alone. Mean age at diagnosis was 5.6 months (0.5-12 months). At diagnosis, four patients were INRG stage L2, one stage MS and one stage M. Five patients had favorable histology and one had unfavorable histology (stage MS). No patients had MYCN amplification. Two patients had diploidy, one near-diploidy and two had hyperdiploidy. All patients were treated per protocol ANBL0531. Number of treatment cycles varied from 2-7 cycles per patient, with a mean of 4.3 cycles per patient. Surveillance modalities off-treatment included physical exam, imaging studies, and urine catecholamines. Mean event-free survival (EFS) after first-line treatment was 32 months (7-79 months). Overall survival was 100%. Two patients had complete resolution of the mass, three had reduction in size and stabilization of the residual mass and one had progression of disease 7 months after 2 cycles requiring 5 additional cycles with reduction and stabilization of disease (subsequent EFS 26 months). None of the patients had surgical excision of the residual mass.

## **Conclusion:**

Our small cohort shows that patients with intermediate-risk neuroblastoma with resectable

masses but with high associated morbidity can be successfully treated with chemotherapy alone. This questions the role of surgery in the treatment of intermediate-risk neuroblastoma of any size. We propose a prospective study to confirm these results and potentially change management guidelines.

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Poster # 512

## **TOXICITY OUTCOMES IN ADVANCED RETINOBLASTOMA: PILOT STUDY FOR UPCOMING CENTRAL AMERICAN PROTOCOL**

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### **Background:**

Retinoblastoma is highly curable, with event-free survival (EFS) of >95% in high-income countries. This success is not maintained in lower-income countries, with EFS of 30-60% due to advanced disease and lack of resources.

The Central American Association of Pediatric Hematology Oncology (AHOPCA) standardized treatment of unilateral advanced retinoblastoma with vincristine, etoposide and carboplatin (CEV) in the AHOPCA Rb I trial. However, poor overall survival was seen in patients with buphthalmia (enlarged painful eyes). AHOPCA Rb II improved outcomes of patients with buphthalmia, from 30% to 68% EFS, by adding neoadjuvant CEV prior to enucleation and completing 6 cycles of chemotherapy. Intensifying therapy by adding vincristine, doxorubicin and cyclophosphamide (VDC), an active regimen against retinoblastoma, may improve outcomes further.

### **Objectives:**

To determine safety and feasibility of alternating chemotherapy of CEV with VDC in advanced retinoblastoma.

### **Design/Method:**

Medical records of 21 patients with newly diagnosed advanced retinoblastoma (International Retinoblastoma Staging System Stage II or greater) were reviewed from February 2016 to March 2019 at the Unidad Nacional de Oncología (UNOP), a single, public pediatric cancer center in Guatemala. Patients were non-randomly assigned to receive either CEV alone (10) versus CEV alternating with VDC (11). 6 cycles were given, unless there was evidence of progressive disease (median cycles 6, range 1-13). Dosing was vincristine 1.5mg/m<sup>2</sup> Day 1, etoposide 100mg/m<sup>2</sup> Days 1-3, carboplatin 500mg/m<sup>2</sup> Day 1 in CEV alone, and vincristine 1.5mg/m<sup>2</sup> Day 1, doxorubicin 20mg/m<sup>2</sup> Days 1-2 and cyclophosphamide 1.2gm/m<sup>2</sup> Day 1 in CEV alternating with VDC. Toxicities were graded according to the CTCAE v4.0.

### **Results:**

Grade  $\geq 3$  neutropenia was observed in 91% of patients receiving CEV + VDC (0.39 events/patient/cycle) compared with 80% receiving CEV alone (0.37 events/patient/cycle).

Febrile neutropenia occurred in 18% receiving CEV + VDC (0.05 events/patient/cycle) compared with 40% receiving CEV alone (0.06 events/patient/cycle). Grade  $\geq 3$  anemia was observed in 18% with CEV + VDC (0.03 events/patient/cycle) vs 20% (0.08 events/patient/cycle). Grade  $\geq 4$  thrombocytopenia was observed in 0% receiving CEV + VDC vs 30% (0.14 events/patient/cycle). Overall Survival was 72.7% in CEV + VDC (median follow-up 287 days) vs 60% in CEV alone (median follow-up 599 days). There were no toxic deaths.

**Conclusion:**

CEV + VDC was found to be safe and feasible. Toxicity was acceptable with combination therapy and there were no deaths attributed to medication toxicity. Although overall survival was not a primary endpoint, preliminary data supports further investigation of CEV + VDC for advanced retinoblastoma in Central America.

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Poster # 513

**SUCCESSFUL TREATMENT OF SERTOLI-LEYDIG CELL TUMORS WITH RHABDOMYOSARCOMATOUS HETEROLOGOUS ELEMENTS**

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**Background:**

Ovarian malignancies comprise approximately 1% of all childhood cancers. Ovarian sex cord-stromal tumors (SCST) constitute approximately 10% of all ovarian tumors in pediatric patients. Sertoli-Leydig cell tumors (SLCTs) are a type of SCST and account for less than 0.5% of all primary ovarian cancers. Heterologous elements are reported to be present in 20% of SLCTs, and more common in moderately and poorly differentiated tumors. Malignant heterologous elements are usually present in more aggressive tumors and are associated with a worse prognosis. Heterologous elements are comprised of various tissue types including muscle and bone. SLCTs with heterologous rhabdomyosarcomatous elements have been described in pediatric and adult patients but there is no standardized treatment for these patients

**Objectives:**

To describe the successful use of surgical resection and adjuvant chemotherapy for pediatric patients with ovarian SLCT with rhabdomyosarcomatous heterologous elements.

**Design/Method:**

We performed a single institution retrospective case series. Potential cases were identified by searching the EPIC electronic medical record for patients diagnosed with ovarian SLCT with rhabdomyosarcomatous heterologous elements.

**Results:**

We identified four female patients who were diagnosed with ovarian SLCT with rhabdomyosarcomatous heterologous elements. Mean age at time of diagnosis was 15.3 years

(range 14.5-16.5 years). Mean length of time from symptom presentation to SLCT diagnosis was 1.4 months (Range 0.5-3 months). The most common presenting symptom was abdominal pain and/or abdominal distension. Only one patient had an elevated alpha-fetoprotein (AFP) at time of diagnosis. Three of the patients were FIGO stage IC at diagnosis with the fourth patient being stage IA at diagnosis. All four tumors pathologically showed intermediate to poorly differentiated SLCT with rhabdomyosarcomatous heterologous elements. No patients had metastatic disease at diagnosis. All four patients received 8 alternating cycles of VIP-VAC (Ifosfamide/Etoposide/Cisplatin and Vincristine/Dactinomycin/Cyclophosphamide). Two patients had DICER1 mutations identified within the tumor itself and were germline negative. One of these patients had a heterozygous germline mutation (c.3007C>T, p.Arg1003\*) identified in one gene. All four patients are more than 1 year off therapy with no evidence of recurrence.

**Conclusion:**

At a single institution we have shown the effective treatment of four patients with the rare diagnosis of ovarian SLCT with heterologous rhabdomyosarcomatous elements. Larger studies are needed to better characterize and standardize treatment for this rare diagnosis.

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Poster # 514

**TARGETING CYCLIN DEPENDENT KINASE 8 IN FUSION POSITIVE  
RHABDOMYOSARCOMA**

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**Background:**

Rhabdomyosarcoma (RMS) is a cancer of skeletal muscle histogenesis and the most common soft tissue sarcoma of childhood. Patients with RMS tumors classified as fusion-positive express PAX3/7-FOXO1 fusion proteins, which are mutant transcription factors that illegitimately reactivate myogenic developmental programs. Survival for the PAX3-FOXO1-positive group of patients is less than 30% for all-comers, and less than 10% when metastatic, due in part to a lack of effective therapeutics. CDK8 is a critical component of the Mediator complex, a large protein assembly that enables physical looping of enhancer regions with transcriptional start sites, and its inhibition is currently being evaluated in adult cancer trials. Our preliminary proteomics data suggests that CDK8 interacts with PAX3-FOXO1, and recent genomic studies nominate CDK8 as an RMS cell-line dependency. We hypothesize that CDK8 is a vulnerability and novel therapeutic target for fusion-positive RMS.

**Objectives:**

Our goals are to understand how CDK8 contributes to RMS tumorigenesis, investigate the value of CDK8 as a therapeutic target in vitro, and assess the pre-clinical efficacy of CDK8 loss of function (LOF) or inhibition (CDK8i) in vivo.

**Design/Method:**

To understand how CDK8 contributes to RMS tumorigenesis, we will assess the impact of CDK8 LOF (via RNAi or CRISPR) on fusion-positive RMS cellular phenotypes including proliferation, apoptosis, differentiation, and stemness. We will use reporter assays to investigate the loss of PAX3-FOXO1 transcriptional power, and use immunoprecipitation/ mutagenesis to define the protein-protein interactions between CDK8 and PAX3-FOXO1. To investigate the value of CDK8 as a therapeutic target in vitro, we will examine CDK8 expression in human RMS tissue microarrays via immunohistochemistry, and perform in vitro drug studies of CDK8i using CDK8 small molecule inhibitors senexin A, cortistatin A, and SEL120-34A. To assess the pre-clinical efficacy of CDK8 LOF in vivo, we will test the impact of genetic (dox-inducible RNAi) or pharmacologic CDK8i in fusion-positive RMS xenografts in immunodeficient mice. Resulting tumors will be analyzed for target validation and mechanisms of tumor inhibition.

**Results:**

Thus far, we have found that genetic inhibition of CDK8 via RNAi inhibits growth of human fusion-positive RMS cells in vitro, in part through induction of myogenic differentiation. Pharmacologic inhibition of CDK8 via senexin A induces cytotoxicity with an IC50 of 286 nM. Biochemical and in vivo studies are planned.

**Conclusion:**

This work provides evidence for targeting CDK8 in fusion-positive RMS.

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Poster # 515

**UNIFORM TIM 3 & GALECTIN 9 POSITIVITY ON IHC STAINING OF TUMOR SAMPLES AT DIAGNOSIS IN EWING SARCOMA**

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**Background:**

Immune checkpoint blockade has gained substantial interest in the past decade. Adult studies have shown that the location, density, and cell type that express negative checkpoint receptors (NCRs) such as PD-1, TIM-3, LAG-3 and their respective ligands PD-L1, Galectin-9, MHC class II vary between and within tumor types. However, our understanding of the onco-immunologic landscape in pediatric solid tumors remains limited, with studies to date mainly focusing on the expression of PD-1 and PD-L1 within the center of tumors and results have been mixed. Furthermore, LAG-3 and TIM-3 have shown great promise in adult cancer therapy, but availability of such clinical trials have not progressed to pediatric patients as the preclinical data of NCR expression in pediatric tumors is not well characterized.

**Objectives:**

To better understand the onco-immunologic landscape of pediatric solid tumors and its effects on peripheral blood T cells.

**Design/Method:**

We performed immunohistochemistry staining for PD-1/PD-L1, TIM-3/Galectin-9, LAG-3/MHC class II on 26 diagnostic tumor samples from pediatric patients with non Hodgkin lymphoma (NHL), Ewing sarcoma, and osteosarcoma.

**Results:**

As with adult tumors, both NCR and ligand expression varied significantly between and within tumor types. One notable finding was uniform positivity of TIM-3 and Galectin-9 on tumor infiltrating lymphocytes (TILs) in Ewing sarcoma specimens. Comparison of NCR/ligand expression of TILs versus peripheral blood T cells showed no correlation within individual patients. Of note, a higher percentage of peripheral T cells from NHL patients showed expression of all three NCRs (8.6%) compared to Ewing sarcoma (1.6%) and osteosarcoma (0.38%) patients, suggesting a higher degree of T cell exhaustion.

**Conclusion:**

In this data set, peripheral blood T cells did not reflect the tumor environment at diagnosis limiting this parameter's prognostic value. Our translational data suggest further investigation of TIM-3 and Galectin-9 for checkpoint blockade in future pediatric solid tumor clinical trials.

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Poster # 516

**THE ROLE OF LONG NON-CODING RNA ANRIL IN CHEMOSENSITIVITY IN OSTEOSARCOMA**

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**Background:**

Osteosarcoma is a skeletal malignancy affecting children, adolescents, and young adults. Chemotherapy and resection is the mainstay of therapy with a three-drug regimen - cisplatin, doxorubicin, and methotrexate - forming the backbone of therapy. However, osteosarcoma prognosis remains poor with a 5-year survival rate around 70%, mainly due to chemo-resistance and/or metastases. It is critical to improve our understanding of chemo-resistance in order to improve osteosarcoma therapeutic outcomes. Emerging evidence has shown that long non-coding RNAs (lncRNAs) are implicated in cancer metastasis and drug sensitivity. Our lab has recently systematically surveyed the role of lncRNAs in drug sensitivity for over 700 drugs using existing high throughput in vitro drug screening datasets. We identified strong significant association between cellular sensitivity to cisplatin and doxorubicin and expression of lncRNA ANRIL in a collection of osteosarcoma cell lines.

**Objectives:**

To evaluate cisplatin and doxorubicin drug sensitivity after ANRIL siRNA knockdown in SAOS2 cells.

**Design/Method:**

SiRNA knockdown experiments were carried out in an osteosarcoma cell line, SAOS2. Cells

were exposed to multiple concentrations of cisplatin or doxorubicin. Cellular sensitivity to these two drugs was quantified after siRNA experiment with siRNA targeting ANRIL and scramble control at 24, 48 and 72h. Each experimental condition was performed in triplicate and expressed as an average +/- SD. Significant differences between groups were estimated using a Student's t-test. A P value <0.05 was considered statistically significant.

### **Results:**

We successfully knocked down ANRIL expression in SAOS2 cells with knockdown efficiency of 88.5% at 24h. For cisplatin dose 7uM, a significant decreased rate of proliferation was detected after 72h in knockdown cells (16.5% +/- 4.1) compared to scramble control (26.4% +/- 0.8). The cisplatin IC50 was decreased in the siRNA knockdown condition as compared to scramble control at 72h (p=0.0214). For doxorubicin, the IC50 was also significantly decreased in the siRNA knockdown condition as compared to scramble control (p=0.0021 and 0.0068 at 24h and 72h, respectively).

### **Conclusion:**

Reducing ANRIL expression led to increased cellular sensitivity to cisplatin and doxorubicin, two key treatment agents for osteosarcoma. These findings may lend credence to ANRIL serving as a novel biomarker of cisplatin and doxorubicin sensitivity in osteosarcoma.

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Poster # 517

## **DISRUPTION OF DNA DAMAGE REPAIR ENHANCES EXPRESSION OF IMMUNE CHECKPOINT PROTEINS IN EWING SARCOMA**

**Lisa Maurer, Rose Venier, Elina Mukherjee, Claire Julian, Haley Raphael, Linda McAllister-Lucas, Kelly Bailey**

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### **Background:**

Ewing sarcoma is a fusion oncoprotein (EWS-FLI1)-driven bone tumor which predominately affects adolescents. Relapsed Ewing sarcoma is nearly uniformly fatal and new treatments are needed. Recent studies revealed that Ewing tumors demonstrate inherent dysfunction in DNA damage repair and sensitivity to agents that inhibit DNA repair such as poly (ADP-ribose) polymerase (PARP) inhibitors. Moreover, a subset of patients with Ewing sarcoma have additional defects in DNA damage repair due to germline mutation in DNA repair pathway genes. Defective DNA damage repair can result in altered tumor immunity in some cancers. For example, the immune checkpoint protein programmed death ligand-1 (PD-L1) can be upregulated in tumor cells as a result of DNA damage. PD-L1 suppresses the immune system's ability to kill tumor cells. Checkpoint inhibitors are a class of immunotherapy drugs that counteract this immune suppressive effect. We sought to determine the impact of PARP-inhibition on Ewing tumor cell checkpoint protein expression and to evaluate the effectiveness of combination treatment with PARP and checkpoint inhibitors for relapsed Ewing sarcoma.

### **Objectives:**

We hypothesize that because Ewing tumor cells demonstrate inherent defects in DNA damage repair, these cells will upregulate PD-L1 following PARP inhibitor treatment. Further, we predict that upregulation of PD-L1 following DNA damage will be augmented in Ewing tumors harboring germline mutations in DNA damage repair genes such as BARD1 (BRCA1-associated RING domain-1).

**Design/Method:**

Patient-derived tumor cells were isolated from a metastatic lung lesion to establish the PSaRC318 Ewing tumor cell line, which harbors a germline BARD1 mutation. Sensitivity to the PARP inhibitor, talazoparib, was determined using live-cell IncuCyte assays. The impact of PARP inhibition and BARD1 knockdown on expression of immune checkpoint pathway proteins was tested via RT-PCR, Western blot, and flow cytometry. Apoptosis assays measuring T-cell anti-tumor cell activity were also performed.

**Results:**

We found that PD-L1 expression is upregulated following treatment of Ewing sarcoma cells with PARP-inhibitors. Reduction in Ewing tumor cell BARD1 level further augments sensitivity to PARP inhibitors and results in enhanced PD-L1 expression. Tumor cells pretreated with talazoparib are rendered more sensitive to T-cell mediated apoptosis when in the presence of checkpoint inhibition.

**Conclusion:**

This preclinical data demonstrates the proof-of-concept that DNA damaging agents can be used to drive PD-L1 expression in Ewing sarcoma and suggest a potential role for novel combination therapeutic regimens that include checkpoint inhibitors.

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Poster # 518

**PEDIATRIC RHABDOMYOSARCOMA INCIDENCE AND SURVIVAL - UNITED STATES, 2003-2016**

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**Background:**

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and adolescents, with approximately 400 cases diagnosed annually in the US. Survival depends on clinical factors including age, anatomic site, histology, tumor size, and cancer stage. Recent published studies investigating RMS incidence and outcomes have largely included patients diagnosed before 2009 or covered <30% of the US population.

**Objectives:**

The objective of this study is to report pediatric (age <20 years) RMS incidence using data from US Cancer Statistics (USCS) and survival from the National Program of Cancer Registries (NPCR), which cover 100% and 93% of the US population, respectively.



**Design/Method:**

Incidence and survival of malignant RMS in pediatric patients were assessed for patients diagnosed during 2003-2016 and 2003-2015, respectively. Age-adjusted incidence rates and corresponding 95% confidence intervals (CI), incidence rate ratios, average annual percent change (AAPC), and 5-year relative survival (RS) percentages were calculated. Incidence and 5-year RS were stratified by sex, age at diagnosis, race/ethnicity, geographic region, county-based economic status, stage, histology, and anatomic site.

**Results:**

We identified 5,266 primary RMS cases in USCS during 2003-2016. The age-adjusted incidence rate was 4.57 per 1 million (95% CI: 4.45 - 4.69) and the male:female incidence rate ratio was 1.27 (95% CI: 1.20 - 1.34). Embryonal and alveolar were the most common histologies, which accounted for 50% (2,651/5,266) and 31% (1,656/5,266) of total cases, respectively. For RMS overall, AAPC was 0.2% (95% CI: -0.9 - 1.2) and the AAPCs for embryonal and alveolar tumors were 0.6% (95% CI: -0.6 - 1.8%) and -0.8% (95% CI: -2.6 - 0.9%), respectively. Among 4,525 cases identified in the NPCR survival database, 5-year RS for all patients was 67.7% (95% CI: 66.1 - 69.1%), including 70.1% (95% CI: 68.1 - 72.0%) for males and 64.5% (95% CI: 62.0 - 66.7%) for females. RS was lowest (by non-overlapping 95% CI) for patients with age >10 years, regional or distant stage, alveolar tumors, and established unfavorable RMS anatomic sites. RS did not vary by race/ethnicity, geographic region, or economic status when comparing 95% CI.

**Conclusion:**

The incidence of RMS was stable during the study period. Notably, the male:female rate ratio was found to be lower than previously reported. Overall, there is room for improvement for survival, and there were survival differences based on demographic and clinical characteristics. This information can be leveraged to better understand RMS susceptibility and inform novel risk stratification strategies that could inform treatment planning.

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Poster # 519

**BMI1 IS A THERAPEUTIC TARGET IN RHABDOMYOSARCOMA**

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**Background:**

Rhabdomyosarcoma (RMS) is an aggressive soft tissue sarcoma which affects mainly children. There are two subtypes: fusion-positive (FP-RMS) and fusion-negative (FN-RMS). FP-RMS is characterized by PAX-FOXO1 fusion proteins and has a worse overall outcome. There is an urgent need to identify targets for this aggressive cancer. The epigenetic complexes PRC1 and PRC2 are overexpressed in a variety of sarcomas and are associated with poor survival. We discovered that BMI1, a protein member of PRC1, is overexpressed in FP-RMS cells. BMI1 is a

known oncogene in other cancers, but its role in FP-RMS has not been interrogated; thus, we aim to study it within this context.

**Objectives:**

To evaluate if BMI1 is a targetable protein in FP-RMS and how loss of BMI1 influences these tumors.

**Design/Method:**

To analyze the function of BMI1 in FP-RMS, we depleted BMI1 in FP-RMS cell line models by both shRNA/siRNA knockdown and measured expression, cell proliferation and apoptosis. We then utilized two small molecule inhibitors, PTC-209 and PTC-028, to obtain IC50s in these cell lines and determined effects on cell proliferation and apoptosis in vitro and in vivo. We assessed the effects of BMI1 loss on candidate oncogenic signaling networks.

**Results:**

Initially we examined RNA-seq tumor datasets and determined that BMI1 is robustly expressed in FP-RMS tumors. We confirmed that BMI1 is also overexpressed in FP-RMS cell lines at the levels of RNA and protein. We depleted BMI1 using multiple shRNAs and siRNAs and found that this led to striking decreases in cell growth and an increase in apoptosis. Pharmacologic inhibitors PTC-209 and PTC-028 mediated similar phenotypes. As PTC-028 is more effective in vitro, we used this drug in vivo by utilizing a subcutaneous xenograft model of FP-RMS. We observed a decrease in tumor burden and an increase in progression-free survival in mice treated with PTC-028. We further investigated the molecular impact of BMI1 loss and found that BMI1 inhibits the Hippo pathway.

**Conclusion:**

BMI1 supports proliferation and survival in in vitro and in vivo models of FP-RMS. Inhibition of BMI1 decreases cell proliferation, increases apoptosis, and additionally promotes activation of the tumor suppressive Hippo pathway. Currently, we are further investigating the molecular mechanisms by which BMI1 promotes FP-RMS aggression. Targeting BMI1 pharmacologically may provide a novel treatment option for patients with FP-RMS and potentially other sarcomas.

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Poster # 520

**OSTEOSARCOMA EXHIBITS PATTERN OF PROTEOMIC ALTERATIONS IN RESPONSE TO HER2-SPECIFIC CAR T CELLS**

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**Background:**

Immunotherapy using chimeric antigen receptor (CAR) modified T cells has the potential to improve outcome for children with recurrent or metastatic osteosarcoma. In a phase I trial,

autologous HER2-targeted CAR T cells were safe with indicators of clinical benefit in a subset of pediatric patients with advanced HER2-positive sarcomas. Nevertheless, extending the overall antitumor efficacy of CAR T cells to a substantial proportion of patients requires a deeper insight into the tumor intrinsic response and potential resistance mechanisms to targeted cellular therapy.

**Objectives:**

Systematically investigate recurrent tumor adaptations to CAR T cell therapy and identify alternate surface receptors and upregulated oncogenic pathways for strategic co-targeting in osteosarcoma.

**Design/Method:**

Osteosarcoma cells with variable surface expression of HER2 (U2OS, 143B, LM7 and two patient-derived lines) were treated with HER2-specific CAR T cells in vitro. Surviving osteosarcoma cells were isolated and collected at 72 hours and analyzed for changes in surface expression for a panel of oncogenic receptors and immune ligands using flow cytometry. Using the same in vitro co-culture assay, a comprehensive assessment of the expression and activation dynamics of cell growth and survival pathways was performed using reverse phase protein arrays (RPPA).

**Results:**

In response to CAR T-cell treatment, decrease in the HER2 surface expression was observed in four of five osteosarcoma cell lines evaluated. In contrast, cell surface expression of the immunomodulatory ligand PD-L1 and the growth receptor tyrosine kinase c-MET increased across all cell lines post-treatment. There was no significant change in the expression of other analyzed surface receptors, including EGFR and IGF-1R. RPPA analysis revealed distinct differences in protein expression between osteosarcoma cell lines treated with HER2-specific CAR T cells in comparison to those treated with non-transduced T cells, though there was variation seen across different cell lines (143B, U2OS, LM7). Notably, there was a consistent upregulation of STAT1, Caspase-7, Caspase-3, and KLF4, demonstrating interferon- $\gamma$  mediated signaling, apoptosis pathway activation, and cell cycle arrest. Interestingly, there was a decrease in the expression of several RAS/MAPK and PI3K/AKT pathway intermediates across all cell lines.

**Conclusion:**

Osteosarcoma cells exhibit distinct and reproducible patterns of altered protein expression in response to HER2-directed CAR T-cell therapy warranting further assessment of signaling pathway dynamics and surface expression of targetable receptors using mouse models of human osteosarcoma. Our results thus far argue for a rational platform for developing strategic combinatorial approaches to augment antitumor responses using small molecules or further T-cell modifications.

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Poster # 521

**EARLY DISCHARGE IN OSTEOSARCOMA PATIENTS RECIEVING METHOTREXATE**

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**Background:**

Eight to 12 doses of High Dose Methotrexate (HD-MTX) (12g/m<sup>2</sup>, max 20g) with Leukovorin rescue and doxorubicin/cis-platinum has been the standard of care for osteosarcoma (OST) for 30 years. Standard protocols recommend in-patient post-MTX monitoring until serum MTX levels are < 0.10 umol/L, despite no evidence for this practice. We retrospectively studied all OST at our institution over the last 11 years to determine if there was evidence of increased short or long term toxicity associated with "early discharge," (MTX > 0.10umol/L) compared to "standard discharge." Early MTX discharge has not been previously studied.

**Objectives:**

Our objective was to study the acute and chronic side effects associated with discharging OST patients with serum MTX levels between 0.11-0.15 compared with MTX < 0.1umol/L.

**Design/Method:**

We retrospectively collected data on all newly diagnosed OST patients, less than 50, treated at Rush University Hospital from 2009–2019 who received at least 2 MTX treatments. Early Discharge (ED) was defined as discharge with MTX levels 0.11-0.15umol/L. We collected clinical (neuropathy, mucositis, SIADH, emesis, rashes, infection, diarrhea, jaundice, renal injury and treatment delays) and laboratory evidence (ALT, creatinine (CR), total bilirubin (TB), cytopenias) of MTX toxicity both acutely and one year after completion of therapy. 1 and 2 way ANOVAs, chi square, and linear regressions were run using RStudio.

**Results:**

Over 11 years, there were 30 patients (mean age = 20, range 6-49, 12F,18M) with 286 MTX admissions. Ninety-four (33%) were categorized EDs. Most patients (25/30 = 84%) had at least one ED. Patients who had no EDs, had 1-6 EDs, or 7-12 EDs, had similar post discharge complications and treatment delays and long term (before v. after protocol) changes in Cr, ALT, and TB [table1; graph1,graph3]]. There was no long term additive effect associated with total EDs on Cr [graph2]. Those admissions that had recorded MTX levels between 0.15-0.11umol/L but were held in hospital until their MTX < 0.10, averaged additional 16 hours (range 3-85; SD = 11.5)

**Conclusion:**

Our retrospective, single institution study of 30 patients over 11 years and 286 MTX admissions, did not show any increase in acute post discharge side effect or long term objective toxicities for "early discharge" patients, with fewer hospital days, suggesting a higher serum MTX level for discharge may be safe, even beneficial, for OST patients less than 50. Prospective multiinstitutional studies are needed to confirm this preliminary finding.

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## IMPAIRMENT OF HIPPO SIGNALING IN OSTEOSARCOMA WITH DGBP

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### **Background:**

Osteosarcoma is the most prevalent form of bone cancer diagnosed in children. It is characterized by the presence of osteoid, unmineralized, immature bone matrix. The five-year survival rate is nearly 70 percent, however if there is metastasis present the survival rates plummet. Several signaling pathways are disrupted in osteosarcoma, such as the Hippo pathway, which promotes cell proliferation, invasion, and tumor progression. Recent studies have shown a link between the Hippo pathway and the mevalonate (cholesterol synthesis) pathway. Rho GTPases can regulate the activity of the Hippo pathway by decreasing the signaling through the terminal transcription factors, YAP and TAZ. Small GTPases, such as Rho, are altered by post-translational modification via prenylation with the mevalonate pathway intermediates geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP). Prenylation is required for proper function of the signaling systems. Digeranyl bisphosphonate (DGBP) reduces levels of GGPP by inhibiting geranylgeranyl diphosphate synthase (GGDPS1) and thus reduces the prenylation equivalents and eventually signaling through the small GTPases.

### **Objectives:**

To examine the effects of DGBP induced inhibition on viability, protein prenylation, and YAP/TAZ signaling in human osteosarcoma cell lines MG63 and U2OS.

### **Design/Method:**

MTT assay were used to determine if GGDPS inhibitor compounds had any cytotoxic effects to the cell lines. We then performed invasion assays with matrigel to determine if these compounds could impact invasive phenotypes. Protein levels of YAP/TAZ and other components of the Hippo pathway were analyzed using western analysis. Localization of TAZ was analyzed by immunofluorescence microscopy.

### **Results:**

We demonstrate that DGBP does not affect cell viability, but reduces invasion in osteosarcoma cell lines. DGBP also reduces TAZ protein levels and transcriptional activity. With treatment of DGBP protein levels of TAZ decrease, but when pre-treated with a proteasome inhibitor MG-132, the levels were increased indicating that TAZ is degraded by the proteasome and that this may be enhanced by DGBP treatment. Localization of TAZ was unaffected by treatment of DGBP.

### **Conclusion:**

Inhibition of geranylgeranylation with DGBP negatively impacts YAP/TAZ signaling and the invasive activity in osteosarcoma cell lines.

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## **YAP1 AND WWTR1 REGULATE PAX3-FOXO1 TRANSCRIPTIONAL PROGRAMMING IN FUSION-POSITIVE RHABDOMYOSARCOMA**

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### **Background:**

Rhabdomyosarcoma is the most common soft tissue sarcoma of children and young adults and is comprised of two molecular subtypes. While tumors not harboring PAX-FOXO1 fusion oncoproteins are associated with favorable outcomes, survival rates for patients with Fusion-Positive Rhabdomyosarcoma (FP-RMS) remain dismal (5-yr O.S.<50%). Although more than 20-years have passed since the discovery that FP-RMS is driven by PAX3-FOXO1 (P3F), which is an inherently disordered transcription factor with no viable drug binding sites, therapeutically tractable components of the P3F tumorigenic program have yet to be uncovered. YAP1 and WWTR1 (TAZ), transcriptional co-activators of the Hippo pathway, are potent oncogenes known to mediate transcriptional addiction in malignancy.

### **Objectives:**

To identify vulnerabilities within the P3F tumorigenic program, our objectives are to investigate mechanisms by which transcriptional co-activators YAP1/TAZ (1) contribute to FP-RMS sarcomagenesis, (2) functionally interact with P3F, and (3) modulate P3F-mediated transcriptional activity.

### **Design/Method:**

Immunohistochemical (IHC) staining of human tissue microarrays were used to identify the relative abundance of YAP1 and TAZ in FP-RMS tumor samples. Functional interactions of YAP1/TAZ and P3F were investigated using P3F reporters, immunoblots, and co-immunoprecipitation (co-IP); while co-IP-coupled mass spectrometry (IP-MS) was used to identify the YAP1/TAZ/P3F interactome. Experiments utilized gain- and loss-of-function vectors expressing control, wild-type YAP1/TAZ, constitutively active YAP1/TAZ (S89A/S127A), and shRNA or CRISPR/Cas9 knockdown. To identify P3F-mediated genes and pathways that are YAP1/TAZ-dependent, we used RNA-Seq and quantitative proteomics via tandem mass tag labeling.

### **Results:**

We demonstrate via IHC that YAP1/TAZ are highly abundant in FP-RMS, and also that YAP1/TAZ regulate many in vitro and in vivo FP-RMS cancer phenotypes. Mechanistically, an interaction between YAP1/TAZ and P3F was demonstrated via co-IPs for endogenous as well as epitope-tagged proteins. This was confirmed with IP-MS, which also revealed that YAP1/TAZ and P3F share an enrichment for co-immunoprecipitated proteins involved in DNA binding and transcriptional regulation. IP-MS also demonstrated that chromatin remodeling complex proteins were enriched with TAZ immunoprecipitation. YAP1/TAZ functionally augment P3F

transcriptional activity in reporter assays as well as expression of candidate P3F target genes. An unbiased approach using RNA-Seq and quantitative proteomics demonstrate that YAP1/TAZ positively regulate differential expression of P3F target genes, as well as proteins involved in cell cycle progression and pan-cancer related proteins that are typically up- or down-regulated in malignancy.

**Conclusion:**

We identify a novel complex between YAP1/TAZ and P3F, show YAP1/TAZ are positive regulators of P3F transcriptional activity, and identify the YAP1/TAZ axis as a vulnerability for P3F-transcriptional reprogramming in FP-RMS.

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Poster # 524

**CREATION OF AN AGGRESSIVE ANGIOSARCOMA ZEBRAFISH MODEL TO IDENTIFY BETTER TREATMENT OPTIONS**

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**Background:**

Angiosarcoma is a clinically aggressive tumor in humans with a high rate of mortality in those affected, especially in the pediatric population. It can arise in vascular or lymphatic tissues involving any part of the body, which creates difficulties with treatment and control of the disease. Unfortunately, there are a lack of treatment options available for these patients due to difficulties with studying angiosarcoma. Historically, cells lines have been difficult to propagate and there are few appropriate in vivo animal models. Due to these limitations, there is reduced ability to study new treatments for angiosarcoma or do large scale drug screens. While originally used in developmental studies, zebrafish models have provided novel insights on tumorigenesis. Recently we generated tp53-null zebrafish and found they spontaneously develop angiosarcomas in addition to other tumors. The angiosarcomas histologically and molecularly resemble the human disease. When using previously published techniques to transplant tumors for propagation, there was a low engraftment rate of angiosarcoma in adult and larval zebrafish.

**Objectives:**

To design a reliable zebrafish angiosarcoma model to screen drugs/compounds that inhibit growth of the tumor.

**Design/Method:**

The spontaneous angiosarcomas that arise in tp53-null CG1 zebrafish are also GFP+ thus enabling in vivo visualization of tumor growth in recipient syngeneic hosts. To resolve previous complications, a new technique for engraftment of the angiosarcoma tumor was developed. A small piece of intact tumor is placed under the skin of adult or larval zebrafish, which results in efficient engraftment of the angiosarcoma tumor. An in vivo drug screen in 6 well plates with

fish bathed in DMSO (control) or active compound was initiated to screen 100 compounds. Rate of growth of the tumor will be measured pre and post drug exposure.

**Results:**

We successfully transplanted angiosarcoma tumors using this novel technique in adult and larval zebrafish. Engraftment rate was approximately >90% within the first 3 days of the tumor transplant. The drug screen is in process using larval zebrafish with engrafted angiosarcoma GFP+ tumor.

**Conclusion:**

In summary, the new transplant technique has overcome previous complications with propagation of the angiosarcoma tumor. Our ongoing study will identify compounds that inhibit growth and metastasis in angiosarcoma. Once hits are identified future studies will focus on molecular mechanisms of action and testing compounds for activity in preclinical murine models.

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Poster # 525

**PEDIATRIC RHABDOMYOSARCOMA OF THE HEAD AND NECK: A NATIONAL CANCER DATABASE ANALYSIS**

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**Background:**

Rhabdomyosarcoma (RMS) is the most common soft tissue head and neck sarcoma in children. Despite treatment advances, there has been minimal improvement in survival. Anatomic limitations often prevent complete surgical resection, and its role in treatment is debated. All treatments, alone or in combination, are associated with potentially significant morbidity. Stringent analysis of survival data is imperative to guide optimal treatment and minimize long-term functional and cosmetic morbidity.

**Objectives:**

To utilize the National Cancer Database (NCDB) to demonstrate trends in treatment and relative survival outcomes dependent on demographics, primary site, histology, and extent of disease for pediatric rhabdomyosarcoma of the head and neck.

**Design/Method:**

The NCDB (2004-2016) was queried for patients ages 0-19 diagnosed with rhabdomyosarcoma of the head and neck. Survival by disease characteristics and treatment was analyzed using log-rank tests, Kaplan Meier, and multivariable Cox-proportional hazards regression.

**Results:**



Among 1,147 patients identified (63.3% age <10 years, 54.3% male), the majority had embryonal (n=625, 54.5%) or alveolar (n=300, 26.2%) histology. 5-year overall survival (OS) was 70.3% with lower mortality risk for embryonal subtype (adjusted HR [aHR] = 0.69, p=0.0038). Most common treatments included chemoradiotherapy (CRT, 48.0%), surgery followed by radiation (SRT, 31.0%), surgery and chemotherapy (SCT, 6.7%), and chemotherapy alone (CT, 6.2%). Patients with embryonal (aHR = 1.04, p = 0.8522) and alveolar (aHR=1.15, p=0.5206) histology had no difference in mortality when comparing CRT vs. SRT. Most patients had non-parameningeal/non-orbital tumors (n=634, 55.3%), followed by parameningeal (n=303, 26.4%) and orbital (n=210, 18.3%). Orbital tumors had best overall survival (5-year OS=92.4%) compared to other sites but mortality increased with CRT (aHR=6.27, p=0.0302) even after adjustment for all other prognostic factors including extent of disease (defined as local, regional, distant). Parameningeal tumors (5-year OS 58.4%) had no survival difference by treatment (aHR = 0.81, p=0.3576). Non-orbital/non-parameningeal tumors (5-year OS 68.5%) demonstrated improved survival with SRT on univariable analysis (p=0.0408), but not on multivariable analysis (aHR=1.16, p=0.4358). A univariable logistic regression model of treatment type by year identified significant trends in treatment approaches. Probability of SC use increased by 13% yearly (p = 0.0010), while utilization of CA, SRT, and CRT did not change significantly.

### **Conclusion:**

In this cohort, the major prognostic factors for best overall survival were embryonal histology, orbital site, local/regional vs distant extension, and use of SRT instead of CRT for orbital subtypes. Larger population studies are needed to demonstrate survival differences between treatment modalities for other sites.

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Poster # 526

## **PRE-CLINICAL HIGH-THROUGHPUT DRUG TESTING USING IMPLANTABLE MICRODEVICES IN EWING'S SARCOMA PDXS**

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### **Background:**

The ability to provide pediatric Ewing sarcoma (ES) patients with effective therapy is critically dependent upon a robust drug discovery pipeline and an efficient method to select promising drug candidates for clinical trial advancement. Optimally, preclinical studies with monolayers, xenografts, or patient-derived tumor explants (PDXs) would accurately predict clinical drug efficacy, and therefore aid in prioritizing which drugs and/or drug combinations should be advanced to early-phase clinical trials. To date, however, this generally is not the case and the vast majority of drugs fail once they reach the clinic. This gap between preclinical and clinical results has major implications for rare tumors like ES, since less than three early phase clinical trials of ES can be conducted in the U.S. yearly.

### **Objectives:**

To completely bypass the obstacles that impede preclinical drug discovery, our lab recently initiated a collaboration with the Langer Lab in the Dept. of Bioengineering at Massachusetts Institute of Technology (MIT) to employ in PDXs a micro-scale implantable device that allows for high-throughput localized intra-tumoral drug delivery of individual drugs and/or drug combinations in a 24 hour period.

**Design/Method:**

The current device contains eighteen reservoirs that can be individually loaded with single agents or drug combinations in micro-dose amounts that diffuse in a controlled fashion ~300 µm into defined regions of the tumor following microdevice implantation. Importantly, by assessing IHC markers of apoptosis (cleaved caspase 3) and proliferation (Ki-67) in those regions as well as image mass CyTOF, one can rapidly, and in parallel, investigate drug sensitivity in vivo, thereby providing a near immediate measure of drug efficacy and potentially predicting global tumor response to systemic therapy in PDXs. Importantly, since the adjacent non-drug treated tumor is recovered with the microdevice, we have the opportunity to comprehensively profile the genomic and proteomic tumor makeup and begin to address the challenge of tumor heterogeneity which can be used to develop predictive biomarkers for each of the drugs and/or drug combinations delivered by the microdevice and pave the way for precision-based, highly-synergistic ES therapies.

**Results:**

The microdevice technology has demonstrated early promise in breast cancer PDX models, and is currently being investigated in pilot trials of adult patients with breast cancer and lung cancer at other institutions. The MDACC/MIT collaboration seeks to validate this technology in ES PDXs and attempts to determine whether in situ micro-dose drug delivery adequately predicts the antineoplastic activity and synergy of systemic chemotherapies.

**Conclusion:**

Our preliminary data in various ES PDX models and xenografts is promising and a clinical trial has been written and approved for clinical validation. We hypothesize that local intratumoral drug efficacy will predict systemic efficacy to today's most promising drug candidates in ES PDXs. If proven accurate, the proposed research herein will pave the way for clinical use in pediatric patients with ES and once validated, this research could significantly accelerate drug discovery for pediatric cancers.

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Poster # 527

**MAXIMIZING CYTOTOXIC EFFECT AND QUALITY OF LIFE IN THE PEDIATRIC AND AYA CANCER POPULATION**

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**Background:**

The prognosis for children, adolescents and young adults (CAYA) with recurrent or metastatic sarcoma remains poor, and many systemic chemotherapy regimens lead to unacceptable toxicities, frequent hospitalizations, and resultant poor quality of life. Chemotherapy regimens do exist, however, that not only keep patients out of the hospital and enhance quality of life, but enhance cytotoxicity and prolong progression-free survival.

**Objectives:**

To share our experience with the use of continuous infusion (CI) ifosfamide and with liposomal doxorubicin at a single institution in this unique patient population.

**Design/Method:**

We retrospectively reviewed and analyzed data from 62 patients with a diagnosis of advanced (recurrent &/or metastatic) sarcoma at a single institution who received either continuous infusion ifosfamide (1gram/m<sup>2</sup>/day IV continuously x 14 days, with 1:1 dosing of Mesna via continuous infusion) or liposomal doxorubicin (30-40mg/m<sup>2</sup> IV monthly, lower dose if combined with MTOR inhibitor or if patients developed unacceptable toxicities at standard 40mg/m<sup>2</sup> dose) from 2015 - 2019.

**Results:**

Preliminary analysis was performed. A total of 24 patients received CI ifosfamide, and a total of 45 patients received a Doxil-containing regimen. Total number of CI ifosfamide cycles given was a median of 2 (range: 1 – 14), with 6 patients receiving ≥3 cycles. Total number of Doxil cycles given was a median of 2 (range: 1-17), with 11 patients receiving ≥5 cycles. Doxil was combined with other agents (i.e., temsirolimus or vincristine) in 31.1% of patients. All chemotherapy was given in the outpatient setting, allowing patients to remain in the comfort of their own home. Further QOL and survival analysis will be performed and reported at the time of the meeting.

**Conclusion:**

Outpatient chemotherapy regimens such as continuous infusion ifosfamide and liposomal doxorubicin are safe, feasible and improve quality of life in advanced CAYA sarcoma patients.

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Poster # 528

**ABDOMINAL INFLAMMATORY MYOFIBROBLASTIC TUMOR: AN UNCOMMON CAUSE OF ABDOMINAL PAIN**

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**Background:**

Inflammatory Myofibroblastic Tumor (IMT) is an uncommon neoplasm of unclear etiology, consisting of a proliferation of myofibroblastic spindle cells mixed with inflammatory cells. Translocations involving the Anaplastic Lymphoma Kinase (ALK) gene have been associated with a more favorable prognosis. IMT tends to affect children or young adults and it is most

commonly found in the lungs and abdomen. Patients typically are asymptomatic or have non-specific symptoms.

Treatment of IMT consists of surgical resection, which provides an overall survival rate exceeding 90%. However, the recurrence rate is high (37%) especially if resection is incomplete. Experimental treatments with targeted therapy such as Crizotinib are promising.

**Objectives:**

Increase awareness of IMT in the differential diagnosis of an abdominal mass in the pediatric population.

**Design/Method:**

A 13-year-old female presented to the emergency department with lower abdominal pain, poor appetite, and a 26-pound weight loss over the previous six months. Family history was significant for colon cancer in the paternal aunt. Physical exam was remarkable for pallor, suprapubic pain, and abdominal distention. Laboratory workup showed a microcytic anemia, elevated ferritin, and C-reactive protein. Abdominal ultrasound and abdomen and pelvis CT imaging revealed a large lobulated mass within the pelvis contiguous with adjacent structures including the sigmoid colon, superior wall of the urinary bladder, and uterus. Chest CT and brain MRI were negative for metastasis.

**Results:**

The tumor was surgically excised and pathology confirmed ALK positive IMT. In the interim, her symptoms resolved. Six weeks post surgery, she developed mild abdominal pain. Follow-up CT imaging demonstrated recurrence of the anterior pelvis mass. Given the positive ALK status of the tumor, Crizotinib treatment was initiated. Three months after initiation of Crizotinib, repeat imaging showed near complete resolution of the tumor.

**Conclusion:**

IMT is a rare neoplasm that should be included in the differential diagnosis of abdominal masses. Presentation, imaging, and laboratory tests are non-specific. Diagnosis of IMT is rarely made before surgery since histologic findings are required. Complete surgical excision is critical and should be performed whenever feasible. When complete resolution is not feasible, Crizotinib should be considered in ALK positive cases. Close follow-up and imaging are needed to monitor for recurrence. In patients with ALK-positive IMT, targeted therapy with Crizotinib should be considered.

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Poster # 529

**TREATMENT OF A PATIENT WITH GENERALIZED INFANTILE MYOFIBROMATOSIS WITH SORAFENIB AND IMATINIB**

**Behzad Bidadi, Andrea Watson, Brenda Weigel, Andre Oliveira, Justin Kirkham, Carola Arndt**

**Background:**

Infantile myofibromatosis (IM) is the most common musculoskeletal tumor in infancy. Multicentric IM with visceral involvement carries a high risk of mortality, and there is no consensus on treatment. Whole-exome sequencing has implicated gain-of-function mutations in platelet-derived growth factor receptor  $\beta$  (PDGFRB) and neurogenic locus notch homolog protein 3 (NOTCH3) in familial IM, and this increased activation was inhibited by imatinib in vitro.

**Objectives:**

To describe the safe and effective use of two different tyrosine kinase inhibitors in a patient with visceral multicentric infantile myofibromatosis.

**Design/Method:**

Case Report

**Results:**

A two-month-old female without family history of IM developed numerous cutaneous lesions that were histologically confirmed to be consistent with IM. At fifteen months of age, due to new lesions, developmental delay, and difficulty gaining weight, imaging was undertaken and revealed innumerable pulmonary nodules. Treatments that followed included intralesional methotrexate, weekly vinblastine and methotrexate, a rhabdomyosarcoma protocol consisting of vincristine, dactinomycin, and cyclophosphamide (VAC), and a monotherapy regimen of 2-chlorodeoxyadenosine (2-CDA). Due to continued symptomatic progression of her disease, these treatments were all stopped, and she was started on sorafenib, with rapid improvement in her pulmonary nodules. After one year of treatment she experienced complete resolution of her pulmonary nodules and a marked reduction in the size of her subcutaneous nodules, so sorafenib was discontinued. Unfortunately, the patient experienced a recurrence, and sorafenib was restarted, again with prompt remission of her disease. Five months following discontinuation of this second course of sorafenib, lesions recurred, so treatment was initiated with imatinib, again with clinical improvement. After cessation of imatinib both subcutaneous and pulmonary nodules recurred. The patient was restarted on imatinib, and has remained on this regimen up to the time of publication with good clinical response. Reports of whole exome sequencing in patients with familial IM have implicated two different germline missense mutations in the PDGFRB gene, and one in the NOTCH3 gene, as being potentially disease-causing. Sorafenib and imatinib are tyrosine kinase inhibitors that have multiple targets, including PDGFRB. Somatic tumor sequencing of the exon regions containing mutations previously identified within PDGFRB and NOTCH3 failed to reveal any mutations in our patient's tumor.

**Conclusion:**

Tyrosine kinase inhibitors may be an effective, minimally toxic treatment for IM, including even the most severe visceral multicentric form. It remains to be seen what the optimal length of treatment is and whether this agent can be discontinued without tumor recurrence.

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## **ADJUVANT LAROTRECTINIB THERAPY IN TWO CHILDREN WITH POOR PROGNOSIS NTRK FUSION-POSITIVE CANCERS**

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### **Background:**

Significant morbidity associated with cytotoxic chemotherapy and radiation in children drives research to elucidate novel targetable lesions in children with cancer. Panel-based next generation sequencing often yields specific molecular pathway mutations, permitting selective targeted intervention. Neurotrophin tropomyosin receptor kinase (NTRK) proteins [TRKA, TRKB, TRKC] are tyrosine receptor kinases expressed in neuronal and non-neuronal tissues that mediate neuronal survival and synaptic plasticity. NTRK fusion mutations occur in approximately 1% of pediatric solid tumors, including sarcomas, carcinomas and nervous system cancers. Larotrectinib, a potent, selective NTRK inhibitor has shown responses and acceptable toxicities in children with progressive, measurable TRK-mutated cancers.

### **Objectives:**

Describe single-agent adjuvant NTRK-targeted larotrectinib therapy in two children diagnosed with poor-prognostic malignancies, one with rapidly progressive undifferentiated embryonal sarcoma of the kidney (UESK) and one with supratentorial high-grade glioma (HGG).

### **Design/Method:**

Retrospective review of patient medical records, radiographic imaging, tissue pathology including panel-based genomic sequencing, and literature review.

### **Results:**

Case 1: A 2-year-old female presented with gross hematuria, hypertension and palpable abdominal mass. Computed tomography scan showed a 9x8x13 cm ruptured left renal mass and peri-aortic metastatic lymphadenopathy. Pathology following biopsy diagnosed UESK. Chemotherapy per AREN0321 was initiated. Short interval worsening physical exam and imaging studies confirmed progressive disease, prompting left nephrectomy and regional lymph node resection. RNA fusion panel-based analysis detected ETV6/NTRK3 gene fusion. Single-agent maintenance larotrectinib was initiated. Patient received no radiation. She is meeting developmental milestones 9 months later.

Case 2: A 3-year-old male presented with headaches, phonophobia, emesis and ataxia. Brain magnetic resonance imaging showed a large right temporal neoplasm, brain stem compression, and obstructive hydrocephalus. Pathology after gross total resection diagnosed WHO Grade 3 HGG. He underwent involved-field proton beam radiation and concurrent temozolomide. Subsequently, panel-based genomic analysis showed NACC2-NTRK2 fusion and CDKN2A/CBKN2B homozygous deletion. Single agent maintenance larotrectinib was initiated.

He remains disease-free 9 months later.

**Conclusion:**

Morbidity associated with chemotherapy and radiation drives research to find novel targetable lesions in children with cancer. Panel-based next generation sequencing often yields specific molecular pathway mutations, permitting selective targeted intervention. Early phase trials in children with progressive NTRK-positive malignancies despite conventional therapies demonstrated remarkable responses without significant adverse side-effects, clearing the path for rapid FDA-approval for use in such patients. We now extend the potential NTRK-inhibitor therapeutic spectrum by describing adjuvant larotrectinib administration in children diagnosed with these malignancies after local control, who failed conventional systemic treatments. Larotrectinib may prolong EFS, increase cure and spare significant adverse treatment-related effects.

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Poster # 531

**USE OF THE GAMMA-SECRETASE INHIBITOR NIROGACESTAT IN PEDIATRIC DESMOID TUMOR: A REPORT OF FOUR CASES**

**John Prensner, Takuto Takahashi, Mona Tewari, Uchenna Iloeje, Caroline Robson, Katherine Janeway, Brenda Weigel**

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**Background:**

Desmoid tumor is a non-metastatic yet locally aggressive tumor that can result in substantial morbidity in adults and children. Historically, the primary choice of therapy for those with symptomatic or progressive tumor has been complete resection. Systemic therapy, such as cytotoxic chemotherapy, tyrosine kinase inhibitors, or non-steroidal anti-inflammatory drugs, are often required due to the high risk of local recurrence after resection or the inability to remove the tumor. Biologically, desmoid tumor is thought to be mediated through the Notch pathway as well as other pathways, which makes gamma-secretase inhibition an attractive therapeutic option. Nirogacestat, a gamma-secretase inhibitor, has shown favorable tumor responses and tolerability in phase I and II trials in adults with desmoid tumor. However, its effect in children with desmoid tumors is yet to be studied. Here, we provide the first report of the efficacy and safety of Nirogacestat in four pediatric/young adult patients with desmoid tumor.

**Objectives:**

The purpose of this retrospective review is to report the outcomes of pediatric/young adult patients with desmoid tumor treated with Nirogacestat.

**Design/Method:**

We performed a retrospective review at two large academic medical centers of four cases of pediatric/young adult patients with desmoid tumor who received Nirogacestat on compassionate use INDs for therapy (three refractory tumors, one treatment-naive tumor). Three patients had familial adenomatous polyposis (FAP) syndrome. We extracted clinical data from the medical

record to determine tumor size before and after treatment as well as side effects attributed to therapy.

**Results:**

Nirogacestat was given to four patients aged 2, 4, 17, and 19 years old with doses adjusted based on body surface area (BSA). All of them demonstrated tumor shrinkage or arrest of progression following Nirogacestat initiation, but at a median follow-up of 8 months (range, 4 - 12), only three had durable benefit: one with sustained complete response; one with partial response; and one with stable disease. The fourth, an FAP patient, had an initial response of the target tumor but developed disease progression on Nirogacestat; repeat genomic profiling of the tumor did not reveal new genetic information that would explain disease resistance to therapy. The only noted adverse event was grade 2 diarrhea in one patient, and none experienced grade 3/4 adverse events.

**Conclusion:**

We conclude that gamma-secretase inhibition with Nirogacestat is a well-tolerated and potentially promising treatment for pediatric/young adult patients with desmoid tumor worthy of further study in this population.

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Poster # 532

**SINGLE AGENT RITUXIMAB FOR TREATMENT OF MULTIFOCAL PULMONARY MYOFIBROBLASTIC TUMOR**

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**Background:**

Inflammatory myofibroblastic tumors (IMTs) are a type of non-malignant but locally invasive masses with inflammatory histopathology. They present in children and adolescents most commonly in the visceral organs. Genetic aberrations can be common and the highest proportion, 50%, express rearrangements of anaplastic lymphoma kinase (ALK).<sup>1</sup> Treatment is difficult as this type of tumor frequently recurs.<sup>2,3</sup> Management can include surgical excision with low rates of recurrence,<sup>4,5</sup> targeted therapies, chemotherapy and/or radiation. Rituximab, an anti CD20 monoclonal antibody has been tried in single cases with some success.<sup>6,7</sup>

**Objectives:**

We present the case of a successful non-surgical treatment modality in a multiply recurrent multifocal pulmonary inflammatory myofibroblastic tumor of an adolescent patient post-treatment for Hodgkin's lymphoma.

**Design/Method:**

Eighteen year old female initially presented with supraclavicular lymphadenopathy and was diagnosed with stage 2A nodular sclerosing hodgkin's lymphoma. Completed treatment with the standard of care: doxorubicin, bleomycin, vincristine, etoposide, prednisone cyclophosphamide



and targeted radiation (2100cGy).

At 3 months off therapy, imaging surveillance showed new pulmonary nodules. Approximately 8 total nodules in 4 total lobes, largest mass 3.2 x 2.6 x 2.7cm. Surgical biopsy identified the masses as IMTs. There were no identifiable mutational targets including no aberrant ALK rearrangement. Treatments included prednisone, pulse dexamethasone, vinblastine, oral methotrexate and celecoxib. Empiric trial of ALK inhibitor, crizotinib, was tried until discontinuation at 6 months due to disease progression. Repeat biopsy showed programmed death ligand 1+ (PDL1+) mutation, so pembrolizumab was initiated with improvement in overall size but disease progression with new pulmonary nodules.

**Results:**

Empiric trial of rituximab 375mg/m<sup>2</sup> every other week for 4 total doses. Treatment course had no grade 3 or 4 toxicities, symptomatic treatment for joint pain. Follow up imaging at end of therapy and at 3 months off therapy showed resolution of pulmonary nodules. Her last imaging at 12 months off therapy continues to show a robust remission without evidence of new nodular disease.

**Conclusion:**

Immunotherapy with anti-CD20 rituximab was used successfully to treat multifocal and multiply recurrent IMTs with complete remission at 12 months off therapy.

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Poster # 533

**ERLOTINIB THERAPY FOR RECURRENT RESPIRATORY PAILLOMATOSIS AND EXTRALARYNGEAL SPREAD IN PEDIATRICS**

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**Background:**

Recurrent respiratory papillomatosis (RRP) with extra-laryngeal spread can be a potentially life-threatening condition and a unique treatment challenge. Local therapies are associated with significant scarring and detrimental effects on voice and respiratory status. EGFR inhibitors have been reported to be an effective adjunctive therapy in patients with RRP.

**Objectives:**

To report our institutional experience with Erlotinib in two pediatric patients with RRP and extra-laryngeal spread.

**Design/Method:**

Retrospective chart review of 2 pediatric patients with RRP and extra-laryngeal spread.

**Results:**

Patient 1 is a 19y/o female who was referred to us at the age of 11. Patient was diagnosed with respiratory papillomatosis at 14months. Since then she had been undergoing micro-laryngoscopy, bronchoscopy with laser or surgical excision of the lesions, on a 1-2 monthly basis. On examination she had no skin lesions. Her voice was only a whisper. No difficulty breathing or stridor. She was pre-pubertal. Endoscopic exam 3 weeks prior to starting therapy showed severely scarred larynx, no obvious laryngeal disease, diffuse subglottic and tracheal papillomatosis with extension into the left main bronchus. Biopsy of the lesion showed squamous papilloma, EGFR positive.

Patient 2 is 14y/o who was referred to us at age 12. Patient was diagnosed at 5 months with respiratory papillomatosis of the larynx undergoing micro-laryngoscopy, bronchoscopy with laser or surgical excision of the lesions, on a 1-2 monthly basis. He developed respiratory distress post laryngoscopy and found to have 3 pulmonary lesions confirmed as papillomatosis post thoracotomy with wedge resections.

Both patients were started on an EGFR inhibitor, Erlotinib at a dose of 85mg/m<sup>2</sup> daily and DIM (diindolylmethane) 150mg twice daily. The skin care regimen included regular moisturizers and sunscreen; topical steroids and antibiotics as needed. Therapy was well tolerated except for grade 1 skin rash in both patients and grade 1 diarrhea as well, in Patient 1.

For patient 1, within a month of therapy there was significant decrease in the lesions and by 6mo complete resolution of papillomatosis. She had 15mo of therapy. She is in remission 6 years off therapy. For patient 2, there has been decrease in lesions and the interval between laryngoscopy since start of therapy. CTs of chest confirm no recurrence of pulmonary lesions since starting Erlotinib.

**Conclusion:**

Erlotinib demonstrates efficacy in RRP with extra-laryngeal spread in children and may be considered as adjunct therapy with surgical excision in this disease. DIM is an aromatase inhibitor that potentiates the effect of Erlotinib.

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Poster # 534

**PAPILLARY THYROID CARCINOMA PRESENTING AS ACUTE RESPIRATORY DISTRESS IN A 12 YEAR OLD MALE**

**Austin Healy, Chibuzo O'suoji**

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**Background:**

Background: Differentiated thyroid cancers (papillary or follicular) are a rare neoplasm in

children and are about 2-3% of all pediatric malignancies. It is estimated that about 50% of thyroid carcinomas present with thyroid nodule enlargement. Papillary thyroid cancer is the most common of the Differentiated Thyroid Cancers responsible for about 83% of all pediatric thyroid malignancies. Although Pediatric thyroid cancers usually present in more advanced stages and are more aggressive than in adults, prognosis and long term survival rates are greater than 95%.

**Objectives:**

Objective: We describe our experience in diagnosing/treating an unusual presentation of Papillary Thyroid Carcinoma in a 12 year old patient.

**Design/Method:**

Design/Method: Case Report

**Results:**

Results: A previously healthy 12 year old male presented to the ER with decreased energy and one to two months of intermittent dry cough. Three days prior to presentation, he began to have worsening cough with shortness of breath and subjective gurgling in his throat. He had recently been diagnosed with hypothyroidism treated and started on Synthroid. In the ER he was started on oxygen due to hypoxia and a CXR revealed diffuse alveolar disease bilaterally. He was found to be rhino/enterovirus positive, but this could not explain the severity of his symptoms and imaging results. His CBC was significant for leukocytosis. The rest of his labs were normal. Extensive work up failed to reveal the etiology of his worsening respiratory status. By the second day of admission he was requiring 15L of oxygen. CT of the chest showed disseminated/miliary lung involvement. Imaging of the Head, Neck, Abdomen and Pelvis, were negative for tumors or thyroid nodules. Of note, he had only the left lobe of his thyroid present as the right lobe never developed. The left node was normal appearing. A wedge biopsy of the lungs was obtained and reported to be Papillary Thyroid Cancer.

Patient underwent a total thyroidectomy and LN removal. He was treated with radioactive iodine 131 therapy due to lymph node involvement and distant metastases. The tumor was found to be B-Ras positive and we are currently awaiting the results of radioactive iodine therapy to determine if a B-Ras inhibitor therapy is warranted.

**Conclusion:**

Conclusion: Pediatric thyroid cancers can behave differently in children than adult patients, but due to the rarity of the disease; a high index of suspicion is needed for prompt and accurate diagnosis.

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Poster # 535

**PARTIAL RESPONSE TO GEMCITABINE-OXALIPLATIN-LENVATINIB IN RELAPSED FIBROLAMELLAR CARCINOMA**

**Michael Terao, Wayne Furman, Paul Kent**

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**Background:**

Fibrolamellar hepatocellular carcinoma (FLC) is a rare disease, found mostly in adolescent and young adult patients which is incurable without complete surgical resection. Many patients relapse with inoperable tumor. There is a need for effective systemic treatments. We describe two patients who had multiple prior surgeries, had failed interferon/5-fluorouracil (5FU), and were unresectable. We chose gemcitabine-oxaliplatin (GEMOX) based on case reports of FLC efficacy. When this failed, we added the oral antiangiogenic/multi-kinase inhibitor lenvatinib (LEN) based on hepatocellular carcinoma data and a similar approach using GEMOX-sorafenib in a trial by the Children's Oncology Group.

**Objectives:**

Describe our experience with GEMOX-LEN in relapsed FLC.

**Design/Method:**

Case Reports

**Results:**

A 17 yo old female presented with a hepatic mass, abdominal, pelvic, omental and lung metastasis, biopsy proven to be FLC. Initial resection removed 98% of the tumor. Post-op she received interferon/5FU for one week with nivolumab (day 1) repeated every 2 weeks. After 12 cycles of stable disease there was inoperable abdominal/pelvic progression. Her new treatment of gemcitabine 1000mg/m<sup>2</sup> and oxaliplatin 100mg/m<sup>2</sup> every 2 weeks, failed in 4 weeks. We then added lenvatinib (LEN) 8mg po daily. After 10 cycles of GEMOX-LEN, her abdominal pain and ascites resolved and she showed a partial response (PR) with -39% change by RECIST1.1 and estimated -57% by volume.

A 14 year old male presented with a hepatic mass, biopsy proven to be FLC that was unresectable and treated with initial liver transplant, but no systemic therapy. Nine months later a relapse in the abdomen/lungs was fully resected. Post-op he received interferon/5FU for one week without nivolumab, repeated every 2 weeks for 6 cycles. An abdominal/pelvic relapse was partially resected 4 months later. He also started GEMOX and also progressed in 4 weeks. Similar to the patient described above, LEN 8mg was added. After 8 cycles of GEMOX-LEN, his abdominal pain improved, ascites resolved, and he was able to travel overseas for vacation. He also showed a partial response (PR) with -76% change by RECIST1.1. He became a surgical candidate.

**Conclusion:**

GEMOX-LEN improved symptoms and produced an excellent partial radiographic response in 2 patients with relapsed and refractory FLC. It is unclear whether this response was due to the combination of Gemcitabine-Oxaliplatin-Lenvatinib or Lenvatinib alone.

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Poster # 536

**INTRA-ABDOMINAL KARPOSI SARCOMA AFTER RENAL TRANSPLANTATION  
IN A PEDIATRIC PATIENT: A CASE REPORT**

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**Background:**

Kaposi sarcoma (KS) is a rare tumour after solid organ transplant, with an estimated incidence of 0.4-6% in adults undergoing renal transplantation. In pediatric patients in developed countries, that incidence is likely lower due to a lower seroprevalence of human herpesvirus 8 (HHV-8) in recipients. Pediatric KS has been reported after liver, bone marrow and, rarely, renal transplantation.

**Objectives:**

Describe a rare case of Kaposi sarcoma in 16-year-old HIV-negative girl after renal transplantation.

**Design/Method:**

Case report

**Results:**

A 16-year-old girl was found to have end stage renal disease secondary to presumed bilateral dysplasia. She subsequently underwent a living-related donor transplant from her mother and remained on immunosuppression with tacrolimus, mycophenolate mofetil and prednisone. She presented 15 months after transplant with gastroenteritis and elevated liver enzymes, prompting ultrasound investigation. This revealed diffuse enlarged retroperitoneal lymph nodes and a focal liver lesion. She underwent biopsy of an involved lymph node, which was found to be KS, positive for HHV-8 by PCR. There was no evidence of active HHV-8 viremia at the time of diagnosis and she was HIV negative. Full staging revealed no lymphadenopathy outside of the abdomen and no cutaneous disease. In consultation with nephrology, the tacrolimus was substituted with sirolimus and she was monitored. Over the next year, the abdominal lymphadenopathy resolved and the liver lesion decreased in size. Unfortunately, two years after the transplant, and ten months after diagnosis of KS, she was found to have acute T cell rejection on routine biopsy, as well as the development of Class 1 donor specific antibodies. She was treated with methylprednisolone pulses followed by initiation of monthly IVIG. Follow-up biopsy showed worsening of the T cell rejection and therefore, tacrolimus was added. A further transplant biopsy showed evidence of chronic cellular- and antibody-mediated rejection with stage 2 chronic kidney disease (CKD). Despite the addition of the calcineurin inhibitor almost one year ago, there has been no evidence of recurrence. She is now 2 years from the original diagnosis of KS and remains in remission.

**Conclusion:**

Kaposi sarcoma is a rare diagnosis in North America due to a low seroprevalence of HHV-8. Here, we describe a unique pediatric case following renal transplantation. Her tumor was successfully treated with substitution of tacrolimus for sirolimus, an mTOR inhibitor that is believed to have antineoplastic effects. She remains in remission following addition of tacrolimus to the immunosuppressive regimen for acute rejection of the transplanted kidney.

## IMATINIB IN THE TREATMENT OF INFANTILE MYOFIBROMATOSIS WITH ACTIVATING VARIANTS IN PDGFRB

Natalie Wu, Anurekha Gollapudi, Tara Wenger, Evan Abrass, Erin Rudzinski, Prasanth Pattisapu, Randall Bly, Jonathan Perkins, Deepti Gupta, Tyler Ketterl, Julie Park, Catherine Albert

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**Background:** Infantile myofibromatosis (IM) is the most common benign soft tissue tumor of infancy and childhood. While the clinical course can vary, more severe phenotypes often require surgical resection and/or systemic chemotherapy. Pathogenic variants in PDGFRB resulting in constitutive activation of the PDGFR- $\beta$  receptor have been determined to cause IM, as well as other related clinical syndromes. Tyrosine kinase inhibitors (TKIs) such as imatinib have been used in isolated reports in patients with PDGFRB-related disorders, but there have been no reports of imatinib use in infants.

**Objectives:** This case series describes two infants with multicentric IM who were diagnosed with pathogenic gain-of-function variants in PDGFRB and subsequently treated with imatinib.

**Design/Method:** Single-institution retrospective review of patients with IM treated with imatinib.

**Results:** Patient 1 was born with innumerable subcutaneous nodules, including a large tongue base lesion measuring 1.9cm that caused obstructive respiratory failure requiring positive pressure ventilation. His mother had several myofibromas excised in childhood. Patient 2 had a 4.5cm pre-auricular mass discovered on prenatal ultrasound which developed central necrosis and cellulitis shortly after birth. Both patients underwent excisional biopsy with histopathology consistent with myofibromatosis. Subsequent imaging demonstrated multiple bone and soft tissue lesions consistent with multicentric IM in both patients with no evidence of visceral involvement. Genetic testing (UW-OncoPlex Panel with targeted next-generation sequencing) demonstrated two activating variants (somatic and germline) in PDGFRB in patient 1 and two somatic activating variants in patient 2. Imatinib monotherapy was initiated at 6mg/kg weight-based dosing, which was extrapolated from pediatric chronic myeloid leukemia dosing of 340mg/m<sup>2</sup> and further reduced by 50% based on previous toxicity data for infants. Patient 1 had dramatic reduction in the size of all myofibromas and discharged without respiratory support 4 weeks after initiating imatinib. Imatinib was discontinued at 4 months with near-resolution of all myofibromas. Patient 2 had complete resolution of all myofibromas; imatinib was discontinued at 6 months due to neutropenia (CTCAE Grade 4) without infectious complications. Patient 2 was subsequently diagnosed with chronic benign neutropenia of childhood at 11 months without other lab or imaging abnormalities. Neither patient underwent extensive surgical intervention nor systemic chemotherapy.

**Conclusion:** We describe two infants with multicentric IM in whom genetic testing led to successful targeted treatment with imatinib monotherapy. Weight-based dosing was safe and resulted in clinical benefit. Additional studies are needed to further examine the efficacy and long-term effects of TKIs in IM.

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Poster # 538

## **TREATMENT OF RECURRENT NASOPHARYNGEAL CARCINOMA WITH HEMATOPOIETIC STEM CELL TRANSPLANTION**

**Mansi Dalal, John Fort**

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### **Background:**

Nasopharyngeal carcinoma is rare in the pediatric population comprising roughly 1% of all pediatric malignancies. It is currently treated with combination of chemotherapy and radiation. Recurrent nasopharyngeal carcinoma occurs in less than 10% of those who are treated with front-line therapy. When it recurs, it is difficult to treat and carries a poor prognosis. Chemotherapy is used to treat recurrent disease but there is no standard salvage regimen in the pediatric population

### **Objectives:**

We report a patient with multiple recurrences of nasopharyngeal carcinoma who underwent hematopoietic stem cell transplantation

### **Design/Method:**

Single subject case report

### **Results:**

The patient was treated three times for multiple, distant metastatic recurrences of nasopharyngeal carcinoma with salvage chemotherapy and local radiation. After completion of each treatment, there was no evidence of residual disease. He underwent hematopoietic stem cell transplant after his third recurrence. Bone marrow evaluation prior to transplant showed no evidence of disease. He received conditioning regimen followed by autologous stem cell transplant. He is now five years after hematopoietic transplantation without evidence of recurrence of disease.

### **Conclusion:**

Multiply relapsed nasopharyngeal carcinoma can be treated with autologous transplant with long-term remission. Further research is needed to determine efficacy of hematopoietic transplantation in the pediatric population.

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Poster # 539

## **PANCREATIC NEUROENDOCRINE TUMOR WITH LIVER METASTASIS IN A 9 YEAR OLD PATIENT: A CASE REPORT**

**Vandana Racherla, Mosopefoluwa Lanlokun, Emily Wisniewski, Amy Nemirovsky, Regina Macatangay, Teresa York**

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**Background:**

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies arising from hormone secreting cells and typically occur in the gastrointestinal and bronchial systems. The small intestine and rectum are the most common locations in the gastroenteropancreatic system while the pancreas is the third most common but with the most rapidly rising incidence. NETs are largely a disease of adults however they can occur in the pediatric population. In children and adults under 30 years of age, the incidence of NET is about 2.8 per million.

**Objectives:**

Discuss an NET of pancreatic origin with liver metastasis and emphasize the importance of considering malignancy in the differential diagnosis in a child with chronic, recurrent non-specific symptoms.

**Design/Method:**

Case report

**Results:**

A 9-year-old female with asthma presented to the pediatric emergency department with a one-year history of intermittent abdominal pain, worsening over five days with distention, vomiting and fever. She had been healthy and active until onset of abdominal pain that would recur monthly. Initial episodes were attributed to viral illnesses and constipation which self-resolved. Her physical exam revealed a distended yet non-tender abdomen with marked hepatomegaly, oropharyngeal candidiasis and cervical lymphadenopathy. Testing revealed a mildly elevated AST with normal ALT, unremarkable CBC, LDH and uric acid. Abdominal ultrasound and CT showed multiple hypoechoic nodules, the largest 2.4 cm in diameter, within an enlarged liver that spanned 16.6 cm. MRI of the abdomen and pelvis demonstrated hepatosplenomegaly with an enhancing lesion arising from the pancreatic neck. There was dilation of the proximal common bile duct due to compression by the pancreatic lesion. The MRI findings were consistent with a primary neuroendocrine tumor with hepatic metastases. Gallium-68 PET scan demonstrated multiple somatostatin avid lesions in the liver with focal uptake in the neck of the pancreas. Pathology results from IR-directed liver biopsy confirmed the diagnosis of neuroendocrine carcinoma. Tumor markers for Cam 5.2, synaptophysin, chromogranin, and CD65 were positive. Chromogranin A was elevated. 24-hour 5-HIAA and metanephrine testing were normal.

**Conclusion:**

Neuroendocrine carcinoma is rare in the pediatric population, however can be associated with significant morbidity and mortality and few therapeutic options are available. Vague presentation of symptoms, the sporadic occurrence, as well as occurrence in unusual sites can result in missed



or delayed diagnoses, inadvertent neglect, and delayed intervention. Multidisciplinary evaluation and broad differentials are important for diagnosis and treatment.

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Poster # 540

## **MYOEPITHELIAL CARCINOMA, A CASE REPORT OF AN AGGRESSIVE BRACHIAL PLEXUS TUMOR**

**Peter Schoettler, Jonathan Wickiser**

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### **Background:**

Myoepitheliomas are benign tumors with an indolent course arising from the salivary glands. Recently, a subset of myoepithelial neoplasms, myoepithelial carcinoma, have been described with an aggressive clinical course. These tumors have been found in the extremities, breast, upper digestive tract, skin, and soft tissue. Cases have been reported with an age range of 3 months to greater than 90 years old, mostly in adulthood. Surgical resection is the mainstay of treatment, but the role of chemotherapy or radiation remains unclear. To date, no long-term survival has been reported in unresectable cases or metastasis outside of the lungs or local lymph nodes.

### **Objectives:**

Demonstrate the aggressive nature of myoepithelial carcinoma and the difficulty of complete surgical resection in a complex location.

### **Design/Method:**

We describe a patient with unresectable myoepithelial carcinoma encasing the brachial plexus and major blood vessels of the neck/shoulder, treated with chemotherapy, radiation, and surgical debulking along with the clinical conundrum of a more aggressive surgical resection.

### **Results:**

A 14-month-old male presented with a history of a mass of the right shoulder and limited movement of his right arm previously cared for at an outside institution. There he had undergone attempted resection of what was thought to be an Ewing Sarcoma. Internal review of his histologic specimens was consistent with myoepithelial carcinoma with positive surgical margins and a SMARCB1-DPP9 fusion. Local imaging revealed a large mass encasing his right brachial plexus and vertebral artery with intraspinal extension. During surgical planning, he was found to have tumor progression with spinal cord compression and underwent surgical debulking and started on VAC (vincristine, actinomycin, and cyclophosphamide), but had progression of tumor. He was then given ICpE (ifosfamide, cisplatin, and etoposide) with concurrent radiation therapy. The tumor decreased in size and had improvement in arm mobility, but the mass remained unresectable without a largely morbid surgery after the 4th cycle of this therapy. Treatment was change to IVE (ifosfamide, vincristine, etoposide), without response. Two months later the patient died due to progressive disease.

**Conclusion:**

Myoepithelial Carcinoma is an aggressive soft tissue malignancy which requires surgical resection for long term survival. This case demonstrates the response of MEC to ICpE and radiation therapy, but illustrates the importance of complete surgical resection.

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Poster # 541

**MESENCHYMAL HAMARTOMA OF THE LIVER WITH A UNIQUE CYTOGENETIC ABNORMALITY: t (15;19) (q15; q13.3).**

**Preethi Reddy Marri, Hamayun Imran, Chibuzo Ilonze, Fatima Al-Saygh, Zohaib Sayyed**

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**Background:**

Mesenchymal hamartoma (MHL) of the liver, a benign tumor, occurs most commonly in the first two years of life. It is believed to arise from a developmental abnormality in the formation of ductal plates during late embryogenesis. Multiple cytogenetic abnormalities involving a breakpoint on chromosome 19q have been observed.

**Objectives:**

We report a case of MHL in a young male child with a novel balanced translocation t (15;19) (q15; q13.3).

**Design/Method:**

Single case report with review of literature.

**Results:**

A 4-year, previously healthy African American male was found to have an incidental RUQ ~8cm smooth, mobile and non-tender mass on routine physical examination. Review of system was entirely unremarkable. Vitals and growth centiles were normal. Routine laboratory data including alpha fetoprotein level were within normal limits. MRI of the abdomen showed a large, well circumscribed 6.0 x 10.7 x 10.4 cm homogenous, solid mass in the left lobe of the liver. Histopathology on the biopsied sample revealed mesenchymal hamartoma with no anaplasia or mitotic activity. A modified left hepatectomy with complete tumor excision and with negative margins was performed which he tolerated very well. Microscopy of the tumor showed broad bands of bland fibrous tissue with haphazardly arranged and distorted bile ducts intermixed with confluent sheets of normal bland hepatocytes. At 6-month mark post-resection, he is doing very well.

**Conclusion:**

MHL accounts for 12.4% of all hepatic tumors in toddlers. Most commonly reported chromosomal translocations are t (11;19) (q13; q13.4) and t (15;19) (q15; q13.4). One child had a translocation t (11;19) (q13; q13.3) which led to an early recurrence within 5 months. Our patient was found to have a balanced translocation t (15;19) (q15; q13.3) which adds to the cytogenetic data of these tumors. Follow up of the child may clarify the relationship between this

interesting novel translocation and the recurrence risk. Therefore, while etiology largely remains unclear, it is still important to evaluate the karyotype in MHL.

The current standard of care of these tumors is complete resection with clear margins. Although benign, there is a certain risk of recurrence if there is disease left behind or margins are not clear. Lastly, MHL has been reported to transform into undifferentiated embryonal sarcoma (UES), an aggressive liver tumor with a median survival of less than 1.5 years. For deemed unresectable MHL, orthotopic or living donor liver transplantation should be considered for long-term survival.

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Poster # 542

## **EPITHELIOID INFLAMMATORY MYOFIBROBLASTIC SARCOMA DRIVEN BY PRRC2B-ALK FUSION WITH COMPLETE RESPONSE**

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### **Background:**

Epithelioid inflammatory myofibroblastic sarcoma (EIMS) is a rare aggressive malignancy typically arising from the omentum or mesentery of young adults. Similar to anaplastic large cell lymphoma (ALCL) and inflammatory myofibroblastic tumor, EIMS frequently expresses CD30 and ALK, but is also positive for desmin and smooth muscle actin (SMA). Nearly all described cases of EIMS have a RANBP2-ALK fusion. Treatment of EIMS generally involves surgical excision and doxorubicin-containing regimens with poor results. Targeted therapy with anti-CD30 or ALK inhibitors may be valuable in treating these patients.

### **Objectives:**

To describe a novel malignant neoplasm, a new treatment regimen, and broaden our understanding of ALK-rearranged tumors.

### **Design/Method:**

Comprehensive genomic profiling included paired tumor/normal exome sequencing and RNA sequencing of tumor sample.

### **Results:**

An 18-year-old female presented with progressive abdominal pain. CT demonstrated multiple omental masses with significant ascites. Biopsy showed sheets of epithelioid cells that were positive for CD30 (strong), CD138, ALK (cytoplasmic), Sal4 (weak), SMA (weak, patchy), and desmin (focal, weak). FISH confirmed ALK rearrangement. Metastatic work-up was negative. Genomic profiling identified an in-frame PRRC2B-ALK fusion retaining the ALK kinase domain, previously reported in a single case of subependymal giant cell astrocytoma. There was also biallelic loss of tumor suppressor BAP1, gain of EGFR and missense and nonsense alterations in the NF1 gene. Due to her clinical presentation and lack of lymphoid marker expression, a diagnosis of EIMS was favored despite lack of inflammatory infiltrate and weak

desmin expression. After failing steroids and a second generation ALK inhibitor, alectenib, she was treated with a combination of brentuximab (anti-CD30), doxorubicin, and vinblastine. Despite tumor response, she developed pulmonary embolus, hemoptysis, multiple organ failure, CMV viremia, and prolonged pancytopenia and died 7 weeks after admission. Autopsy demonstrated complete tumor responses to chemotherapy with no viable tumor cells present. The cause of death was diffuse alveolar damage and hemorrhage with concurrent *Candida parapsilosis* pneumonia.

**Conclusion:**

We describe a case of an aggressive malignant neoplasm, most consistent with EIMS with a novel PRRC2B-ALK fusion. The unique morphological features and immunophenotype posed significant challenge and delay in diagnosis. The tumor was eradicated completely by a combination therapy of anti-CD30 inhibitor, doxorubicin, and vinblastine. The effect of this regime in our patient may provide a new way to treat this rare malignancy. Genomic profiling provides comprehensive information of genetic mutations, which is valuable for both diagnosis and treatment.

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Poster # 543

**CHEMOTHERAPY FOR HIGH RISK HEPATOBLASTOMA IN AN ANEPHRIC PATIENT**

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**Background:**

Hepatoblastoma is the most common pediatric liver tumor, with most cases occurring before the age of 5. The majority of patients are treated with chemotherapy. Several of the active agents are renally cleared. There is no standard dosing for patients undergoing peritoneal dialysis.

**Objectives:**

To discuss the challenges and strategies used in treating hepatoblastoma in an anephric patient on dialysis.

**Design/Method:**

This case report includes a discussion of chemotherapy modifications to treat an anephric patient on peritoneal dialysis (PD) pre-liver transplant and on hemodialysis after liver transplant.

**Results:**

Our patient presented at 13 months of age after liver lesions were discovered on routine imaging in preparation for renal transplant due to autosomal recessive polycystic kidney disease. Core needle biopsy of the liver lesion confirmed mixed epithelial and mesenchymal type hepatoblastoma with foci of small undifferentiated cells. Her initial AFP was 57. She was diagnosed with high risk Hepatoblastoma. Her disease was multifocal in her liver with no evidence of extrahepatic disease; unresectable but she was still a transplant candidate. As there

was little data for dosing and concern for excess toxicity with cisplatin/5 fluorouracil/vincristine/doxorubicin (C5VD) in PD patients, we began therapy with vincristine and irinotecan (VI) with a plan of continuing therapy as long as patient was responding awaiting a donor liver. She thus received 11 total cycles of VI. She had initial response with decrease in AFP to 11. However, her AFP started rising to 52 during therapy. We then transitioned to treatment with C5V, for 3 cycles, with 50% dose reduction of cisplatin. After a total of 10.5 months of therapy our patient received an orthotopic liver transplant, and was converted to hemodialysis post-transplant. Post treatment pathology showed a mainly epithelial fetal pattern with focal bone and rare microscopic foci of squamous islands. Her AFP has been 4-6 since transplant. She received 2 cycles of dose reduced C5VD Post transplant. She has been tolerating her immunosuppression with tacrolimus and MMF well, with plans for renal transplant at approximately 1 year from completion of all therapy.

**Conclusion:**

Treatment of Hepatoblastoma patients that require chemotherapy in the setting of dialysis is challenging as there is a lack of evidence supporting a standard regimen or chemotherapy dosing. Successful therapy is possible with careful planning and multidisciplinary involvement.

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Poster # 544

**UNIQUE PRESENTATION OF HEPATOBLASTOMA IN A PATIENT WITH SPONDYLOEPIPHYSEAL DYSPLASIA CONGENITA**

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**Background:**

Spondyloepiphyseal dysplasia congenita (SEDC) is a rare genetic nonlethal skeletal dysplasia of a mutation in type 2 collagen, COL2A1. We describe a case of a patient with a previously unknown mutation c.3400 G>A in the COL2A1 gene who also developed hepatoblastoma. Hepatoblastoma is itself a rare condition most often diagnosed under five years of age with an incidence of less than two per million children less than 15 years old. Hepatoblastoma is at increased risk in patients with certain genetic conditions. COL2A1 mutations have been noted in the literature in cases of chondrosarcoma. To our knowledge this is the first reported case of hepatoblastoma in patients with COL2A1 gene mutation.

**Objectives:**

Report the presentation, genetic workup, treatment, and outcome of a case of hepatoblastoma occurring in a patient with SEDC.

**Design/Method:**

This is a single institution case report of a patient followed from 2012-2019.

**Results:**

A male patient was prenatally diagnosed with osteochondrodysplasia by fetal ultrasound and

confirmed as SEDC with genetic testing via a mutation in the COL2A1 gene. The genetic variant was c.3400 G>A and had not been described previously in the literature to our knowledge. This variant occurred in a highly conserved region with known pathology for dominant negative effects from mutations in that region. At the age of 20 months, he presented with a palpable abdominal mass measuring 8cm on MRI and significantly elevated alpha-fetoprotein (AFP). He underwent tumor resection with pathology consistent with hepatoblastoma of epithelial subtype, stage 1, PRETEXT group 2. The patient began antineoplastic chemotherapy per the Children's Oncology Group Protocol, AHEP0731, with cisplatin, 5-fluorouracil (5-FU), and vincristine within the first month following resection. He completed 2 cycles of antineoplastic chemotherapy, which he tolerated without significant adverse effects. His AFP levels down trended to undetectable levels by 4 months after diagnosis. He is now over 5 years since completion of chemotherapy and tumor resection without recurrence.

**Conclusion:**

SEDC and hepatoblastoma are rare conditions seen in the pediatric population each with genetic associations. A case of these two rare conditions occurring together with a previously unknown genetic variant for SEDC suggests that further research is required to determine if a subset of patients with SEDC may be at increased risk for hepatoblastoma.

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Poster # 545

**HEPATOCELLULAR CARCINOMA IN A 6-YEAR-OLD WHO PRESENTED WITH ABDOMINAL DISTENSION AND HYPOGLYCEMIA**

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**Background:**

Hepatocellular Carcinoma (HCC) like many other childhood abdominal primary cancers presents with non-specific symptoms, leading to a delayed diagnosis. We report a case of HCC in a 6-year-old patient who has negative hepatitis markers and negative underlying liver pathology.

**Objectives:**

This case report highlights the importance of focusing on common diagnosis but at the same time not forgetting about other rare diagnosis, as not doing so can lead to a delay in reaching the correct diagnosis.

**Design/Method:**

Single subject case report.

**Results:**

A 6-year-old patient presented to the emergency department after numerous PCP visits for 4 weeks of abdominal pain, distension, and palpitations that resolved after eating. The patient's parents were told she has constipation. The parents decided to take the patient to the ED because of worsening distension, lethargy and development of puffy face, where she was found to have

severe hypoglycemia (BS 37 mg/dl), AST 51 mg/dl, ALT 151 mg/dl, Alb 2.7 mg/dl, and large hepatosplenomegaly (HSM). Hepatitis markers were negative for A, B, and C. US showed portal hypertension, and HSM. GI was consulted and felt that etiology was auto-immune hepatitis or vascular malformation. MRI-MRCP/MRA were done. Imaging showed diffuse hepatic infiltration and portal vein tumor thrombus, and Oncology was consulted. AFP was 761, and liver biopsy was obtained. Because of the young age as well as the negative hepatitis B and C markers, the pathologic diagnosis of HCC was taken with skepticism leading to delay in starting HCC specific chemotherapy regimen until a 2nd review by a liver tumor pathology expert was obtained, which confirmed poorly differentiated HCC. A diagnosis of Stage IV HCC with metastasis to the lungs was made. Patient was started on chemotherapy, with platinum, doxorubicin, and sorafenib with significant improvement of ascites, cachexia, hypoglycemia, and HSM. The patient is awaiting results of restaging and eligibility for liver transplant.

**Conclusion:**

HCC in pediatrics is a very rare diagnosis. There was 4 weeks of delay between the initial presentation seen by PCP and definitive diagnosis. The case highlights the challenge of PCP not keeping cancer in their differential of abdominal distension in pediatric age because of its rarity, and rather attributing symptoms and even physical findings to constipation. In this case, this occurred even at the subspecialist levels (GI and oncology).

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Poster # 546

**ATYPICAL PRESENTATION OF PEDIATRIC MELANOMA IS ASSOCIATED WITH DIAGNOSTIC DELAYS AND ADVANCED STAGE**

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**Background:**

Melanoma is the leading cause of skin cancer in the pediatric population, but accounts for <1% of all new melanoma diagnoses in the US. Melanoma prognosis is correlated with stage at diagnosis in all age groups. Early detection is therefore of critical importance. However, conventional ABCDE (Asymmetry, Border irregularity, Color variegation, Diameter > 6 mm and Evolution) clinical detection criteria for identifying melanoma are less useful in pediatric patients. A low index of suspicion in this age group, and atypical presentation often leads to diagnostic delays and suboptimal outcomes.

**Objectives:**

Describe the clinical presentation and its association with time to diagnosis in a series of patients with pediatric melanoma over a 5-year period at one tertiary care academic institution.

**Design/Method:**

Case series

**Results:**

We describe twelve cases of pediatric cutaneous melanoma observed at the University of Pittsburgh Medical Center in patients aged 19 months to 22 years at diagnosis (median, 7.5 years; mean, 10.6 years). Atypical melanocytic neoplasms lacking overt melanoma diagnosis were excluded. Skin lesions meeting conventional ABCDE detection criteria were present in 3 of 12 patients and all were biopsied within 2 months of lesion recognition. Stage I superficial spreading melanoma was present in 2/3 of these patients, while 1/3 showed stage IIIA Spitzoid melanoma. Seven of 12 patients presented initially with a pink, papular, or amelanotic lesion with 5 months being the shortest time from recognition to biopsy. Of these 7 patients, 5 had stage III disease, two had IIIC disease and both were under the care of pediatric providers for 7 and 15 months, respectively. These patients were treated for alternative diagnoses (warts and molluscum). Two patients did not have available descriptions of their primary lesion on chart review; one presented with stage IV metastatic disease after prior diagnosis of atypical Spitz nevus 3 years prior and ultimately succumbed to her disease. The other patient was initially diagnosed with stage IIIB Spitzoid melanoma and experienced extranodal recurrence of disease.

**Conclusion:**

Conventional ABCDE cutaneous melanoma detection criteria are often insufficient to identify pediatric melanoma. Atypical appearance of pediatric melanoma (often amelanotic, pink papules) and Spitzoid histology are common and not protective against advanced disease or melanoma progression and disease mortality. Early recognition and biopsy are critical in the management of cutaneous lesions suspect of melanoma in all ages. Increased awareness and education for providers is important to prevent diagnostic delays and ultimately to improve outcomes of pediatric melanoma.

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Poster # 547

**NEW ONSET SEIZURE AS PRESENTATION OF PRIMARY CENTRAL NERVOUS SYSTEM MELANOMA IN 17-YEAR-OLD MALE**

**Alexandra Rodriguez, Viviava Vidal-Anaya, Maria Echevarria-Escudero**

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**Background:**

Pediatric melanoma accounts for 1–4% of all melanoma cases and 1–3% of all pediatric malignancies with brain metastases causing significant morbidity and mortality. Primary central nervous system (CNS) melanomas are even rarer and constitute about 1% of all cases of melanomas and 0.07% of all brain tumors. These lesions originate from the melanocytes within the leptomeninges and are classified as meningeal melanocytosis, meningeal melanocytoma, meningeal melanomatosis, and meningeal melanoma.

**Objectives:**

Describe a case of pediatric primary CNS melanoma after new onset seizures in Puerto Rico.



**Design/Method:**

Case Report

**Results:**

A 17-year-old Hispanic male with past medical history of premature birth, hypotonia, unspecified metabolic disorder, esophagitis, scoliosis, bronchial asthma, and absence seizures since 4 years-old, presented with new onset tonic-clonic seizures. Physical examination remarkable for lower back 1 cm regularly pigmented plaque and few macular pigmented lesions on trunk and extremities and no neurologic deficit. Brain imaging remarkable for an extra-axial mass along the upper convexity of the right parafalcine region of the right frontal lobe demonstrating T1 hyperintensity and contrast enhancement with susceptibility artifact, measuring approximately 2.6 cm anteroposterior by 1.9 cm transverse by 3.0 cm craniocaudal. Cytotoxic analysis of cerebrospinal fluid (CSF) negative for malignant cells. Patient underwent right medial frontal craniotomy with gross mass resection. Tumor pathology showed malignant melanoma with positive S-100, HMB45, and Melan A markers and K167 positive in up to 10% of neoplastic cells. BRAF V600E mutation negative. Further imaging showed no evidence of metastatic disease to the spine or spinal cord and no residual tumor. Ophthalmology evaluation was negative for retinal lesions. Skin pathology negative for malignancy. Evaluation completed with Bone scan and PET/CT, both negative. Patient was diagnosed with primary CNS malignant melanoma. Patient completed five sessions of radiosurgery and was started in adjuvant chemotherapy with pembrolizumab. Cytotoxic CSF analysis after initial treatment was positive for melanoma for which patient was started on monoclonal antibodies, Nivolumab and Ipilimumab. One year after diagnosis, imaging shows no evidence of residual or recurrent disease.

**Conclusion:**

To our knowledge, this is the first reported case of primary CNS melanoma in a pediatric patient in Puerto Rico. Primary CNS melanoma is a rare diagnosis and current standard treatment includes surgical resection and radiotherapy. There are various treatment options but further investigation regarding efficacy for the pediatric population is needed.

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Poster # 548

**CONGENITAL MELANOMA WITH DISEASE-FREE SURVIVAL: CLINICAL REPORT AND REVIEW OF THE LITERATURE**

**Laura Moynihan, Rebecca MacDonnel-Yilmaz, Julie Monteagudo, Sonja Chen, Wen-I Chang, Francois Luks, Thomas Renaud**

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**Background:**

Worldwide, melanoma occurs in 3/100,000 individuals. Approximately 0.3-0.4% are pre-pubertal children and, of these, 10% are under the age of ten. Congenital melanoma, in which the disease is recognized at birth, is exceedingly rare. To our knowledge, fewer than 35 cases of congenital melanoma diagnosed at birth have ever been reported.

**Objectives:**

To share our institution's experience with a case of this exceedingly rare disease and to perform a comprehensive review of previously documented cases with close attention to the historical incidence and outcomes related to this disease.

**Design/Method:**

Review of this patient and literature review of all English language publications describing congenital melanoma. All abstracts were reviewed as well as full text articles where available.

**Results:**

A full-term baby girl presented at birth with a darkly-pigmented lesion in the left temporal region measuring 3 cm in diameter, with a 0.5 cm satellite lesion. Whole-body imaging demonstrated abutment without invasion of the orbital periosteum, no intracranial or ocular involvement, and no additional lesions. Biopsy on day 1 showed an atypical melanocytic neoplasm favored to be congenital melanoma. Next-generation DNA sequencing revealed copy number gain of Chromosome 7q (BRAF, MET, SMO), which has been reported in cutaneous melanomas, and copy number loss of TP53, which is commonly identified in malignancies. Both lesions were resected with negative margins and a complex closure of the resection site was carried out using Integra® dermal template. No systemic therapy was administered. Post-operatively, a mild cranial nerve VII palsy was noted, which subsequently resolved. Two years and five months post-diagnosis the patient continues to grow and develop appropriately with no signs of recurrence on surveillance imaging. The patient's mother was evaluated for disease given concern for transplacental spread; no disease was identified and she remains healthy.

The literature review identified forty published accounts chronicling thirty-two cases described as congenital melanoma. Clinical features at diagnosis, pathology, treatment, and outcome were extracted. Localized disease at time of diagnosis generally conferred more favorable prognoses. In articles that did specify histologic subtype, those with animal-type tended to have better outcomes.

**Conclusion:**

Congenital melanoma is a rare disorder recognized for its variable presentation and prognosis. Recent differentiation between melanoma subtypes suggests a wide spectrum of pathological characteristics previously grouped as a single entity. As pathology techniques and technology evolve, a more sophisticated classification system may be established to better inform prognostication of this disease.

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Poster # 549

**MYCN-AMPLIFIED NEUROBLASTOMA WITH VASOACTIVE INTESTINAL PEPTIDE SYNDROME AND BRAF V600E MUTATION**

**Sanam Shahid, Brian Kushner, Shakeel Modak, Ellen Basu, Elyssa Rubin, Stephen Roberts**

**Background:**

Neuroblastoma, the most common pediatric extracranial solid tumor, occasionally produces vasoactive intestinal peptide (VIP) resulting in secretory diarrhea (VIP-D). Patients with this paraneoplastic phenomenon usually have low-risk localized disease; resection is typically curative of the neoplasm and the VIP-D. Rarely, patients with metastatic high-risk neuroblastoma (HR-NB) develop VIP-D during induction chemotherapy, which is hypothesized to induce differentiation and VIP expression. Management is a major challenge because of the VIP-D in the setting of strongly myelosuppressive chemotherapy.

**Objectives:**

To report on two HR-NB patients who developed VIP-D during induction.

**Design/Method:**

With IRB approval, clinical and genomic information on two patients with VIP-secreting HR-NB treated at Memorial Sloan Kettering Cancer Center was retrospectively analyzed. Tumor sequencing was performed by CLIA-certified platforms: either MSK-IMPACT or Foundation One.

**Results:**

Two females with MYCN-amplified HR-NB (abdominal primary with metastases to bones, bone marrow, and liver) acutely developed massive VIP-D after two cycles of induction chemotherapy (cyclophosphamide and topotecan as per ANBL0532). Both patients had a somatic BRAF V600E mutation. In patient #1 (age 19 months at diagnosis), severe VIP-D persisted despite chemotherapy, octreotide therapy, and tumor resection. However, diarrhea and serum VIP levels decreased within days after starting dabrafenib (BRAF inhibitor). Four weeks later, the patient relapsed in brain with BRAF wild-type neuroblastoma. Dabrafenib was stopped and diarrhea recurred. Trametinib (MEK inhibitor) was added and dabrafenib restarted. Although the diarrhea improved, the neuroblastoma rapidly progressed leading to death 13 months post-diagnosis. Patient #2 (age 11 months at diagnosis) had prompt resolution of diarrhea and decrease in serum VIP levels after starting dabrafenib and trametinib with induction cycle five. These agents were discontinued after six cycles of post-induction chemo-immunotherapy without return of diarrhea or increased VIP levels. Subsequent therapy included anti-GD2 antibody and anti-neuroblastoma vaccine. She remains progression-free 27 months post-diagnosis. At the time of primary tumor resection, metastatic sites (liver and lymph nodes) showed the BRAF mutation, but the adrenal neuroblastoma that was previously biopsied and BRAF-positive no longer had the BRAF mutation.

**Conclusion:**

HR-NB patients who develop VIP-D during induction chemotherapy may have somatic BRAF V600 mutations. BRAF inhibitors lead to rapid improvement in symptoms and facilitate continuation of anti-neuroblastoma therapy. Both patients demonstrated tumor heterogeneity, suggesting that combination therapy with BRAF and MEK inhibitors is warranted. Tumor sequencing should be performed in all patients with HR-NB, especially those with VIP-D since

timely treatment with appropriate inhibitors can contribute to a favorable outcome in these rare patients.

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Poster # 550

## **PERSISTENT HARLEQUIN SYNDROME FOLLOWING MICROWAVE ABLATION IN A CHILD WITH PARASPINAL NEUROBLASTOMA.**

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### **Background:**

Harlequin Syndrome is a rare neurological condition characterized by unilateral flushing of the face and/or upper chest. The specific mechanism is unclear, but the majority of cases are believed to be a result of contralateral lesions along the sympathetic chain. Though Harlequin Syndrome does not affect long term survival, quality of life may be negatively impacted by the persistent neurological condition. In addition to reporting a rare case report, we hope to increase awareness of the psychological suffering that results from the symptoms associated with Harlequin Syndrome.

### **Objectives:**

We describe a case of Harlequin Syndrome associated with microwave ablation in the treatment of a child with a symptomatic paraspinal mass.

### **Design/Method:**

We conducted a literature search on PubMed and Google Scholar using the keywords and phrases, “harlequin syndrome,” “paraspinal mass,” and “pediatric.”

### **Results:**

There are six reported cases of pediatric patients with Harlequin syndrome associated with iatrogenic treatment of a paraspinal mass. All six cases presented after surgical resection of a mass in the cervical neck or thoracic paraspinal region.

Case report: We describe a 16-month-old female with NCMY non amplified, intermediate risk neuroblastoma of the posterior mediastinal who failed induction following Children’s Oncology Group (COG) ANBL1231 protocol, INRG stage “L2” with 4 cycles of chemotherapy (carboplatinin, cyclophosphamide, doxorubicin, Etoposide). An MRI showed an increase in the size of the mass with further encroachment of the cervical spinal cord and a metaiodobenzylguanidine (MIGB) scan had increased uptake. A biopsy of the mass showed that the neuroblastoma had differentiated into a ganglioneuroblastoma. At our multidisciplinary tumor board, discussion with neurosurgery and pediatric surgery concluded that a resection so close to the T6-T7 sympathetic region would be very risky. Instead, microwave ablation therapy was offered after informed consent. The patient was 3 years of age at this time. CT guided microwave ablation at the left T3-T6 region was performed by interventional radiology and was well tolerated. Immediately following ablation therapy, symptoms characteristic of Harlequin

Syndrome were contralaterally manifested in the patient: unilateral flushing and redness of the face. The patient remains in clinical remission after 4 years, but the Harlequinism has not resolved. However the parents and child report psychological harm associated with teasing.

**Conclusion:**

This case describing the development of persistent Harlequin Syndrome following microwave ablation therapy to a paraspinal mass, in an effort to avoid laminectomy, emphasizes the potential risks.

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Poster # 551

**SUCCESSFUL TREATMENT OF HIGH RISK NEUROBLASTOMA WITHOUT AUTOLOGOUS STEM CELL TRANSPLANT**

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**Background:**

Neuroblastoma is the most common extracranial malignancy in childhood, of which high-risk tumors are considered challenging and have suboptimal outcome. Survival depends on factors as age, stage and histology. The standard of care for these tumors uses a multimodal approach with chemotherapy, surgery, radiation, myeloablative therapy with autologous stem cell transplant (ASCT) followed by immunotherapy and isotretinoin. We present a case with a different approach to treatment.

**Objectives:**

Expressing the importance of tailoring therapy based on individualized assessment of risk factors in patients with high risk neuroblastoma.

**Design/Method:**

Case report with literature review.

**Results:**

Thirteen-month-old female presented with increasing lethargy, vomiting and anuria. Physical exam concerning for irritable child with facial edema and left sided hard abdominal mass. Initial assessment showed acute renal failure with creatinine 5.8mg/dl, BUN 61 mg/dl, hyperkalemia (7.5mmol/L), hyperphosphatemia (8.4mg/dl). CT scan revealed a bulky retroperitoneal adenopathy extending caudally into the pelvis with bilateral ureteric obstruction and significant bilateral hydronephrosis. Emergent placement of nephrostomy tubes was done to help relieve the obstruction and replaced later by ureteral stents. Biopsy confirmed the diagnosis of neuroblastoma. She was classified as INSS stage 4 disease with distant metastasis into the bone marrow, pelvic bone, right femur, right humerus, right clavicle and right retroorbital bones. Despite having favorable features including age, MYCN non amplified and DNA Index (DI) more than 1, our patient was determined to be high risk per Children's Oncology Group (COG)

assignment due to lack of Shimada histology. Patient received a regimen of chemotherapy with combinations of cyclophosphamide, topotecan, doxorubicin, vincristine, cisplatin, and etoposide. Patient underwent surgical resection, removing 80% tumor mass, followed by radiation therapy of 21Gy, dinutuximab, with interleukin-2/GM-CSF and isotretinoin. Elected not to treat with ASCT. Patient continues to be in remission 3 years post therapy.

**Conclusion:**

Children with neuroblastoma have widely different outcomes, with cure rate of >90% in patients with low risk disease but <50% for high risk disease. A previous trial showed similar overall survival between therapy with ASCT and those without. Our case proposes that ASCT may not be needed to improve outcome when immunotherapy and isotretinoin are used for consolidation after conventional chemotherapy; especially with presence of more favorable features such as younger age, nonamplified MYC and negative minimal residual disease (MRD).

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Poster # 552

**LONG TERM SURVIVAL IN PEDIATRIC RENAL CELL CARCINOMA DESPITE MULTIPLE RELAPSES: A CASE STUDY**

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**Background:**

Although common in adults, renal cell carcinoma (RCC) is extremely rare in pediatric populations, comprising less than 5% of malignant renal tumors. Literature on the topic is scarce, and there currently is no standard protocol for the treatment of pediatric RCC. In this study, we present a patient with pediatric RCC who experienced multiple relapses of the disease, and outline the various forms of therapy that were implemented to treat the patient's condition and to achieve remission.

**Objectives:**

To increase clinicians' knowledge of treatment approaches that have shown positive results for this rare pediatric neoplasm, and to advocate for the development of a collaborative treatment protocol.

**Design/Method:**

A 6 year old male presented in 2006 with a chief complaint of 1 week of painless hematuria, and was found to have a renal mass by abdominal examination. He was diagnosed with type II papillary RCC based on pathological examination of tissue following radical nephroureterectomy and regional lymph node excision. Over the next 7 years the patient had several regional and distant metastases of the disease, which required multiple approaches including a right pneumonectomy, stereotactic spinal radiosurgery, external beam radiotherapy, and targeted chemotherapy with Sunitinib.

**Results:**

Despite several relapses between 2007 and 2013, the patient achieved a state of complete remission, and has not shown any evidence of metastasis or active disease in the last six years, with the most recent follow up being in 2019. As a result of the right pneumonectomy, he developed displacement of his heart into the right postero-lateral thorax. However, he has not experienced any cardiovascular complications from this, and his quality of life has not been affected.

**Conclusion:**

Renal cell carcinoma is an extremely rare malignancy in pediatric populations, and research on it is sparse. Studies for the development of appropriate treatment protocols are being explored, however, nothing concrete exists currently. The patient in our case study portrays the success of an individualized approach, yielding extended disease-free survival despite multiple relapses and calls for attention to the possibility of long-term remission despite regional and distant metastatic disease developing over the course of several years.

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Poster # 553

**FAMILIAL WILMS TUMOR SECONDARY TO GERMLINE REST MUTATION**

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**Background:**

It is estimated that 1-2% of patients who are diagnosed with Wilms Tumor (WT) will have a documented genetic predisposition. Abnormalities in genes WT1, GPC3, and DIS3L2, along with Fanconi anemia genes, and chromosome 11p15 defects have been associated with increased risk of WT. More recently, variants in REST (which encodes RE1-silencing transcription factor) have been recognized in patients with WT.

**Objectives:**

To report a novel familial variant (c.666del p.Y223T) in the REST gene found in a patient with WT and his family.

**Design/Method:**

Case Report

**Results:**

A 3-year-old male presented with abdominal pain and distention, and was diagnosed with Stage III favorable histology WT. Family history revealed multiple family members with WT including the patient's father, paternal uncle, and paternal second cousin once removed. Testing of our patient and his second cousin once removed revealed identical germline variants in the REST gene (c.666del p.Y223T). There are 12 direct family members who have not had WT, including 5 children under 10 years of age. Some family members have undergone genetic testing for this REST variant, which is currently pending. Our patient is undergoing standard of

care treatment, with no evidence of disease on his mid-therapy imaging. Once genetic testing results returns, this report will be broadened with an understanding of inheritance and WT penetrance within affected families.

**Conclusion:**

Our patient and his family now represent the largest family with a unique REST variant. This particular variant has not to our knowledge been previously reported. REST is thought to act as a tumor-suppressor gene, similar to many other known genes that are known to predispose to pediatric cancers. One series identified REST variants, primarily clustered in the DNA-binding domain, in 4 families with multiple patients affected by WT and 9 others without documented familial disease<sup>1</sup>. The clinical information for these families is sparse, posing a challenge to clinicians on recommendations for screening. An autosomal dominant inheritance pattern has been proposed for REST variants, however determination of the penetrance is still ongoing<sup>2</sup>. Patients with a family history of Wilms tumor should undergo testing for genes associated with known familial WT, which should include the REST gene.

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Poster # 554

**GENE NEGATIVE ATYPICAL HUS IN A PATIENT WITH METASTATIC WILMS' TUMOR**

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**Background:**

Atypical hemolytic uremic syndrome (aHUS) is a severe form of systemic thrombotic microangiopathy (TMA) caused by inappropriate activation of the complement system resulting in hemolytic anemia, thrombocytopenia and renal injury. Genetic mutations involving the complement cascade have been identified in approximately 70 percent of aHUS cases. Drugs have been implicated in the development of TMA including chemotherapy agents gemcitabine and mitomycin C in adults.

**Objectives:**

We describe the case of a 6 year old female with metastatic Wilms' tumor who developed aHUS during treatment as evidenced by serological markers and renal biopsy.

**Design/Method:**

She was initially diagnosed with metastatic favorable histology Wilms' tumor and underwent radical nephrectomy. She received vincristine, doxorubicin, and dactinomycin with abdominal radiation due to local tumor rupture. Her lung nodule persisted and was resected followed by lung radiation and upstaging of her chemotherapy to Regimen M (dactinomycin, cyclophosphamide, etoposide, doxorubicin, vincristine). Subsequently she developed hypertension, hematuria and renal dysfunction. Serum creatinine rose six fold above her baseline with elevated lactate dehydrogenase (LDH), undetectable haptoglobin and thrombocytopenia. Renal biopsy showed TMA with positive soluble membrane attack complex (MAC) consistent



with aHUS. Genetic testing revealed no disease associated mutations. She was initiated on anti-complement C5 monoclonal antibody eculizumab and then increased to 600 mg weekly after poor response to standard dosing. Due to renal dysfunction etoposide dosing was reduced by 25%. Vincristine was eliminated as a possible contributing agent. Her course was complicated by hypertensive urgency, severe hypervolemia with ascites, pleural/pericardial effusions and ocular lesions. She remained on the higher dose of weekly 600 mg eculizumab with stabilization of creatinine, LDH and haptoglobin until chemotherapy completion.

**Results:**

Eculizumab frequency and dosing has been slowly weaned with continued improvement in aHUS. Now nine months post completion of chemotherapy she receives 300 mg eculizumab every 4 weeks with anticipation of discontinuation soon.

**Conclusion:**

This case illustrates gene test negative aHUS in a patient receiving chemotherapy. Eculizumab use allowed her to complete a modified chemotherapy regimen with improvement in her aHUS and continued tumor remission. There have been reports of successful treatment of drug induced aHUS in adults, however nothing has been reported in children. Although the causative agent was not directly identified, aHUS developed once the number of chemotherapeutic agents used were increased. Anti-neoplastic antibiotic mitomycin c has been linked to aHUS development. Our patient received the similar medication dactinomycin as well as anthracycline doxorubicin which may have contributed to aHUS development.

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Poster # 555

**THROMBOTIC MICROANGIOPATHY SECONDARY TO VINCRISTINE IN A PATIENT WITH WILMS TUMOR: A CASE REPORT**

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**Background:**

Thrombotic microangiopathies (TMA) are disease processes that result in small-vessel platelet microthrombi with clinical features of microangiopathic hemolytic anemia, acute kidney injury, and thrombocytopenia. There are several pathologies, including drug induced TMA (DITMA), an acquired condition that occurs after exposure to a medication which creates drug-dependent antibodies resulting in microangiopathic changes, causing immune and non-immune mediated pathology. Although chemotherapy drugs are a well-known cause of DITMA, it is rarely seen secondary to vincristine therapy in Wilms Tumor.

**Objectives:**

Demonstrate the rare finding of TMA in a pediatric patient with Wilms tumor likely secondary to vincristine treatment.

**Design/Method:**

Chart review.

**Results:**

Patient is a 3-year-old female with Wilms tumor who, after 2 months of chemotherapy, presented to the emergency department with febrile neutropenia and was found to be hypertensive to 194/109. Since her hypertension did not subside after pain control, she was treated with amlodipine and isradapine. Further evaluation included TSH, cortisol, renin, aldosterone, ANA, ANCA, Anti-DNAse B ab, ASO ab, C3 & C4 complement ( BK virus, SHIGA toxin, and plasma metanephrines, all of which was negative except for mild elevation of C3 and C4.

She subsequently developed gross hematuria, and her creatinine increased from 0.3 to 0.9 mg/dl. Urinalysis showed greater than 300 RBCs, protein greater than 500, and granular casts. Despite additional anti-hypertensive, fluid restriction, and sodium restriction patient continued to be hypertensive. A renal biopsy was obtained due to concern for a glomerular pathology, which revealed a diagnosis of thrombotic microangiopathy (TMA). Additional laboratory results supporting TMA included platelet transfusion refractory thrombocytopenia, DAT positive with anti-IgG positive, LDH 1,004, and mild elevation SC5b-9. Since thrombotic thrombocytopenic purpura and hemolytic uremic syndrome work-ups were negative and C3/C4 only slightly elevated, DITMA became the favored causative etiology.

Patient was treated with plasmapheresis for 5 days, which provided improvement of fluid overload but without improvement of proteinuria or blood pressure. With persistent hypertension requiring three medications and the slightly elevated complement level, eculizumab was started. She has had gradual improvement in her renal function and proteinuria, and her hypertension is under better control. A genetic panel for atypical HUS is pending.

**Conclusion:**

This case report highlights TMA as a rare sequelae of treatment with vincristine in a patient with Wilms tumor.

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Poster # 556

**EVALUATION OF GAIT ABNORMALITIES IN PATIENTS WITH A HISTORY OF RETINOBLASTOMA**

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**Background:**

Retinoblastoma (Rb) is the most common primary ocular malignancy of childhood, with a reported incidence of approximately 1 in 15,000. Rb can be inherited or develop insidiously and can be fatal if untreated. Due to advances in recognition and treatment, current survival rate is >95%.

The incidence of metastatic Rb is rare in developed countries, occurring in about 5% of cases.

This can make recognition and diagnosis of these cases challenging. The treatment outlook for patients with metastatic Rb is less promising than that of primary malignancy and varies depending on the extent of disease dissemination. Current studies estimate survival rates of 80-90% for patients with metastatic disease without central nervous system (CNS) involvement, but that falls to just 8% if the CNS is afflicted.

**Objectives:**

To highlight the need for physicians to thoroughly evaluate gait abnormalities in patients with a history of Rb.

**Design/Method:**

Case reports and literature review.

**Results:**

Case #1: Six-year-old female with a history of unilateral Rb that was ultimately treated with enucleation followed by chemotherapy. She presented to her primary care physician seven weeks after completing treatment because her mother noticed she had begun to limp a few days earlier. Clinical exam was unremarkable, so no further evaluation was recommended. Symptoms progressed to include intermittent fevers and increasing low back pain. Two months after her limp began a diagnosis of metastatic Rb with dissemination to bone was established.

Case #2: Fifteen-year-old male with a history of bilateral Rb diagnosed and treated in infancy. He presented to an Emergency Department complaining of intense thigh and knee pain that was preventing him from playing sports. X-rays of the thigh and knee were reported as normal. He was diagnosed with patellofemoral syndrome and no further evaluation was recommended. Symptoms progressed to include intermittent fevers and worsening leg pain. Five months after the initial complaint, a diagnosis of metastatic Rb with dissemination to bone was established.

**Conclusion:**

The prognosis of metastatic retinoblastoma correlates highly with the extent of disease dissemination. Therefore, early recognition and initiation of treatment is essential to enhance patient survival. Episodes of non-specific bone pain were reported as initial complaints in these two cases. This provoked gait abnormalities either reported by the patients or their families. These findings indicate that an insidious onset of gait abnormalities in patients with a history of Rb may be an early indicator of metastatic disease and warrants prompt evaluation.

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Poster # 557

**RADIATION INDUCED HEMORRHAGIC GASTRITIS TREATMENT IN PEDIATRIC SOLID TUMOR PATIENT**

**Sarah Koblick, George Zacur, Rama Jasty Rao**

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**Background:**

Radiation induced hemorrhagic gastritis is a rare cause of severe life-threatening gastrointestinal (GI) bleed. A few cases have been described in adult patients receiving abdominal radiation. The onset of hemorrhagic gastritis after radiation is variable, ranging from 2 to 8 months post-radiation therapy. Multiple treatment modalities have been described, including use of proton-pump inhibitors, oral steroids and thermal local endoscopic therapy. There is currently no standard treatment regimen or length of treatment described in the literature. There is also limited information available regarding when radiation induced hemorrhagic GI bleeding will resolve.

**Objectives:**

We performed a retrospective chart review of a 10-year-old girl with stage IV metastatic alveolar rhabdomyosarcoma, who developed multiple GI bleeds after abdominal radiation. We reviewed the patients' presentation, treatment courses and outcomes. We also performed a review of the literature available regarding presentation and treatment of radiation induced hemorrhagic gastritis.

**Design/Method:**

Case report

**Results:**

10 year old female with stage IV metastatic alveolar rhabdomyosarcoma, with primary disease located proximal to head of the pancreas, with extensive metastases to the omentum, subdiaphragmatic region, and right foot plantar muscle, requiring whole abdomen radiation. Induction chemotherapy initiated with vincristine, dactinomycin and high dose cyclophosphamide. Local control achieved with whole abdomen radiation with boost to primary abdominal disease. Approximately 8 weeks after completion of radiation, patient presented with melena and hematemesis with profound anemia and thrombocytopenia. EGD performed, biopsies revealing congested, eroded friable gastric and pyloric mucosa with contact bleeding. Initial management with Carafate and PPI and support with blood products. Argon plasma coagulation (APC) used during endoscopy to achieve hemostasis. Patient continued to have life threatening GI bleeds despite initial therapy, requiring ICU stay. Therapy with oral steroids and aminocaproic acid (amicar) was initiated. After prolonged course with steroid wean and amicar, patient is asymptomatic and has resumed chemotherapy. She remains on PPI therapy, with close follow up with GI providers. Her oncologic disease remains in complete remission.

**Conclusion:**

Radiation induced hemorrhagic gastritis is a rare complication of whole abdomen radiation and is often difficult to manage. It should be considered as a potential cause of GI bleeding in patients receiving abdominal radiation therapy. More literature is needed to help with diagnosis and management of this condition. Oral steroids, antifibrinolytic therapy, such as amicar, and APC should be considered as treatment options to manage this condition.

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Poster # 558

# NOVEL FINDING IN PEDIATRIC LEIOMYOSARCOMA: EXPANDING SPECTRUM OF FGFR MUTATIONS IN CHILDHOOD CANCERS

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## **Background:**

Soft tissue sarcomas (STS) are rare in the pediatric age group, accounting for 7% of all pediatric tumors. Leiomyosarcoma, a sub-type of STS, is exceedingly rare in pediatric population. Due to the rarity of this condition, management is extrapolated from other common STS which involves surgery, chemotherapy and radiation. Chemotherapy is not very effective in management of leiomyosarcoma and molecular information may help guide targeted therapies.

## **Objectives:**

Here we describe molecular information derived from a case of pediatric head and neck leiomyosarcoma

## **Design/Method:**

Case report

## **Results:**

An 11 year Caucasian female presented with a 5 cm firm left sided, non-tender neck mass, with no constitutional symptoms. She was treated with a course of antibiotics to no avail. Surgical resection was performed which revealed a low grade leiomyosarcoma with positive microscopic margins. Her CT chest was negative for metastatic disease and PET scan showed mild FDG avidity in left side of the neck – level IIb node (likely reactive) - with no other area of PET avidity. 3months later, the PET CT was unchanged. A second surgery was attempted but still could not attain negative margin. At this time, as patient was deemed to have a G1, T1b, N0, M0 disease by AJCC guidelines. We opted for no further treatment as a third surgery seeking negative microscopic margin will be disfiguring and disabling with unclear benefit. Furthermore, radiation has unclear benefits with long-term consequences. NGS showed chromosomal re-arrangement involving FGFR1-TACC1 as well as copy number loss of MTAP, CDKN2A, and CDKN2B. This FGFR gene fusion was first described in gliomas but has since been described in many adult sarcomas such as breast, prostate, gastric, NSCLC, adenocarcinoma and colorectal carcinomas. To our knowledge this is the first description of this fusion gene in pediatric soft tissue sarcomas and pediatric leiomyosarcomas. This gene fusion predicts for sensitivity to FGFR inhibitors and potentially, in the event of recurrence remains a therapeutic option for this patient. Although, yet to be described in in vivo models, this fusion protein may also predict sensitivity to MEK inhibitors. Among other copy number losses reported in this patient, only CDKN2A has been reported previously in leiomyosarcomas.

## **Conclusion:**

Pediatric leiomyosarcoma is exceedingly rare, with limited systemic treatment options. Molecular analysis should be attempted for these rare tumors given the lack of viable treatment options. This may give us insight into tumorigenesis and potential treatment options.

## **USE OF PEGYLATED LIPOSOMAL DOXORUBICIN IN AN ADOLESCENT WITH RELAPSED METASTATIC RHABDOMYOSARCOMA**

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### **Background:**

A significant improvement in the overall survival of pediatric rhabdomyosarcoma (RMS) has been due to collaborative trials, improvement in localized control and enhanced understanding of the genomic landscape. Despite this progress, the 5-year survival of children with fusion positive, metastatic RMS remains dismal (< 10%.) A recent study by Trucco et al, had promising results in a Phase II study of pegylated liposomal doxorubicin (PLD) and Temsirolimus for recurrent sarcomas. We report our experience with single agent PLD in a patient with relapsed fusion positive RMS.

### **Objectives:**

To report the use of PLD monotherapy in an adolescent with a relapsed metastatic RMS who failed multiple therapies.

### **Design/Method:**

At age 16, she was diagnosed with a high risk (Stage 4, Grade 4) PAX3-FOXO1 fusion positive RMS of the right hand. She had biopsy proven metastatic disease in her right axillary lymph nodes and bone marrow. She was treated with VAc/VI (ARST0531) with radiation therapy to primary and axillary nodes followed by maintenance with Vinorelbine, oral Cyclophosphamide and Avastin (modified ARST0921.) Maintenance was discontinued after 3 cycles due to prolonged neutropenia, microscopic hematuria and suspicion of relapse in left axillary and inguinal nodes. She was then treated with oral Pazopanib for 10 months until she developed a painful mass in right hand, a subcutaneous mass in the right biceps and the left triceps. Treated with Levanitinib and Everolimus with resolution of the pain and mass in her hand but the other lesions continued to grow. After 5 months, she had clear progression with an increase in size of the right biceps mass to 5 cm as well as increased FDG avidity of the mass. Treated with PLD 45 mg/m<sup>2</sup>/dose every 4 weeks.

### **Results:**

During Cycle 1 of PLD, pain resolved and there was a decrease in her palpable mass by Day 16. Prior to cycle 3 the skin findings nearly resolved. PET-CT revealed residual mass but significant response to therapy. No significant adverse effects.

### **Conclusion:**

PLD is a well-tolerated drug without significant toxicity and decreased long term cardiac toxicity. Given the long-established track record of doxorubicin for newly diagnosed and recurrent RMS, the ease of administration and a favorable toxicity profile, its use in pediatric

patients with recurrent, metastatic RMS is reasonable. Especially when biologically or genomically targeted agents and agents with novel mechanisms of action are not available.

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Poster # 560

## **METASTATIC EWING SARCOMA IN A PATIENT WITH CROHN'S DISEASE TREATED WITH USTEKINUMAB**

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### **Background:**

Biologic immunosuppressive drugs such as infliximab, adalimumab, secukinumab, and ustekinumab used to treat autoimmune conditions, such as rheumatoid arthritis, psoriasis, and Crohn's disease, have been known to cause secondary malignancy. However, they have not been associated with Ewing Sarcoma.

### **Objectives:**

Describe an adolescent Crohn's disease patient treated with ustekinumab, a monoclonal antibody to interleukin-12 (IL-12) and interleukin-23 (IL-23), who developed metastatic Ewing's sarcoma.

### **Design/Method:**

A chart review was conducted on the patient that developed metastatic Ewing's sarcoma after treatment for his Crohn's disease with ustekinumab as well as a literature review regarding ustekinumab.

### **Results:**

A 17-year-old male, previously diagnosed with Crohn's disease at the age of 13, presented to the Emergency Department with pain and unilateral swelling of the left hip, groin, thigh, and knee. He was previously treated with multiple immunomodulatory agents including infliximab, adalimumab, and eventually for 17 months with ustekinumab. X-ray imaging of the left femur showed a soft tissue mass surrounding the proximal left femur with periosteal reaction and irregularity of the bony cortex. MRI showed a large aggressive mass arising from the left femur with a marrow infiltrating component extending from the femoral neck to the middle and distal thirds of the left femoral diaphysis involving 28.5 cm of the femur. Computer tomography (CT) of the lung demonstrated a 4 mm nodule in the medial right lung base and a 7 mm nodule in the medial left lung base. Final pathology of the biopsied mass was consistent with Ewing's Sarcoma with CD99+, FLI-1+, and EWSRI rearrangement. The patient was treated off study per the Children's Oncology Group AEWS1221 protocol.

### **Conclusion:**

Ustekinumab, a monoclonal antibody that targets the shared p40 subunit of IL-12 and IL-23, has demonstrated efficacy in the treatment of multiple autoimmune diseases including Crohn's disease, psoriasis, and psoriatic arthritis. Reported adverse effects of ustekinumab include headaches, arthralgias, opportunistic infections, and malignancies, such as B-cell lymphoma,

epithelioid sarcoma as well as cancer of the lung, esophagus, ovary, testis, kidney and thyroid. However, to our knowledge there are no documented cases of a patients treated with ustekinumab developing Ewing Sarcoma. There is no conclusive evidence linking the use of ustekinumab for the treatment of Crohn's disease resulting in the development of his Ewing sarcoma; nonetheless, caution and long-term surveillance for signs and symptoms of malignancies are necessary.

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Poster # 561

## **EWING'S SARCOMA PRESENTING AS SPONTANEOUS HEMOTHORAX**

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### **Background:**

Ewing's sarcoma is a bone malignancy in the primitive neuroectodermal tumor (PNET) family of tumors, which most commonly affects pediatric and young adult population. The disease most commonly affects the major long bones but is also notorious for affecting the pelvis and ribs, with the ribs representing about 10% of primary lesions. However, presentation as a spontaneous hemothorax is exceedingly rare.

### **Objectives:**

To discuss the unique case of Ewing's sarcoma presenting as right hemothorax in a pediatric patient, and thereby emphasize the importance of symptom recognition and clinical investigation in such rare presentations.

### **Design/Method:**

Case report and PubMed review of literature. Data was collected retrospectively by analyzing hospital records.

### **Results:**

A 13-year-old-male presented with acute onset dyspnea and chest pain. He had intermittent right-sided rib pain 1 week prior to presentation. History was negative for cough, fevers, lymphadenopathy, or weight loss. Physical exam revealed mild tachycardia and moderate respiratory distress with retractions; breath sounds were markedly diminished throughout the right lung fields with dullness to percussion from right subcostal margin to 2nd rib space. CBC revealed mild anemia. CXR revealed large right loculated pleural effusion. CT angiography of the chest revealed a large multiloculated right-sided pleural effusion with compression atelectasis without underlying pneumonia. Frank blood of about 600mL in volume was observed upon chest tube placement consistent with massive hemothorax. MRI of the chest showed generalized pleural thickening in the right lung involving both visceral and parietal pleura. Video Assisted Thoracic Surgery was performed after sufficient hemothorax drainage, with removal of a small mass from the 7th right hemivertebrae. Immunohistochemical staining & genetic evaluation of



the mass revealed Ewing's sarcoma. Whole body PET/CT scan confirmed malignancy of right chest wall and paratracheal region without extra-thoracic involvement. Patient was started on chemotherapy according to COG protocol starting with Vincristine, Doxorubicin and Cyclophosphamide with Mesna alternating with Ifosfamide and Etoposide. To date, he has completed cycle 6 of chemotherapy with good response. Repeat MRI showed significant improvement in pleural thickening previously noted and patient is now preparing for radiation therapy.

**Conclusion:**

Spontaneous non-traumatic hemothorax in a pediatric patient should raise suspicion of an underlying malignancy and requires a detailed investigation. After stabilization of the patient, a diligent investigation in terms of appropriate imaging and laboratory work up must be employed.

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Poster # 562

**RELAPSED METASTATIC EWING SARCOMA INITIALLY RESPONSIVE TO DINUTUXIMAB IN A PEDIATRIC PATIENT**

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**Background:**

Five-year survival for metastatic Ewing Sarcoma is only about 30 percent despite multi-drug, interval-compressed chemotherapy in addition to surgery or radiation. Immunotherapy improves the immune system's ability to fight cancer and has shown promising results for some malignancies. Dinutuximab is commonly known for its effectiveness in high risk neuroblastoma by targeting protein GD2 which is a disialoganglioside expressed on tumors of neuro-ectodermal origin. Current clinical trials are looking into Dinutuximab efficacy in other tumors, specifically sarcomas. Since some Ewing Sarcomas express GD2 and Dinutuximab has been discussed in the pediatric oncology field as a potential future clinical trial idea, we offered it to a patient at the end-of-life secondary to refractory metastatic Ewing Sarcoma with concurrent myelodysplastic syndrome.

**Objectives:**

To present a case of a patient with relapsed Ewing sarcoma who responded to therapy with Dinutuximab.

**Design/Method:**

Case Report.

**Results:**

A 15-year old male with history of widely metastatic Ewing sarcoma with the EWSR1-FLI1 fusion, with primary disease of the left kidney and adrenal gland originally underwent radical nephrectomy and was started on therapy on COG AEWS1221, on the experimental Ganitumab

arm. End of induction PET-CT showed near resolution of his widespread metastatic disease with negative bone marrow biopsies. During consolidation therapy, he developed left pulmonary and bony recurrent metastatic disease. Despite radiation therapy with Vincristine/Irinotecan/Temodar, Cyclophosphamide/Topotecan/Vincristine, Pazopanib, and Doxorubicin/Dexrazoxane/Olaratumab, he continued to have disease progression. He also developed myelodysplastic syndrome, disqualifying him from any open clinical trials. He was started on therapy per COG ANBL1221 with Temozolomide, Irinotecan, and Dinutuximab. He completed days 1-5 of cycle 1 and was discharged home in stable condition. He experienced worsening hypoxia and altered mental status on day 9. Chest x-ray showed improvement in right-sided mass effect and improved central air bronchograms suggestive of tumor response to Dinutuximab. Unfortunately, he experienced aspiration pneumonia and Citrobacter Freundii bacteremia, at which point care was de-escalated by the family to prevent further suffering.

**Conclusion:**

Some Ewing sarcoma tumors express GD2. We present a case of a patient with relapsed Ewing sarcoma whose tumor appears to have responded to Dinutuximab. While this is one patient and we did not have the ability to assess the extent or duration of response, these findings further support the need for clinical trials evaluating Dinutuximab therapy for relapsed Ewing sarcoma.

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Poster # 563

**INFANTILE FIBROSARCOMA-LIKE TUMOR DRIVEN BY NOVEL FUSION RBPMS-MET CONSOLIDATED WITH CABOZANTINIB**

**Ajay Gupta, Jennifer Belsky, Kathleen Schieffer, Kristen Leraas, Elizabeth Varga, Richard Wilson, Vincent Magrini, Elaine Mardis, Selene Koo, Catherine Cottrell, Bhuvana Setty**

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**Background:**

Infantile fibrosarcoma (IFS) is the most common non-rhabdomyosarcoma soft tissue sarcoma in infants. Histologically, the tumor has spindle cells arranged in fascicles with high mitotic activity, positive immunohistochemical staining for vimentin, and focal positivity for smooth muscle actin (SMA), desmin, S100, or CD34. IFS is thought to be nearly universally driven by gene fusions involving the NTRK family and demonstrates favorable response to TRK inhibition. Prior to the era of highly selective TRK inhibitors, a rhabdomyosarcoma-like protocol was typically used. ETV6-NTRK3 fusions account for approximately 85% of alterations with much of the remainder attributed to NTRK-variant fusions. Rarely, other genomic aberrations have been described in association with tumors identified as IFS or IFS-like (e.g. BRAF or MET fusions); however genomic characterization is expanding knowledge and treatment of these rare neoplasms. MET functions as an oncogene and, when associated with the RNA binding protein RBPMS, forms an in-frame fusion product that retains the MET kinase domain. This is associated with aberrant cell signaling pathway expression and subsequent malignancy.

**Objectives:**

To describe the utility of genomic characterization and the successful treatment combination of rhabdomyosarcoma induction followed by tyrosine kinase inhibitor (TKI) consolidation in an aggressive IFS-like tumor.

**Design/Method:**

Comprehensive genomic profiling included paired tumor/normal exome sequencing and RNA sequencing of the disease-involved specimen.

**Results:**

This patient was diagnosed at birth with a right facial mass extending over the temporal fossa and the mandible measuring 4 x 4.1 x 5.4 cm, enlarging at 1 month to 4.9 x 4.5 x 6.3 cm. Core biopsy demonstrated hypercellular fascicles of spindle cells with positivity for SMA (patchy), CD163 and negativity for S100, desmin, myogenin, and MyoD1. PET scan was negative for metastatic disease. Due to continued growth of the mass, chemotherapy was started at 2 months of age with VAC (vincristine, actinomycin, cyclophosphamide) for a duration of 10 months. Resection of a 1.1 cm right cheek remnant at 13 months of age demonstrated positive margins. Targeted RNA sequencing identified a novel RBPMS-MET fusion with confirmed absence of ETV6-NTRK3, and the patient was diagnosed with an IFS-like tumor. Due to the morbidity of additional surgery or radiation, cabozantinib, a MET-targeting TKI, was initiated. The patient tolerated cabozantinib well and has no evidence of gross disease at 20 months of age.

**Conclusion:**

We describe the successful use of a targeted agent, cabozantinib in a patient with a novel RBPMS-MET driver fusion associated with a locally aggressive congenital IFS-like tumor.

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Poster # 564

**USING ZEBRAFISH TO MODEL A RARE GERMLINE TP53 MUTATION IDENTIFIED IN A PATIENT WITH OSTEOSARCOMA**

**Amanda Lipsitt, Kunal Baxi, Jiangfei Chen, Shawn Gessay, Aaron Sugalski, Gail Tomlinson, Myron Ignatius**

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**Background:**

Germline TP53 mutations are known to lead to Li-Fraumeni syndrome (LFS) that leads to early-onset and multiple malignancies. These include adenomas, sarcomas, breast cancer as well as CNS tumors. Over 1532 germline TP53 mutations have been catalogued in the International Agency for Research on Cancer (IARC) TP53 database. The mutation TP53p153del is a rare mutation that was previously reported in a patient with this same mutation who was treated for breast cancer and later developed (EGFR) mutated non-small cell lung cancer. There are no reported cases of osteosarcoma with this variant. The commercial genetic testing lab has classified this alteration as a “variant of unknown significance” (VUS).

**Objectives:**

We identified a rare TP53 germline mutation in a patient with refractory osteosarcoma. Zebrafish provide a rare opportunity to model this TP53p153del mutation in an in vivo model. By modeling the mutation in zebrafish, tumor growth can be quantified and there are opportunities to study tumor behavior.

**Design/Method:**

Case report, literature review, genomic database search and cloning and expression of the TP53 mutation in a zebrafish model.

**Results:**

An 18 yo Hispanic female with refractory osteosarcoma was found to have a TP53 pro153del. Significant family medical history includes her mother with osteosarcoma at age 26 years who died 2 years later. After the mutation was discovered in the patient, the TP53 pro153del was cloned using overlap extension PCR and ligated to a plasmid containing the zebrafish rag2 promoter that is expressed in the endothelial cell lineages (including muscle cells). This construct was linearized using XhoI and injected into TP53-null and wildtype zebrafish. The fish are currently being monitored for tumor formation.

**Conclusion:**

TP53 p153del is a rare Li Fraumeni syndrome germline variant associated with osteosarcoma and the effect of the mutation is unknown on disease occurrence/progression. By using zebrafish as a model for this mutation it is possible to quantify rate of tumor growth and progression of disease in an in vivo. In the future, this technique may be useful in classification for its role in pathogenicity as well as predicting tumor behavior.

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Poster # 565

**EXTENDED SURVIVAL WITH MULTIPLE CYCLES OF SAMARIUM / NIVOLUMAB FOR RELAPSED OSTEOSARCOMA**

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**Background:**

Osteosarcoma (OST) is the most common primary tumor of the bone in children and young adults. The long-term survival rate with localized OST is 70-75%. However the long-term survival rate drops to 20% for a first relapse and less than 5% at 2 years for 3 or more relapses. There are no standard therapies for multiply relapsed patients. The immune system plays an important role in OST as first described more than 100 years ago. More recently select patients have benefited from interferon therapy, liposomal-muramyl-tripeptide-phosphatidylethanolamine, inhaled GM-CSF, and other immunostimulator strategies. The newest immunotherapies, checkpoint inhibitors, allow CD8(+) T-cells to overcome tumor-induced T-cell quiescence and recognize tumor antigens. These drugs are now more commonly used in combination other therapies with the hope that tumor cell injury from radiation, surgery, ablation or chemotherapy will produce immunoreactive neo-antigens that promote a robust T-cell

response, similar to the abscopal principle.

**Objectives:**

To report a case of prolonged survival in a child with multiply relapsed OST treated with 3 cycles of nivolumab and samarium-153 ethylene-diamine-tetramethylene-phosphonate.

CASE REPORT: A 13-year-old female with localized OST treated initially with methotrexate, doxorubicin, cis-platinum, ifosfamide, etoposide experienced 4 relapses in: isolated bone, isolated lung, disseminated lung, disseminated lung, soft tissue and bone, at 9 months, 5 months, 4 months after surgery and systemic therapies (denosumab, gemcitabine/taxotere, zoledronic acid, bevacizumab), respectively. More than 2 years ago she was offered hospice/palliative care. At that point the family opted for a strategy of samarium every 6 months with nivolumab and gemcitabine every 4 weeks. Now 2.5 years later, she has had steady clinical and radiologic improvement (now PET/ bone scan negative), excellent QoL (she has returned to school, on no pain medication, regained normal weight, and has traveled overseas x 2) with no new lesions and dramatic decrease in alkaline-phosphatase (from over 2,000 to 100). She has had no serious side effects and maintained normal bone marrow function.

**Design/Method:**

We conducted a literature search on PubMed/Google Scholar with the keywords: “Osteosarcoma”, “Relapse”, “Immunotherapy”, “Samarium”.

**Results:**

This appears to be the only reported case of prolonged response in multiply relapses of OST with combining immunotherapy and samarium.

**Conclusion:**

We believe the combination of check point inhibitors and samarium is worthy of further investigation in select patients with OST relapse who have few other options.

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Poster # 566

**LIN28B-PDZ BINDING KINASE SIGNALING PROMOTES NEUROBLASTOMA METASTASIS**

**Julie Chen, Julie Cox, Jayabhargav Annam, Melanie Weingart, Grace Essien, Komal Rathi, Jo Lynne Rokita, Priya Khurana, Selma Cuya, Adeive Pilgrim, Daisy Li, Cara Shields, Oskar Laur, Robert Schnepf**

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**Background:**

Neuroblastoma, an aggressive cancer of the developing sympathetic nervous system, continues to cause significant morbidity and mortality, highlighting the need to identify novel therapeutic vulnerabilities. LIN28B is an RNA binding protein that plays key roles in normal development

and, when deregulated, oncogenesis; mechanistically, it blocks the processing of the let-7 family of tumor suppressors and binds mRNAs directly. We previously demonstrated that LIN28B induces neuroblastoma proliferation, in part by regulating the expression of RAN GTPase and Aurora kinase A.

**Objectives:**

Given the widespread metastases seen within neuroblastoma, we investigated whether and how LIN28B influences neuroblastoma metastasis.

**Design/Method:**

We generated GFP-luciferase expressing neuroblastoma cell line models in which LIN28B levels were manipulated, injected these models into the tail veins of NSG mice, and tracked dissemination using an IVIS Spectrum system. We used gain and loss of function approaches to manipulate transcripts of interest in neuroblastoma cells and measured effects on self-renewal, invasion, and downstream signaling. To discover LIN28B-associated pathways, we assessed clinically annotated mRNA expression datasets.

**Results:**

Mice injected with LIN28B-depleted neuroblastoma cells exhibit delayed onset of tumor metastasis, reduced tumor burden, and extended survival (103 days vs. 50 days,  $p < 0.0001$ ), compared to mice bearing neuroblastoma cells expressing control scrambled shRNA. We next demonstrated that LIN28B promotes, and let-7 opposes, self-renewal and migration, two hallmarks of metastasis. As we discovered that AURKA is a novel LIN28B target, we speculated that LIN28B might positively regulate diverse oncogenic kinases to promote metastasis. We evaluated the TARGET dataset of neuroblastoma tumors and found LIN28B mRNA expression to be robustly correlated with PBK (PDZ-binding kinase) mRNA expression (PBK;  $r = 0.67$ ;  $p = 3.2 \times 10^{-33}$ ), a kinase with roles in cell proliferation/survival, self-renewal, and metastasis that is overexpressed in multiple malignancies. We demonstrated that LIN28B directly promotes, and let-7 opposes, the expression of PBK protein, and, indeed, that PBK is a novel and direct let-7 target. Moreover, we revealed that MYCN binds to the promoter of PBK and positively regulates PBK RNA and protein expression. Finally, PBK depletion mimics the effects of LIN28B depletion, with respect to self-renewal and invasion.

**Conclusion:**

Our findings suggest that LIN28B/let-7 shapes neuroblastoma metastasis, in part through influencing PBK, a kinase not previously implicated in the pathogenesis of aggressive pediatric solid tumors. Current studies are defining whether PBK, a therapeutically tractable target for which clinically relevant inhibitors exist, represents a novel therapeutic vulnerability in metastatic neuroblastoma.

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Poster # 567

**TRK INHIBITOR FOR INFANTILE FIBROSARCOMA: A CASE REPORT**

**Marjilla Seddiq, Sarah Ramiz, Maxim Yankelevich**

**Background:**

Infantile fibrosarcoma (IFS) is the most common non-rhabdomyosarcoma soft tissue tumor with an incidence of 24.5% of all soft tissue sarcomas in the first year of life. IFS is characterized by a specific translocation t(12;15)(p13;q25) coding for ETV6-NTRK3 gene fusion. Historically, surgical resection has been the mainstay of treatment, with neoadjuvant chemotherapy used when surgical resection is not initially feasible. Challenges with treatment arise when radical surgery leads to increased morbidity, and chemotherapy alone is not curative. Recently, a specific tropomyosin receptor kinase (TRK) inhibitor, larotrectinib was approved for the treatment of cancers harboring a fusion in the neurotrophic tyrosine receptor kinase (NTRK). Here we present a case of a two month old female with a right lower leg IFS treated with larotrectinib.

**Objectives:**

Review the presentation of IFS and subsequent management with larotrectinib.

**Design/Method:**

Case Report

**Results:**

A two month old female diagnosed with right lower leg IFS with NTRK fusion. Initial magnetic resonance imaging (MRI), revealed a mass 6.6 x 3.8 x 4 cm with neurovascular bundle encasement and diffuse muscle infiltration preventing upfront radical surgery. Positron emission tomography (PET) and computed tomography (CT) done at the time which only showed FDG uptake in right lower extremity. Four cycles of vincristine and dactinomycin chemotherapy resulted in only minor tumor response without significant reduction of tumor size clinically and radiologically. Moreover, end of therapy imaging still showed persistent neurovascular bundle encasement which prevented surgical resection without causing permanent neurological damage and mutilating the limb.

Subsequently the patient was started on a NTRK inhibitor larotrectinib. Following six months of treatment, a repeat MRI showed significant (> 80%) interval decrease in size with no obvious diffusion restriction consistent with positive treatment response. Importantly, the size of the mass was significantly reduced and barely palpable clinically to the degree that an interventional radiologist could not identify any residual mass suitable for a needle biopsy to evaluate for any viable tumor/ NTRK fusion. Patient has been maintained on larotrectinib for 12 months with no significant toxicity. The patient is growing and developing appropriately and maintaining all her developmental milestones. She is ambulating well with no limitations.

**Conclusion:**

IFS is a rare soft tissue sarcoma that presents in a young age group. Previous treatment modalities resulted in mutilated extremities. This case highlights the successful treatment of IFS with a TRK inhibitor with minimal toxicity.

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## EVALUATING PEDIATRIC SOLID TUMOR METABOLISM IN-VIVO

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### **Background:**

Survival of children with high risk solid tumors, especially neuroblastoma and fusion positive sarcomas, remains poor. Advancing care in these patients is limited by a lack of biomarkers and novel therapeutic targets to personalize therapy. Cancer cells alter their metabolism, including by activating aerobic glycolysis, to promote macromolecular synthesis, growth, and survival. Since oncogenes regulate metabolism in cultured cancer cells, we hypothesize that in-vivo studies of tumor metabolism will provide insight into processes acting downstream of oncogenes and may identify onco-metabolites that are traceable as biomarkers or serve as therapeutic targets.

### **Objectives:**

1. Identify metabolic pathways in-vivo with isotope tracing and metabolomics
2. Compare metabolic phenotypes with histopathological and genetic tumor features
3. Evaluate tumor metabolism in primary, recurrent, and metastatic tumors
4. Evaluate if tumor metabolism correlates with patient outcome

### **Design/Method:**

Children identified by the oncology and surgery services who are scheduled for a biopsy or resection of extra-cranial solid tumors are eligible. Carbon labeled glucose ( $^{13}\text{C}$ -glucose) is peri-operatively infused until the tumor sample is removed. Once removed, the tumor sample is snap frozen then processed for metabolic analyses.  $^{13}\text{C}$ -glucose is a non-radioactive, labeled isotope that allows for a dynamic evaluation of glucose entry into energetic and biosynthetic pathways within tumors. Metabolomics provides snapshots of metabolites from pathways such as glycolysis, amino acid, and nucleotide metabolism.

### **Results:**

We have enrolled 28 children with a median age of 5 years and several histologies including 8 with neuroblastoma and 8 with sarcoma. One tumor was metastatic, one was recurrent, and the remainder were primary tumors. Preliminary data provides evidence that these tumors take up and utilize the labeled glucose, that there are no adverse events, and that labeling is detected in glycolytic and citric acid cycle intermediates. Interestingly, we have found that neuroblastoma tumors have higher lactate labeling than has been observed in other tumor types.

### **Conclusion:**

We have confirmed and optimized the delivery of  $^{13}\text{C}$ -glucose to children with extra-cranial solid tumors, and have identified metabolic intermediates in glycolysis and the citric acid cycle indicating that both pathways are active. We have identified a relative increase in lactate labeling in neuroblastoma and continue to enroll patients to allow further clarification of this observation.



This may suggest that lactate represents an alternate energy source for tumor growth but such hypothesis will require further validation. Continued study will also indicate if metabolic features correlate to patient outcomes.

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Poster # 569

## **CASE SERIES OF EXTRAOSSEOUS EWING SARCOMA ASSOCIATED WITH REGIONALITY AND PEDIATRIC OBESITY**

**Leighton Elliott, Robin Tanner, Michal Miller**

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### **Background:**

Ewing sarcoma (ES) is a rare malignancy, most commonly presenting as a bone tumor, histologically characterized by sheets of poorly differentiated cells with small, blue, round nuclei and scant cytoplasm. A t(11;22) rearrangement with the EWSR1 gene is 90% sensitive and 100% specific for ES. According to United States Surveillance, Epidemiology, and End Results data, incidence is 3.1 per million and 20-30% of cases present as extraosseous Ewing sarcoma (EES). There are limited data regarding risk factors for ES, however parental farming, family history of certain tumors, and congenital mesenchymal defects have been found to be potential risk factors. Hydraulic fracturing ("fracking") wells are abundant in northeast and southwest Pennsylvania and utilize known carcinogenic compounds. Five pediatric cases of EES presented to our oncology clinic within a 3-year period. Considering its rarity, further investigation was warranted into this surprisingly high incidence rate.

### **Objectives:**

The purpose of this study was to evaluate for commonalities as potential risk factors in our 5 pediatric EES cases. Clinical features, tumor characteristics, and outcomes were also evaluated.

### **Design/Method:**

Clinical data of 5 pediatric patients with EES, treated at Geisinger Medical Center between 2014 and 2017 were analyzed. Patient characteristics at the time of diagnosis was detailed.

### **Results:**

Of the 5 cases, 3 were male and all were Caucasian. Excluding one 5-year old, the average age at time of diagnosis was 15.8. BMI at time of diagnosis for 4 patients was >98 percentile. Only 2 were passively exposed to cigarette smoke. There were no associations with previously studied potential risk factors. All patients lived in rural cities abutting the Susquehanna River; 4 lived in northeast Pennsylvania (the 5th lived in a county bordering the region); and 2 lived within 10 miles of each other. Three patients lived in areas with a high density of fracking wells and 1 patient lived in the county with the highest environmental violations for fracking in the state. There were only 2 axial tumors and tumor location varied for each case; 2 were greater than 8 cm. All of the tumors were localized and did not involve bone. All patients achieved remission and survival up to the point of this writing.

**Conclusion:**

There may be a potential association between pediatric obesity and EES. Additionally, the regionality of this rare malignancy requires further research into potential environmental risk factors for developing EES.

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Poster # 601

**SURVEILLANCE IMAGING IN PEDIATRIC EPENDYMOMA**

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**Background:**

Current management of pediatric patients with ependymoma includes post-treatment surveillance imaging, performed with the rationale that early identification of asymptomatic recurrences leads to improvement in outcome. While this practice may identify tumor recurrence before symptoms develop, there is little contemporary data suggesting early detection confers improved survival.

**Objectives:**

To determine whether detection of ependymoma relapses on surveillance imaging confers a survival benefit over symptomatic detection.

**Design/Method:**

Under IRB approved protocol, patients with ependymoma who were treated in the Nemours' Children's Health System and University of Florida Proton Therapy Institute between January 2003 and October 2016 underwent chart review via the electronic medical record. Included patients were aged < 21 years and completed a treatment regimen of surgical resection, radiation therapy, and/or chemotherapy. Charts of relapsed patients were further examined to assess details of initial therapy, surveillance imaging regimen, timing of relapse, means of detection, relapsed therapy, and outcome. Median follow up of the entire cohort was 6.5 years from diagnosis and 3.5 years from relapse.

**Results:**

Ninety of 198 (45%) patients experienced relapse. Of those patients, 61 (68%) were detected with surveillance imaging while 29 (32%) were detected based on symptoms. Median time to relapse in both groups was 12 months from end of treatment. Median time since last negative image in both groups was 4 months. Following relapse, 82/90 (91%) patients underwent salvage therapy: 58/61 (95%) when detected by surveillance vs 24/29 (83%) when detected by symptoms (Odds Ratio 4.02). Five-year overall survival in the surveillance group was 67% (Confidence Interval 55-81%, Standard Error 0.1) vs 51% (CI 35-73%, SE 0.19) in the symptoms group (P=0.077). The 3-year survival from time of relapse in the surveillance group was 62% (CI 49-77%, SE 0.11) vs 55% (CI 39-76%, SE 0.17) in the symptoms group (P=0.07). Following treatment of recurrence, the 3 year progression free survival was 45% (CI 33-62%, SE 0.16) in the surveillance group vs 32% (CI 19-55%, SE 0.27) in the symptoms group (P=0.031).

**Conclusion:**

Given the current limited salvage options for children with recurrent ependymoma, the survival advantage of frequent surveillance imaging in asymptomatic patients remains ambiguous. Surveillance imaging may identify recurrences in patients when they are more amenable to salvage therapy, resulting in superior 3-year progression free survival. However, further research is necessary to define the role of surveillance imaging.

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Poster # 602

**DEVELOPMENT OF A NOVEL IMMUNOCOMPETENT MOUSE MODEL FOR DIFFUSE INTRINSIC PONTINE GLIOMA**

**Maggie Seblani, Markella Zannikou, Liliana Ilut, Oren Becher, Irina Balyasnikova**

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**Background:**

Diffuse intrinsic pontine glioma (DIPG) is a devastating brain tumor which unfortunately has retained a dismal prognosis. Immunotherapies hold promise to improve outcomes, however a lack of immunocompetent models which recreate a faithful tumor microenvironment has hindered the development of effective targeted therapies.

**Objectives:**

We hypothesize an immunocompetent mouse model can be engineered to overexpress interleukin 13 receptor alpha 2 (IL13R $\alpha$ 2), a tumor-associated antigen overexpressed by glioma cells. Our objective is to create a model recapitulating drivers of tumorigenesis within an intact immune system and tumor microenvironment to facilitate comprehensive preclinical assessment of IL13R $\alpha$ 2- targeted immunotherapeutics.

**Design/Method:**

Our novel model uses the viral vector delivery system of retroviral avian leucosis and sarcoma virus (RCAS) for in vivo gene delivery for expression of IL13R $\alpha$ 2 in proliferating progenitor cells in mouse pup brains. Transfected cells express IL13R $\alpha$ 2 and the ligand for platelet derived growth factor receptor A, PDGFB, which is overexpressed in DIPG, alongside induced p53 loss via the Cre-Lox system. Following intracranial injection of virus-generating cells, mice were monitored for clinical signs and symptoms of tumor burden.

We validated expression of PDGFB and IL13R $\alpha$ 2 transgenes in vitro and in vivo through flow cytometry and western blot analysis. Subsequently, we will further characterize tumor microenvironment through systematic evaluation of the peripheral and tumor immunological compartments using immunohistochemistry and flow cytometry for markers of innate and adaptive immune system, microglia and astrocytes.

**Results:**

We generated a construct encoding both IL13R $\alpha$ 2 and PDGFB via a self-cleaving T2A peptide in a single expression vector. The transfection of DF1 cells and expression of PDGFB and IL13R $\alpha$ 2

was confirmed via flow cytometry and western blot analysis. Side-by-side comparison of survival dynamics in mice inoculated with RCAS-PDGFB and RCAS-PDGFB+IL13R $\alpha$ 2 viruses demonstrated that co-expression of IL13R $\alpha$ 2 did not significantly affect mice survival and is consistent with previously described tumor growth dynamics for the PDGFB model. At time of application, we have initiated experiments to characterize tumor microenvironment.

**Conclusion:**

Preliminary data demonstrate establishment of tumors within and adjacent to the brainstem and expression of target transgenes. With creation and validation of a DIPG model expressing IL13R $\alpha$ 2 in mice with an intact immune system we can assess novel IL13R $\alpha$ 2-targeted immunotherapeutics including chimeric antigen receptor T-cell therapy. Preclinical findings in a model which better recapitulates the tumor microenvironment may be insightful of outcomes upon translation to clinical application as part of endeavors to improve the therapeutic landscape of this incurable tumor.

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Poster # 603

**CRANIOPHARYNGIOMA: EXPERIENCE AT A TERTIARY CARE HOSPITAL IN BANGLADESH**

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*National Institute of Neuroscience & Hospital, Dhaka, Bangladesh*

**Background:**

Craniopharyngioma is a rare tumor; incidence varies from 0.5-2 per million. It accounts for 3% to 5% of all pediatric brain tumors, with the peak age ranging between 6 and 14 years. But last two years' hospital records at National Institute of Neuroscience & Hospital (NINS&H), Dhaka showed it to be the commonest brain tumor-referred for surgery (accounting for 23% of all brain tumors). Precise incidence of this tumor in Bangladeshi children remains unknown.

**Objectives:**

To analyze pattern of presentation, treatment approach & current status of patients with Craniopharyngioma treated at NINS&H.

**Design/Method:**

This was a descriptive observational study based on hospital records from November 2017 to December 2019. Some missing data were collected over telephone from parents or legal guardians.

**Results:**

Total 35 cases attended NINS&H during the study period. Among them 24 (68.8%) were male & 11 (31.4%) were female. Mean age was 8.7 years (range 5 months to 17 years). Twenty-eight patients were treated with primary surgery, two patients refused surgery, one patient expired

while waiting for surgery, four attended only outpatient. Only one child received radiation therapy. Twenty-five patients could be reached by phone and were included in the analysis, the rest ten were lost to follow up. Mean duration of symptoms was 9.42 months (range 7 days to 4 years). Headache (19, 76%) was the most common symptom followed by visual impairment (11, 44%), vomiting (9, 36%), convulsion (6, 24%), fever (3, 12%), increased frequency of micturition (2, 8%). Regarding extent of tumor removal, it was partial (15, 42.9%), complete (8, 22.9%). Thirteen patients are still alive & on follow up, two patients are taking homeopathic treatment, ten patients died.

**Conclusion:**

Unlike other centers in the world craniopharyngioma was found to be commonest paediatric cancer at our center. Further large-scale study is necessary to see the real scenario present in Bangladesh.

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Poster # 604

**CHARACTERIZATION OF MURINE MEDULLOBLASTOMA CELL LINES FOR RESEARCH IN IMMUNO-ONCOLOGY**

**Sarah Rumler, Zarema Arbieva, Melline Fontes Noronha, Kevin Kuntsman, Mark Maienschein-Cline, M. Kelly Nicholas**

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**Background:**

Tumor cell lines are invaluable tools in cancer research. Those derived from inbred and genetically engineered (GEM) mice are essential in immuno-oncology, as strict control of genetic factors is crucial. Although immunotherapy has proven effective against a number of tumors, those of the central nervous system (CNS) have not responded to current strategies, for poorly understood reasons. Medulloblastoma (MB) is a common childhood solid tumor associated with significant post-treatment morbidity. Better tools are required to conduct immune-oncology research in MB. Although there are over sixty human-derived MB cell lines in use, no inbred or GEM-derived MB tumor cell lines are in regular use.

**Objectives:**

Identify and characterize murine MB tumor-derived cell lines to further immune-oncology (and other) research.

**Design/Method:**

We used PubMed and contacted MB researchers internationally to identify potential cell lines of interest. Once identified, we characterized the cells behavior in culture, performed routine histology and immunohistochemical studies, and have begun next generation sequencing (NGS) to determine the extent to which these cell lines resemble both human and mouse MB. RNA and DNA were extracted from fresh cells according to manufacturer protocol and quality and quantity assessed. Mouse exome sequencing was performed and post-capture libraries sequenced.

**Results:**

We identified seven lines from two laboratories. Two lines (GTML3 and GTML5) were derived from FVB/N p53-null mice carrying the N-MYC oncogene. The other five (MM1 – MM5) were derived from C57Bl6/J p53-null mice. The GTML cells grow in suspension, are small and uniformly round, expanding in clusters. The MM cells are adherent, cuboidal, extend processes and grow in monolayers. All lines express class 1 major histocompatibility antigens. Programmed death receptor ligand-1 is low to undetectable. We have performed NGS on four of these lines (GTML3, GTML5, MM1, and MM3). Analyses of these data are underway, with specific reference to: 1) the commonalities between them and human MB, especially as they relate to known or suspected MB drivers of oncogenesis and, 2) whether mutations previously unknown in MB might be identified.

**Conclusion:**

Given the promising results of immunotherapy in oncology, model systems to study the mechanisms that underlie challenges to treatment, as seen in primary tumors of the CNS, are needed. In MB research to date, even reliable murine cell lines for future research are lacking. Our data will provide the MB research community a better understanding of seven murine MB cell lines for further expansion of immune-oncology research.

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Poster # 605

**IL-13R(ALPHA)2 TARGETING AND FERRITIN HEAVY CHAIN EXPRESSION IN DIPG**

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**Background:**

Malignant gliomas overexpress the IL-13Ra2 plasma membrane receptor. This receptor expression is absent in normal brain tissue. IL-13Ra2 binds IL-13 with high affinity. IL-13Ra2 depletion enhances the IL-13-mediated JAK-STAT6 pathway. FTH1P3 is overexpressed in glioma cells with upregulation correlated to glioma cell proliferation and apoptosis. Diffuse Intrinsic Glioma (DIPG) is a universally fatal childhood cancer of the brain.

**Objectives:**

Recent development of DIPG tumor models should help accurately identify and validate therapeutic targets and small molecule inhibitors in the treatment of this deadly tumor. Early phase clinical trials exploring novel immunotherapies targeting IL-13Ra2 have demonstrated activity in this disease. SU DIPG VI cell line should demonstrate over-expression of FHC and IL-13Ra2.

**Design/Method:**

SU DIPG VI cells were treated with Anti-IL-13Ra2 antibody, fixed, and imaged to visualize IL-13Ra2 expression. SU DIPG VI and U87 lysates were compared via western blot for IL-13Ra2

and H Ferritin Heavy Chain expression. Anti-IL-13Ra2 band located at 44 kD. Anti-Ferritin Heavy Chain band located at 21 kD.

**Results:**

Confocal microscopy imaging revealed overexpression of IL-13Ra2 on SU DIPG VI cells. Confocal imaging confirmed appropriate DAPI signal along with IL-13Ra2 overexpression at 63x power. Western blot comparison of SU DIPG VI revealed higher expression of IL-13Ra2 in SU DIPG than in U87 cell lysates. Both SU DIPG VI and U87 samples overexpressed Ferritin Heavy Chain.

**Conclusion:**

IL-13Ra2 overexpression in the SU DIPG VI cell line was demonstrated via immunocytochemistry and western blot techniques. SU DIPG VI cells overexpressed Ferritin Heavy Chain as expected. Surprisingly, IL-13Ra2 was more highly expressed in SU DIPG VI cells than U87 cells in this experiment. This may have been artifact related to cell collection or storage, as IL-13Ra2 overexpression is well documented in GBM. Targeting this receptor should provide reproducible results for further DIPG targeted therapy research.

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Poster # 606

**DEFINING AND TIMING OF PALLIATIVE OPPORTUNITIES IN PEDIATRIC NEURO-ONCOLOGY**

**A. McCauley Massie, Kristen Allen, Jonathan Ebelhar, Nicholas DeGroot, Karen Wasilewski-Masker, Katharine Brock**

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**Background:**

Children with brain tumors experience relatively high morbidity and mortality due to tumor location and general prognosis. Thus, these children and their families stand to benefit from palliative care (PC), specialized supportive care aimed at alleviating suffering and improving quality of life. It is recommended to introduce palliative care support early in the disease course, however, this is often not done, and many “palliative opportunities” are missed.

**Objectives:**

To better understand palliative opportunities in pediatric neuro-oncology for future intervention and optimization of care, we aim to assess the frequency, type and timing of palliative opportunities in children who died from brain tumors.

**Design/Method:**

A single-institution retrospective review was performed on patients diagnosed with a brain tumor between 0-18 years of age who died between 01/01/2012-11/30/2017. Demographic, disease, treatment, palliative opportunity, and end-of-life data were collected. A priori, nine palliative opportunity categories were defined (disease progression; relapse; hospital admission for severe symptoms; intensive care admission; bone marrow transplant; phase 1 trial enrollment; hospice;

do-not-resuscitate status). Descriptive statistics were analyzed and palliative opportunities compared for all variables. Palliative opportunities were evaluated per patient per quartile from diagnosis to death.

**Results:**

Amongst 101 patients with a median age at death of 8 years (range 0-22), there were 781 defined palliative opportunities, and a median of 7 (IQR 6) palliative opportunities per patient. Patients were predominately male (55.4%), white (64.4%), non-Hispanic (86.1%), and Christian (87.1%). The most common diagnoses were high-grade gliomas (56.4%) and medulloblastoma/embryonal tumors (32.7%). Number and type of palliative opportunities did not vary by demographics or diagnosis. Palliative opportunities increased closer to death. Thirty-four patients received PC consultation, a median of 2.24 months before death. Likelihood of PC consultation did not differ by diagnosis (p=0.59) or total opportunities (p=0.09). PC consultation was associated with having a do-not-resuscitate order (p=0.0028). Hospice was involved for 71.3% of patients.

**Conclusion:**

Children with brain tumors incur many events warranting psychosocial or palliative support, which increase toward the end-of-life. Cumulative tracking of palliative opportunities can be used to map the course and trajectory of disease. Recognition of palliative opportunities should inform clinical care especially at the level of the primary oncologist, such that PC consultation is considered before the majority of palliative opportunities occur. Future research should examine and compare palliative opportunities across all pediatric oncology diagnosis groups. Future research should also assess strategies and interventions to optimize care through recognition of palliative opportunities and early introduction of PC.

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Poster # 607

**DECREASED RISK OF HYPOTHYROIDISM AFTER PROTON CRANIOSPINAL IRRADIATION IN MEDULLOBLASTOMA PATIENTS**

**Mehmet Okcu, Danielle Aldrich, Vince Horne, Rona Sonabend, Arnold Paulino, Anita Mahajan, Kevin Biemalowicz, Murali Chintagumpala, Austin Brown**

*Department of Pediatrics Baylor College of Medicine, Houston, Texas, United States*

**Background:**

Craniospinal radiation (CSI) often results in endocrine deficiencies in children with medulloblastoma. There is limited experience evaluating whether CSI with proton radiation (PRT) decreases the risk of pituitary and thyroid hormone deficiencies.

**Objectives:**

To compare the risk for pituitary and thyroid hormone deficiencies in patients with medulloblastoma treated with photon (XRT) or PRT.

**Design/Method:**

This is an updated analysis for 102 patients consecutively diagnosed with medulloblastoma



(n=95) or PNET (n=7) at Texas Children's Hospital between 2000 and 2016 who received CSI as part of initial therapy. All patients had baseline and yearly follow-up endocrine studies. We used univariate and multivariable proportional hazards regression analyses to calculate hazard ratios (HR) for development of hypothyroidism, adrenal insufficiency (AI) and growth hormone deficiency (GHD) including the following variables: age at RT, sex, race/ethnicity, treatment protocol, CSI dose (< vs ≥ 30 Gy), and RT modality.

**Results:**

With a mean follow up from the end of therapy of 6.28 years (4.20 years in PRT and 9.01 years in XRT), 34 (33%) patients developed hypothyroidism (median time: 2.67 years). Hypothyroidism was more common in patients treated with XRT [24/44, 54.5%] compared to patients treated with PRT [10/58, 17%), (multivariable HR=2.92, 95%CI 1.21-7.05, p<0.05). No other clinical or demographic variable was significantly associated with hypothyroidism. There was no difference for occurrence of AI or GHD between the RT modalities.

**Conclusion:**

The use of PRT for CSI in patients with medulloblastoma is associated with a decrease in the risk of hypothyroidism confirming less exposure of the thyroid gland to radiotherapy. This indirectly implies that these patients have less radiation exposure to other organs anterior to the spine including heart and the lungs. Further studies must be performed to assess whether lower radiation doses achieved with PRT can reduce the risk of late effects in the heart, lungs and other long-term effects on the thyroid gland such as thyroid malignancies.

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Poster # 608

**RESOLUTION OF EXTRANEURAL METASTATIC OSSEOUS LESIONS OF MEDULLOBLASTOMA WITH ORAL ETOPOSIDE THERAPY.**

**Upendra Mahat, Tanya Tekautz, Aimee Carlson**

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**Background:**

Medulloblastoma is the most common primary CNS tumor of childhood. The presence of leptomeningeal disease (LMD) is associated with poor prognosis. The spread of medulloblastoma beyond the neuroaxis is sparsely described in the existing literature, and is often considered a harbinger of poor outcome.

**Objectives:**

Describe the successful treatment of extraneural metastatic lesions of medulloblastoma with metronomic oral etoposide therapy.

**Design/Method:**

Case Report Presentation

**Results:**

Our patient is a 10-year-old male with WHO Grade IV medulloblastoma, of classic histology, with cervical and thoracic LMD. Patient underwent gross total resection of the tumor. Craniospinal radiation was commenced 5 weeks after the surgery due to postoperative complications. Repeat imaging with MRI of brain/spine showed marked improvement of the intracranial and spinal LMD. However, the development of new multifocal osseous enhancement of bilateral iliac bones was noted. Whole body PET was performed, which showed multifocal FDG avid sclerotic osseous lesions in the bilateral iliac bones, femurs and fibula. Biopsy from the left iliac crest confirmed the presence of metastatic medulloblastoma. Thereafter, the patient was treated with maintenance chemotherapy as per COG ACNS0332 with cisplatin, vincristine and cyclophosphamide. After receiving 2 cycles of chemotherapy, repeat MRI of brain and spine was performed, which revealed no evidence of new or recurrent lesion or LMD. However, the PET showed extensive progression of metastatic osseous lesions involving the pelvis and bilateral femur and proximal fibula with new patchy marrow lesions in the cervical, thoracic and lumbar spines. Bilateral bone marrow aspiration and biopsy did not reveal marrow involvement. At this point, further salvage treatment options including ifosfamide, cisplatin and etoposide, doxorubicin/zolindronic acid, oral metronomic etoposide, etc, as well as the option of not pursuing further therapy, were discussed with the family at length. The family decided to pursue treatment with metronomic oral etoposide. Thereafter, the patient was commenced on 28 days cycles of oral etoposide therapy at 50 mg/m<sup>2</sup>/day (21 days out of 28 days). Patient tolerated the therapy well with occasional nausea and vomiting. After 2 cycles of oral etoposide, repeat MRI brain/spine showed stable CNS disease and improvement in the metastatic bony lesions in the pelvis. Furthermore, repeat 18FDG PET performed after 4 cycles of oral etoposide therapy revealed complete resolution of hypermetabolic osseous lesions and patchy areas of marrow hypermetabolism within the pelvis, proximal femurs and fibula.

**Conclusion:**

Our case demonstrates a great response of a ‘difficult to treat metastatic cancer’ to an old conventional chemotherapeutic agent.

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Poster # 609

**CARBOPLATIN-INDUCED HEMATURIA IN A PEDIATRIC PATIENT WITH LOW-GRADE GLIOMA AND REVIEW OF LITERATURE**

**Alex Hoover, Mariko Sato**

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**Background:**

Platinum-based chemotherapeutic agents are very commonly used in pediatric oncology, primarily in treatment protocols for solid tumors and brain tumors. Cisplatin was the initial platinum analogue introduced and remains in use for many pediatric malignancies despite its broad and substantial side effect profile including significant nephrotoxicity, severe nausea, and ototoxicity. Carboplatin was developed with the goal of similar anti-tumor efficacy with a reduced degree of toxicity. Literature review suggests that in some patients, carboplatin may be toxic to the transitional epithelial cells of the urogenital tract causing hemorrhage from the renal

pelvis and ureters. If untreated, this may lead to urinary outflow obstruction and subsequent obstructive nephropathy.

**Objectives:**

We present a case of gross hematuria and hydroureteronephrosis associated with high dose carboplatin in a pediatric patient. Because of the paucity of data on this side effect in pediatric patients, we also conduct and present a review of literature.

**Design/Method:**

A 6 year old Caucasian female with history of Type 1 neurofibromatosis and seizures was diagnosed with a low grade glioma after experiencing left leg weakness and MRI showed a growing, contrast-enhancing lesion of the right globus pallidus. The patient was initiated on chemotherapy according to LGG14C03, Regimen 2B – monthly high dose carboplatin (560 mg/m<sup>2</sup>) every 28 days for 13 cycles.

After cycle 8 of therapy, the patient developed severe nausea and vomiting and was admitted locally for dehydration. She was noted to have microscopic hematuria on urinalysis at that time. After cycle 9 of therapy, the patient again developed severe nausea, vomiting and gross hematuria with clots. She was admitted and treated with IV hydration. Renal ultrasound showed newly developed bilateral hydroureteronephrosis. Platelet levels and coagulation studies were normal. Multiple cultures and viral studies were negative. Hematuria cleared spontaneously after 4 days of aggressive hydration.

**Results:**

Subsequent treatments with aggressive hydration were performed in our patient and minimized this toxicity including both nausea/vomiting and hematuria. Literature review showed rare cases of carboplatin-induced hematuria, including only one other pediatric case that occurred in a thrombocytopenic patient.

**Conclusion:**

We present a case of gross hematuria related to high-dose carboplatin, a novel side effect of this therapy in the pediatric oncology population. Providers should be aware of this rare toxicity and provide timely hydration and supportive care to prevent development of obstructive kidney injury or renal failure.

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Poster # 610

**INTRASPINAL GANGLIOGLIOMA IN A CHILD WITH ROSS SYNDROME: CASE REPORT AND LITERATURE REVIEW**

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**Background:**

Gangliogliomas are low-grade tumors comprised of both neoplastic glial and neuronal elements. In children, gangliogliomas account for 15% of intramedullary neoplasms. While gross total resection alone is associated with excellent outcomes and 90% 5-year overall survival, the indolent growth pattern of gangliogliomas may result in delayed diagnosis of a large infiltrative tumor that may not be found until symptomatic. Malignant transformation from WHO grade I to grade III can occur, making early diagnosis and treatment of these tumors imperative.

**Objectives:**

To report the case of a child with Ross Syndrome and hemihypertrophy diagnosed with an intramedullary spinal ganglioglioma harboring an NTRK fusion.

**Design/Method:**

Retrospective review of patient's medical records and review of the literature.

**Results:**

A previously healthy 9-year-old boy presented with 8 months of daily episodic, excessive right facial, scalp, axilla, and hand sweating and right larger than left pupil anisocoria. MRI of the spine demonstrated a symmetrically expansile midline intramedullary cervico-thoracic spinal cord mass extending from C5 to T3. A diagnosis of Ross Syndrome was subsequently made. A rare disorder characterized by hyperhidrosis, areflexia and tonic pupil, and left-sided hemihypertrophy. Biopsy of the tumor demonstrated a WHO grade I ganglioglioma. Immunohistochemistry was negative for BRAFV600E and H3K27M mutations. Panel-based next generation sequencing (NGS) identified a pathogenic BCR-NTRK2 gene fusion. He was treated with six courses of monthly carboplatin and vincristine and had stable disease (SD) by MRI before developing significant carboplatin hypersensitivity. He was enrolled on a clinical trial using entrectinib monotherapy. Three months later, MRI spine showed SD, but he experienced an unprovoked tibial fracture, a recently identified adverse effect associated with entrectinib. Entrectinib was discontinued, and the patient initiated therapy with larotrectinib. He has had SD for 2 months without new fractures or other adverse effects.

**Conclusion:**

Primary intraspinal medullary gangliogliomas are rare pediatric tumors that are often clinically indolent which allows them to grow significantly, before they cause symptoms that then lead to them being diagnosed. When gangliogliomas are unresectable, progressive, or symptomatic, carboplatin/vincristine is generally standard first-line therapy. Biopsy with molecular analysis may reveal targetable mutations, including BRAF aberrations and, as with this child, less commonly occurring NTRK gene fusions. Adverse effects of entrectinib may not preclude subsequent use of larotrectinib due to their different toxicity profiles.

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Poster # 611

**ROSAI DORFMAN AND CHRONIC MYELOMONOCYTIC LEUKEMIA:  
SECONDARY NEOPLASMS POST MEDULLOBLASTOMA TREATMENT**

**Dipti Kamath, Danielle Bell, Adonis Lorenzana**

**Background:**

Medulloblastoma is the most common malignant brain tumor in children. Survivors of childhood medulloblastoma experience long-term sequelae as a result of chemotherapy and radiation treatment. While learning difficulties and poor growth are the most common long term effects, secondary neoplasms are also known to occur including brain tumors such as meningiomas and high grade gliomas, thyroid cancer, basal cell carcinomas, and hematological malignancies.

**Objectives:**

We report two unusual cases of rare secondary neoplasms after medulloblastoma treatment.

**Design/Method:**

Case report and review of literature.

**Results:**

Patient 1: A 3-year-old female was diagnosed with medulloblastoma after she presented with headaches, vomiting and ataxia. MRI revealed a large posterior fossa tumor extending to the CP angle and associated hydrocephalus. She had complete resection and was treated with chemotherapy (cisplatin, cyclophosphamide, vincristine) and radiotherapy (cranial with posterior fossa boost 55.80 Gy and spinal 23.40 Gy) per the COG A9961 regimen B. Ten years after completion of treatment, she presented with progressively worsening headaches, change in mental status and lethargy. MRI revealed a temporal lobe mass, which was completely surgically resected. Pathology revealed extra nodal Rosai-Dorfman disease. Patient was followed by observation alone and has had no recurrence for over 10 years.

Patient 2: A 23-year-old female presented with intermittent headache and nausea associated with blurred vision and unintentional weight loss. MRI revealed midline cerebellar mass with central necrosis, surrounding edema, and mild hydrocephalus. Complete resection of the tumor was done. Pathology and cytogenetic studies indicated medulloblastoma; group 4 [del(11)q(21)]. She completed chemotherapy ( cisplatin, vincristine, lomustine and cyclophosphamide) and radiation per the COG protocol ACNS0331. Two years later she developed bruising and was found to have monocytosis with thrombocytopenia. Bone marrow studies were done which revealed chronic myelo-monocytic leukemia (CMML). Leukemia cytogenetics showed deletion of 7p12. Patient underwent allogeneic stem cell transplant (SCT) and is still in remission 3 years later.

**Conclusion:**

Here we present two secondary neoplasms that have never been previously reported after treatment of medulloblastoma, supporting the need for long term follow up of this patient group.

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Poster # 612

**HIGH GRADE GLIOMA WITH LYNCH SYNDROME IN A CHILD AND THE RESPONSE TO CHECK POINT INHIBITOR NIVOLUMAB**

**Maria Lopez Garcia, Melanie Suaris, Ossama Maher, Matthew Hall, Toba Niazi, Ziad Khatib**

*Nicklaus Children's Hospital, Miami, Florida, United States*

**Background:**

There is a paucity of literature describing pediatric high-grade gliomas (pHGGs) in the setting of Lynch syndrome, which have shown a favorable response to immune checkpoint blockade

**Objectives:**

We report a child diagnosed with left parietal HGG who was found to have a heterozygous germline frameshift mutation in the MLH 1 gene diagnostic of Lynch syndrome. Following total resection of the tumor and focal radiation, the patient was started on adjuvant nivolumab and bevacizumab with a durable response.

**Design/Method:**

PubMed search was done with search for terminology including “High grade glioma”, “Lynch Syndrome” and “Immunotherapy”. Relevant papers were selected for literature review

**Results:**

16-year-old female presented with worsening morning headache. MRI brain showed a left parietal cystic mass with a rim of enhancement, mild surrounding edema and mild restriction diffusion at the periphery of the lesion. She underwent craniotomy and complete resection of the tumor. The pathology showed high-grade astrocytoma grade IV, positive for GFAP and OLIG2. The tumor was negative for IDH1 and H3K27M and strongly positive p53 in greater than 90% of cells. MGMT was unmethylated. The molecular panel identified 25 somatics variants consistent with hypermutated tumor. The peripheral blood sample demonstrated heterozygous frameshift mutation in the MLH 1 gene consistent with Lynch syndrome. She received focal proton radiation (59.4 Gy) followed adjuvant therapy with Nivolumab and bevacizumab for one year with no clear radiographic evidence of recurrence.

**Conclusion:**

pHGGs with DNA repair defects may have a distinct phenotype that could be targeted by immune checkpoint blockade. Long term close monitoring of these patents is warranted to ensure durable clinical and radiographic responses.

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Poster # 613

**PATTERNS OF EXTRANEURAL METASTASES IN PEDIATRIC EPENDYMOMA:  
CASE SERIES AND REVIEW OF THE LITERATURE**

**Priya Chan, Nicholas Whipple, Arie Perry, David Solomon, Holly Zhou, Luke Linscott, John Kestle, Carol Bruggers**

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**Background:**

Ependymomas account for 10% of all malignant pediatric intracranial tumors. Standard therapy includes maximal safe surgical resection followed by involved-field radiation. Unfortunately, up to 50% of localized ependymomas recur in children. As ependymomas arise from ependymal cells lining the ventricular system, recurrences along the neuroaxis are common. Extranatural metastases are rarely reported.

**Objectives:**

To describe extraneural metastases of ependymomas in three children.

**Design/Method:**

Retrospective review of patients' medical records, imaging, pathology, and literature review.

**Results:**

A 6-year-old girl with a locally recurrent, WHO grade II supratentorial ependymoma underwent gross total resection (GTR) and involved-field photon radiation therapy for a second localized recurrence. At age 10, she developed an enlarged cervical chain lymph node which was avid on PET scan. Biopsy revealed metastatic ependymoma. Comprehensive evaluation demonstrated no CNS or other systemic metastases. Treatment included chemotherapy per ACNS0831, right cervical lymph node dissection, and involved-field photon radiation. She remains alive without disease, at four years since resection of the metastasis.

An 11-year-old boy underwent GTR of a locally recurrent supratentorial anaplastic WHO grade III, RELA fusion-positive ependymoma followed by involved-field proton re-irradiation. Four months later, he developed an isolated scalp nodule at the exit site of a subgaleal drain placed during prior resection. Pathology following nodule resection revealed WHO grade III anaplastic ependymoma, RELA fusion-positive. Before planned post-operative radiation, he developed enlarged cervical lymph nodes and multiple discrete scalp nodules. He is currently receiving palliative care, at four months following this metastasis.

A 4-year-old girl underwent GTR of a locally recurrent supratentorial WHO grade III anaplastic ependymoma, followed by proton re-irradiation. GTR was complicated by hemorrhagic stroke requiring ventriculoperitoneal (VP) shunt placement. One year later, MRI demonstrated isolated dural recurrence at the exit site of her VP shunt, distant from prior radiation fields. Following GTR, pathology revealed recurrent WHO grade III, RELA fusion-negative, anaplastic ependymoma. She died of progressive disease 18 months later.

There are rare reports of extraneural metastatic anaplastic ependymoma to bone, lung, or liver. Reports of lymph node or scalp metastases are exceedingly rare. Outcome in cases of extraneural disease is poor.

**Conclusion:**

Extranatural manifestations of ependymoma are rare. Regional seeding from prior surgical drains or shunts may play a role in metastatic spread. Extranatural metastases should be considered in children previously treated for ependymoma who develop nodal or skin findings even in the absence of CNS relapse. Salvage therapy with curative intent should be considered using a multimodal approach.

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## **DISSOCIATIVE IDENTITY DISORDER AS INITIAL PRESENTING SYMPTOM WITH FRONTAL MENINGIOMA**

**Alejandra Ramirez, Lenore Omesi, William Woolbright, Mary Ann Bonilla, Alissa Kahn, Jill Menell**

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### **Background:**

Central nervous system tumors are the second most common cancers in children and adolescents. Intracranial meningiomas are rare in children, accounting for 0.4-4.6% of all primary brain tumors, and may be more aggressive than in adults.

Meningiomas are slow-growing tumors arising from the meninges and are usually asymptomatic. Neuropsychiatric manifestations have rarely been reported. Here we present an unusual case of a patient with pre-existing psychiatric comorbidities who had a change in symptoms which were not discovered to be organic until she developed a seizure.

### **Objectives:**

To recognize atypical presentation of meningioma that may be misdiagnosed as psychiatric disorder increasing the morbidity due to delay in diagnosis

### **Design/Method:**

17 y/o female with history of congenital heart disease, depression and anxiety that developed dissociative identity disorder symptoms including switching between 17 different personalities. Shortly thereafter, she developed persistent headaches that awoke her from sleep without nausea/vomiting or changes in vision or gait, nine months prior to presentation at our hospital. Initially she was treated by an outside therapist for her psychiatric symptoms and neurologist for headaches until she developed a seizure. Head CT showed left frontal extra-axial tumor. She underwent surgery and pathology was consistent with atypical meningioma. Immediately following surgery, she had complete disappearance of her personality "alters," without resolution of her anxiety and depression.

### **Results:**

The most common symptom reported by children with a newly diagnosed brain tumor is headache. Behavioral and psychological symptoms have been reported, but there are no reports of childhood meningioma presenting with multiple personalities.

Meningiomas are often asymptomatic and, if symptomatic, symptoms are determined by mass location and time course to progression. Patients typically present with seizures or local findings like visual changes, loss of hearing or smell, mental status changes, extremity weakness or obstructive hydrocephalus. Atypical meningiomas are more locally aggressive and progress more rapidly. Despite optimal surgery, local recurrences may occur. They have poorer prognosis when compared to benign meningiomas.

Infrequently pediatric brain tumors present only with psychiatric symptoms when the mass externally compresses the frontal lobes. Patients can present with progressive changes in



personality and intellect. There is a higher incidence of atypical meningiomas in children and prolonged period between symptoms onset and diagnosis. This delay is associated with increased morbidity.

**Conclusion:**

There should be high index of suspicion for organic cause in patients presenting with atypical psychiatric symptoms.

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Poster # 615

**ANAPLASTIC OLIGODENDROGLIOMA: EXCLUSIVE TREATMENT WITH SURGICAL RESECTION**

**Melanie Suaris, Jessica Wein, Ziad Khatib, Natalie Gallegos, Ossama Maher**

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**Background:**

Oligodendrogliomas are rare intracranial tumors that account for approximately 5% of primary brain tumors in children and are divided into either grade II or III tumors, with the latter being high grade anaplastic oligodendrogliomas (AG). Due to the tumor's predilection to infiltrate the brain, AGs are typically managed with surgical resection and adjuvant radiation with or without chemotherapy.

**Objectives:**

We report a child diagnosed with AG. The patient underwent gross total resection of the tumor. Decision was made to observe with serial images.

**Design/Method:**

PubMed search was done with search for terminology including "anaplastic oligodendrogliomas in pediatrics". Relevant papers were selected for literature review.

**Results:**

Four-year-old male presented with a one-week history of staring episodes. Video electroencephalogram was abnormal with diffuse cortical dysfunction. Subsequent brain MRI showed a heterogenous partially calcified mass 3x 3 cm in the right insula and right superior temporal lobe. The lesion was hypointense on T1, hyperintense on T2 with some area of restricted diffusion and no associated pathological enhancement. He underwent a gross total resection of the lesion. Morphology and immunohistochemical findings were suggestive of AG with positive GFAP and OLIG2 stains, and negative for IDH mutant protein. Tumor genetic sequencing did not yield any pathological mutations.

The patient was maintained on seizure prophylaxis medications and was discharged home. Periodic surveillance MRI of brain did not show evidence of residual or recurrent tumor. Our patient is now 2.5 years status post resection and his most recent brain MRI continues to be negative for any recurrence of disease.

**Conclusion:**

This case contributes to the literature showing that AGs may be cured after gross total resection, thus avoiding exposure to radiation and treatment related toxicities.

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Poster # 616

**MALIGNANT GLOMUS TUMOR OF THE NECK IN A PEDIATRIC PATIENT**

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**Background:**

A paraganglioma (or glomus tumor) is an abnormal mass of mesenchymal tissue that arises from smooth muscle cells. Neoplasms that arise in these cells characteristically present in areas such as the carotid body, jugular foramen, along the vagus nerve, and the middle ear. Glomus tumors can affect individuals within any age group, but are most commonly seen in adults between the ages of 30 and 50. It is most often benign and slow growing with low mortality rates. We present the case of a 6-year-old Guatemalan boy with a malignant glomus tumor of the neck. There are only three reported cases in the literature of pediatric malignant glomus tumor of the shoulder, arm, and neck. These cases discuss chemotherapeutic treatment options in one case of metastasis, histological characteristics in a case of tumor expansion in the arm without metastasis, and complete surgical resection of glomangiosarcoma of the neck without recurrence or metastasis.

**Objectives:**

To report a case of glomus tumor in a pediatric patient that was originally diagnosed as neuroblastoma and failed chemotherapy.

**Design/Method:**

Case report

**Results:**

A 6-year-old male from Guatemala was originally diagnosed with neuroblastoma at age 3 years after initially presenting with neck pain and difficulty with neck movement. He received alternating cycles of chemotherapy including cisplatin, etoposide, ifosfamide, and doxorubicin for 2.5 years. However, his symptoms continued to progress, and when he developed right arm weakness, he immigrated to the U.S. about 1 month prior to admission to establish oncologic care. During hospitalization, computed tomography scan of the head/neck with IV contrast revealed a cervical mass with displacement, marked compression of the upper cervical spinal cord, and involvement of the right vertebral artery, confirmed with follow up magnetic resonance imaging. On Day 3, he underwent transoral biopsy of the lesion, which demonstrated tumor cells positive for smooth muscle actin (SMA) and focally for synaptophysin, insulinoma-associated protein (INSM1), and Ki67 protein. These findings were consistent with glomus tumor with atypical features. He underwent palliative resection of the mass without complications and was discharged to acute inpatient rehabilitation.

**Conclusion:**

Glomus tumors are rarely described in children, and therefore have no standard treatment course for pediatric patients. This case highlights the importance of raising one's index of suspicion for rare tumors such as malignant glomus tumors, especially in cases such as this where the tumor did not respond to initial therapy targeted towards the original diagnosis.

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Poster # 617

**BIOPSY OF PRE-CHIASMATIC OPTIC PATHWAY GLIOMA TO INFORM THERAPEUTIC DECISION MAKING**

**Michell Lozano Chinga, Carol Bruggers, Judith Warner, David Solomon, Nicholas Whipple**

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**Background:**

Optic pathway gliomas (OPG) are most commonly low-grade gliomas that account for 3-5% of pediatric brain tumors with 25% being pre-chiasmatic. Symptoms include visual loss, proptosis, and strabismus. Patients with OPG and Neurofibromatosis Type 1 (NF1) have a more favorable course. Therapeutic options include surgery, radiation, and chemotherapy. Although generally curative, surgical resection with enucleation results in complete vision loss in the affected eye. Radiation may further impair vision or cause cosmetic deformity. Approximately 80% of non-NF1 OPGs harbor BRAF aberrations, of which KIAA1549-BRAF fusion is the most common. MEK inhibitors such as trametinib have been successful at reducing tumor volume and improving vision in patients whose tumors harbor a KIAA1549-BRAF fusion and represents a new treatment option for many patients with OPG.

**Objectives:**

To describe two cases of pre-chiasmatic OPG refractory to standard of care therapies for which MEK inhibitors are a new therapeutic option.

**Design/Method:**

Review of medical records and medical literature.

**Results:**

A 2-year-old boy without any NF1 stigmata presented with unilateral proptosis and strabismus. Magnetic resonance imaging [MRI] showed a 2.6 x 1.8cm right pre-chiasmatic OPG. He was treated with 3 monthly cycles of carboplatin/vincristine complicated by pancreatitis. Needle biopsy of the tumor demonstrated a WHO grade I Pilocytic Astrocytoma with a KIAA1549-BRAF fusion detected by panel-based genomic evaluation. Trametinib therapy was offered but parents elected enucleation.

A 12-year-old girl without NF1 presented with unilateral proptosis and intact vision. MRI showed a 2.9 x 2cm right pre-chiasmatic OPG. She was observed with serial MRI and vision

evaluations, but after 6 months, she developed decreased visual acuity and was started on monthly carboplatin/vincristine. After 3 cycles, MRI brain showed progressive disease. Therapy was switched to vinblastine/bevacizumab for 1 year. Surveillance imaging performed 9 months after completion of therapy showed disease progression, prompting needle biopsy of the tumor. Pathology showed a WHO grade I Pilocytic Astrocytoma with a KIAA1549-BRAF fusion detected by panel-based genomic evaluation. She began trametinib with stable vision for 3 months.

**Conclusion:**

Surgery or radiation have historically been the treatments of choice in patients with pre-chiasmatic OPG refractory to conventional chemotherapy. Performing a biopsy with panel-based genomic evaluation for targetable mutations including testing for BRAF aberrations early in the clinical course may provide additional targeted efficacious treatment options, especially in refractory cases. Trametinib is a viable treatment option in patients with BRAF fusions and may prevent further disease progression, improve vision, and delay or obviate enucleation or radiation.

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Poster # 618

**PRIMARY LEPTOMENINGEAL CENTRAL NERVOUS SYSTEM NEOPLASMS PRESENTING IN CHILDREN**

**Batool El-Atoum, Carol Bruggers, Kevin Moore, Holly Zhou, David Solomon, Matthew Poppe, Nicholas Whipple**

*The University of Utah, Salt Lake City, Utah, United States*

**Background:**

Central nervous system (CNS) tumors are the most common solid tumors in Children. Primary leptomeningeal CNS neoplasms are an exceptionally rare form of benign or malignant disease presentation in which there is not an associated mass. These disease presentations often lead to a delay in diagnosis and treatment.

**Objectives:**

To describe 3 cases of primary leptomeningeal CNS neoplasms - Medulloblastoma (MB)=2, Rosette-forming glioneuronal tumor (RGNT)=1.

**Design/Method:**

Retrospective review of patients' medical records and review of the literature.

**Results:**

Case 1: A 10-year-old girl presented with altered mental status, headache, and diplopia. Extensive work up including MRI brain and Lumbar puncture (LP) were unremarkable. Repeat MRI brain 14 days later demonstrated interval development of diffuse leptomeningeal enhancement in the basilar cisterns, initially attributed to meningitis. As symptoms worsened, a repeat LP was performed which revealed small round blue cells. MRI spine demonstrated diffuse

leptomeningeal enhancement throughout the lower thoracic and lumbar spine with an intradural spinal cord plaque at T8-T9. Biopsy of the spinal cord plaque revealed medulloblastoma.

Case 2: An 8-year-old boy recently emigrated from Mexico presented with a 3-year history of seizure and ataxic gait. MRI brain from Mexico 3 years prior demonstrated probable basilar cistern arachnoid cyst. His clinical course and exposure history of his father working at a pig farm were concerning for neurocysticercosis, but imaging features were atypical of the disease. Serologic and cerebrospinal fluid (CSF) testing for neurocysticercosis were negative. Repeat MRI brain in the United States demonstrated leptomeningeal nodular and cystic foci involving the basal cisterns, sylvian fissures, anterior hemispheric fissure, and the 3rd and 4th ventricles without a mass. Biopsy revealed RGNT with mutations in FGFR1 p.K656E and PTPN11 p.E69K.

Case 3: A 9-year-old boy presented with headache, vomiting, ataxia and upward gaze palsy. MRI brain revealed diffuse cerebellar leptomeningeal enhancement without an associated mass. MRI spine and CSF were negative for tumor. He was treated with corticosteroids and antibiotics for cerebellitis with minimal improvement. Two months later, repeat brain MRI demonstrated progressive thickening of the cerebellar leptomeningeal disease. Biopsy revealed primary leptomeningeal medulloblastoma, classic histology, non-WNT/non-SHH, without gain/amplification of MYC/MYCN, and P53 wild type pattern.

**Conclusion:**

Primary leptomeningeal enhancement without an associated mass is an extremely rare form of CNS neoplasm disease presentation and may be misdiagnosed as infectious or inflammatory processes. Given diversity of histologic diagnosis, biopsy should be considered early to enable timely diagnoses and treatment. Panel-based genomic analysis may aid in diagnosis.

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Poster # 619

**TARGETED TREATMENT FOR SHH+ MEDULLOBLASTOMA IN A PEDIATRIC PATIENT WITH GORLIN SYNDROME**

**Melissa Johnnidis**

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**Background:**

We present a case of metastatic medulloblastoma (MB) of the sonic hedgehog (SHH) molecular subgroup in a patient with previously undiagnosed Gorlin syndrome who was subsequently treated with Vismodegib, a hedgehog signaling pathway inhibitor. A 4-year-old female with history of macrocephaly and ocular abnormalities presented with a 6-month history of worsening ataxia. Imaging at diagnosis showed a posterior fossa mass with intracranial and spinal metastases which was determined to be MB with unfavorable histology following biopsy. Due to the patient's young age, metastatic presentation of the tumor, and the patient's unique clinical features, genetic testing was performed which identified a PTCH1 gene mutation, consistent with the diagnosis of Gorlin syndrome.

**Objectives:**

To describe a case of a patient with Gorlin syndrome diagnosed with metastatic medulloblastoma treated with Vismodegib, a targeted therapy for the SHH molecular subgroup of the tumor.

**Design/Method:**

A chart review was performed for this single case study.

**Results:**

Following resection, the tumor was determined to be SHH+ MB, anaplastic histology type with focal nodularity, Chang stage M3b due to the presence of intracranial and intraspinal metastases. After genetic testing confirmed the diagnosis of Gorlin syndrome, radiotherapy (RT) was no longer recommended for the patient due to the increased risk of developing basal cell carcinomas, which are common in the disease. After the tumor continued to grow through chemotherapy, she was started on a trial of Vismodegib, an SHH signaling pathway inhibitor targeting the specific molecular subgroup of the tumor. The drug was initially beneficial, and the patient was clinically stable for a few months until further metastases were found on imaging; she was off the drug shortly thereafter and began palliative care.

**Conclusion:**

Mainstay treatment of MB consists of a combined-modality approach utilizing RT, but that is risky in patients with Gorlin syndrome. Therefore, the use of Vismodegib as targeted therapy in our patient was initially promising, but the tumor still progressed. We present this case to raise awareness to the potential complications of treating MB in those with Gorlin syndrome and to discuss the possible benefit of Vismodegib for these patients. Multi-institutional studies are required to determine whether the drug should be included in a comprehensive treatment plan for patients with Gorlin syndrome and SHH+ MB.

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Poster # 620

**NEURO-ONCOLOGIC TIE TO BECKWITH-WIEDEMANN AND ISOLATED HYPERPLASIA?**

**Caitlin Combs, Ana Aguilar-Bonilla, Amy Smith**

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**Background:**

Beckwith-Wiedemann is a well-known, uncommon, pediatric overgrowth disorder that carries a strong predisposition for tumor development<sup>1</sup>. Manifestations of Beckwith-Wiedemann syndrome (BWS) include hemihypertrophy, macrosomia, macroglossia, and development of embryonal tumors. The estimated risk for tumor development in patients with BWS is about 7.5%, but has been described as high as 21 percent. These malignancies often occur prior to eight years of age, and most commonly develop as Wilms tumor or hepatoblastoma. Tumor surveillance with serial abdominal and renal ultrasonography is recommended; in some centers the need for surveillance is affected by genetic and epigenetic markers. An association between

BWS and CNS tumor development is not established.

**Objectives:**

In this report, we present two cases of intracranial ependymoma in BWS and associated hyperplasia.

**Design/Method:**

Case series.

**Results:**

Patient A is a 29-month-old male with history of Beckwith-Wiedemann syndrome who presented with three days of somnolence, vomiting, and fever. On day two of hospitalization, the patient began complaining of headache and then had an acute change in mental status and became lethargic, with response only to pain. An MRI revealed a posterior fossa mass. Patient underwent suboccipital craniotomy for gross resection of the mass. Pathology later confirmed an ependymoma diagnosis. Patient B is a 29-month-old male with history of left-sided hemihypertrophy as well as tracheoesophageal fistula status post repair, tracheomalacia, ventricular septal defect, and asthma who presented with persistent right-sided headache and Horner's syndrome with no other neurologic symptoms. A head CT was obtained which demonstrated a right cerebellopontine angle posterior fossa mass. Patient underwent gross tumor resection and pathology revealed a grade II ependymoma.

**Conclusion:**

Patients with Beckwith-Wiedemann and similar hyperplastic etiologies have been shown to have higher predisposition for tumor development. There is not been an established link between overgrowth syndromes and central nervous system tumors, however there may be an unknown association. This case series demonstrates two such instances and suggests that tumor surveillance may need to be broadened. Most interestingly, these two cases raise questions of tumorigenesis and the genetic and epigenetic drivers of tumor development. This may be relevant to the surveillance and management of patients with BWS, and to the management of patients who develop a CNS malignancy in the setting of BWS.

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Poster # 621

**MAINTENANCE THERAPY WITH DABRAFENIB IN A PATIENT WITH ATRT AND BRAFV600E MUTATION: A CASE REPORT**

**Joseph Bernardo**

*Arnold Palmer Hospital for Children, Orlando, Florida, United States*

**Background:**

Atypical Teratoid/Rhabdoid Tumor (ATRT) is a rare and aggressive CNS childhood tumor, occurring in 0.07 per 100,000 children with 1 year and 5 year survival rates of 47% and 28%. Patients will commonly present with lethargy, headaches, and neurologic defects. ATRT has the characteristic loss of protein expression of INI-1 due to changes in the tumor suppressor genes

SMARCB1 or SMARCA4. Occasionally there have been case reports of ATRT arising from a gliosarcoma.

**Objectives:**

Here, we report a case of a 6 year old male who presented with lethargy, headache and emesis found to have an intracranial temporal lobe mass and intracranial metastases.

**Design/Method:**

Initial pathology report was consistent with gliosarcoma, WHO grade 4, BRAFV600E mutation positive, INI-1 preserved. Tumor was sent to two other institutions for review, both of whom concluded his tumor was consistent with ATRT with INI-1 loss as well as a BRAFV600E mutation. The patient underwent a subtotal resection of the tumor and started therapy for gliosarcoma. He received Temozolomide 90mg/m<sup>2</sup>/day for 42 days and 54Gy radiation therapy to the primary tumor site. Results from second opinion was received after patient had started treatment and thus we decided to start Dabrafenib, a BRAFV600E inhibitor as maintenance therapy.

**Results:**

He showed a favorable response to treatment and is now 4 years from diagnosis and approximately 12 months since the end of therapy without progression.

**Conclusion:**

Although BRAF is suggested to be mutated in approximately 14% of high grade pediatric gliomas and 66% of low grade gliomas, the presence of a BRAF mutation and INI-1 deletion in conjunction in ATRT has not been well defined outside of its role in potential post-translational modifications and its aggressive behaviors.

There are very few cases which report simultaneous INI-1 loss and BRAF V600E mutation. Here we present a rare case with both findings. As sequencing becomes more frequent, it would be interesting to examine the co-occurrence of these findings which may have previously been unrecognized. This patient presented a pathological challenge and ultimately we decided to treat the patient with BRAF V600E inhibitor as maintenance therapy. The use of BRAF inhibitors as first-line therapy should be approached cautiously until further clinical trials provide reliable data. Ongoing surveillance must be judicious due to the fact that BRAF mutant tumors have a tendency to develop resistance.

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Poster # 622

**DIFFERENTIAL EFFECTS OF SURGERY AND CHEMOTHERAPY IN CHILDREN WITH POSTERIOR FOSSA BRAIN TUMORS**

**Sofia Dhanani, Sharon O'Neil, Jeffrey Tanedo, Katrina Huft, Aditi Tondulkar, Jemily Malvar, Benita Tamrazi, Katherine Maina, Francesca Trane, Vidya Rajagopalan, Natasha Lepore, Mary Baron Nelson**

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**Background:**

While cranial radiation therapy (CRT) is linked to significant cognitive detriments in children with brain tumors, less is known about independent effects of the tumor, surgery, and chemotherapy. Few neuroimaging studies of children with pediatric brain tumors treated with chemotherapy without radiation exist, and the neuropsychological effects of chemotherapy alone on this population remain unclear.

**Objectives:**

We aimed to determine the differential effects of surgery and chemotherapy on brain microstructure and cognition, using diffusion tensor imaging (DTI) and neuropsychological assessment.

**Design/Method:**

Twenty-eight children with a history of posterior fossa tumor (17 treated with surgery alone and 11 treated with surgery and chemotherapy) underwent neuroimaging and neuropsychological assessment a mean of 4.5 (surgery group) to 9 years (surgery + chemotherapy group) after treatment in this cross-sectional study. Twenty-one healthy sibling controls (n=49) were also included. Psychometric measures focused on general intelligence, executive functions, processing speed, learning and memory, and social-emotional functioning, with age at diagnosis and time since diagnosis covariates in the analyses. Group differences in DTI findings and psychometric scores, and correlations between psychometric scores and DTI results were examined.

**Results:**

We found significant differences in fractional anisotropy (FA) in the prefrontal cortex, large white matter tracts, hippocampus, putamen, globus pallidus, thalamus, and pons with lower mean FA in children in the surgery + chemotherapy group compared to the children treated with surgery alone. The only exceptions were an increased mean FA in the left middle frontal gyrus and left medial thalamic nucleus in the surgery + chemotherapy group, potentially attributable to age-related developmental differences and the higher prevalence of hydrocephalus in the surgery + chemotherapy group. In neuropsychological evaluation, the two patient groups differed only in receptive vocabulary, with children treated with chemotherapy scoring lower; however, both patient groups scored lower than healthy sibling controls on visuoconstructional reasoning and visual-spatial memory, as well as on behavioral measures of aggression and externalizing problems. Higher FA in the right thalamus associated with higher scores on visual-spatial memory and working memory. Higher FA in white matter tracts associated with better performance in nonverbal reasoning, memory, and processing speed.

**Conclusion:**

Treatment of a pediatric posterior fossa brain tumor with surgery and adjuvant chemotherapy causes a significant impact on the microstructure of the prefrontal cortex, white matter tracts, hippocampus, putamen, globus pallidus, thalamus, and pons, and on neuropsychological functioning years into survivorship, compared to treatment with surgery alone.

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## **AGGRESSIVE CEREBELLAR HIGH GRADE GLIOMA WITH TPM3-NTRK1 FUSION**

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### **Background:**

Cerebellar high grade gliomas occur in less than 1% of patients and thus tumor characteristics are yet to be well defined. TRK fusion proteins are constitutively active and promote oncogenic signaling to support tumorigenesis. NTRK fusions are characteristic of rare tumors types such as infantile fibrosarcoma but have been described in melanoma, glioma, and carcinomas. Little is known regarding the clinical course of CNS NTRK fusion cancers.

### **Objectives:**

To describe an aggressive presentation of cerebellar high-grade glioma (HGG) driven by a TPM3-NTRK1 fusion transcript.

### **Design/Method:**

Literature review yielded 5 reports of pediatric cerebellar GBM (cGBM), all without association to NTRK fusions.

### **Results:**

A 17-year-old female presented with worsening migraines over a six-month duration with later onset emesis and ataxia. Imaging was notable for a right posterior fossa mass measuring 3.6 cm with effacement of the fourth ventricle. She underwent partial tumor resection. Unfortunately, pathology was non diagnostic. She was referred to our institution twenty days following her initial presentation with recurrent migraines, ataxia, and visual disturbances. Subsequent MRI brain notable for a 2.5 x 3.5 x 3.2 cm right cerebellar lobe tumor with central necrosis and hemorrhage. Gross total resection was obtained via stereotactic right cerebellar craniotomy for resection. While awaiting molecular pathology, our patient presented with diplopia on right lateral gaze and nausea. MRI brain remarkable for a recurrent large enhancing mass within the resection bed, measuring 4.0 x 2.1 x 2.4 cm. Pathology from second resection was consistent with high grade glioma, IDH wildtype, with TPM3-NTRK1 fusion. Based on recent evidence of therapeutic efficacy in refractory solid NTRK tumors, patient was started on Entrectinib with concurrent cranial radiotherapy.

### **Conclusion:**

Neurotropic TRK (NTRK) fusions are an evolving area of interest after recent FDA approval of Larotrectinib and Entrectinib created heightened awareness of this fusion in targeting patients with resistant tumors. Robinson et al. demonstrated a remarkable response to NTRK targeted therapy in patients with refractory solid tumors, six of whom were described with CNS tumors. Historical data suggests that cerebellar HGGs appear to be distinct in pathogenesis but have failed to describe NTRK fusions as molecular alterations specific to these tumors. We suspect that the NTRK fusion is the primary oncogenic driver contributing to the rapid tumor progression

in our patient. Due to the aggressive nature of her tumor, this case supports future analysis of tumor biology, location, and NTRK to assess if NTRK fusion positive CNS tumors exhibit increased aggressive features.

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Poster # 701

## **SKEWED MERCAPTOPURINE METABOLISM SUCCESSFULLY CORRECTED WITH ALLOPURINOL IN PEDIATRIC LEUKEMIA**

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### **Background:**

6-Mercaptopurine (6-MP) is the most frequently used chemotherapy agent in the management of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL). Individuals with skewed drug metabolism can shunt toward the production of the hepatotoxic byproduct, 6-methyl-mercaptopurine (6-MMPN) over the desired therapeutic product, 6-thioguanine nucleotide (6-TGN). Holding or lowering the dose for toxicity, results in decreased intensity of 6-MP treatment, which increases risk of relapse. Allopurinol can alter 6-MP metabolism to maximize 6-TGN production while reducing the hepatotoxic metabolite, 6-MMPN.

### **Objectives:**

We sought to identify patients with skewed 6-MP metabolism, report on effects of allopurinol as an intervention, and provide an algorithm for combining allopurinol in patients with skewed 6-MP metabolism to the chemotherapy regimen.

### **Design/Method:**

We performed a single institution, retrospective study for ALL and LL patients treated for at least one year of maintenance therapy from January 1, 2009 to June 1, 2019. Incidence of hypoglycemia, and hepatic inflammation were recorded. If available, metabolite levels were collected. If the patient was started on allopurinol, we noted the effects of the intervention on the aforementioned lab values and their clinical course. Stata was utilized for all statistical analysis.

### **Results:**

Chart review on 42 eligible patients gathered demographic information and lab values for potential markers of toxicity. Seventy four percent of patients had a least one episode of documented hypoglycemia, and 88% had at least one episode of an elevated ALT. Metabolites were checked in 66% of our patients. Fifty-four percent of the entire cohort had 6-MMPN levels  $>10,000$  pmol/ $8 \times 10^8$  RBC suggestive of shunting on at least one occasion during the study period. Allopurinol was initiated by the primary team for metabolite and laboratory derangements in 12 patients. All patients who received allopurinol had improvement in clinical course and metabolite profiles.

### **Conclusion:**

In our population of pediatric and young adults treated for leukemia and lymphoblastic

lymphoma, over half of the patients had 6-MP metabolite derangements and associated signs of toxicity. Prior gastroenterology publications suggest a much lower incidence of 6-MP metabolite shunting at 15%. The patients who received allopurinol during their treatment period showed reversal of undesired toxicities, suggesting that combination therapy may be beneficial for additional patients. All of these patients remain in remission through 1 Jun 2019. From our experience, we propose an algorithm for the use of allopurinol in conjunction with chemotherapy for patients with ALL or LL who have inappropriate 6-MP metabolism to optimize treatment while decreasing 6-MP associated toxicities.

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Poster # 702

## **EXOSOMAL MIR-181a INHIBITION BY VINCRISTINE AND PREDNISONE IN PEDIATRIC ACUTE LYMPHOCYTIC LEUKEMIA**

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### **Background:**

Vincristine and prednisone are standard therapeutic agents in pediatric acute lymphocytic leukemia (P-ALL). Mechanistically, vincristine induces apoptosis by blocking microtubule formation, while prednisone binds to cytoplasmic receptors and inhibits DNA synthesis, both of which lead to apoptosis. The effect of these agents on exosomal micro-RNA expression and its functional regulation has not been investigated. Elevated levels of miR-181a in circulating exosomes (nanoparticles) have been shown to lead to progression in several cancers, including ALL. We have previously shown that leukemia-derived exosomes induce leukemia cell proliferation via up-regulation of miR-181a expression; and silencing of exosomal miR-181a reverses this exosome-induced cell proliferating effect.

### **Objectives:**

To investigate the effect of vincristine and prednisone on cellular and exosomal miR-181a in ALL.

### **Design/Method:**

JM1, SUP-B15, and NALM-6 leukemic cell lines were treated in vitro with vincristine (0.1 to 4.0  $\mu$ M) or prednisone (0.1 to 12.0  $\mu$ M) in exo-free medium and apoptosis was measured by MTS assay. Total RNA of exposed cell lines was isolated and cDNA was prepared for miR-181a expression analysis by q-PCR.

Exosomes from conditioned medium of exposed cell lines were isolated by ultracentrifugation method. Purity and particle size of exosomes were confirmed by western blot and nanoparticle tracking analysis (NTA) assay respectively. Total exosomal RNA was isolated from exosomes (Exo-RNA) by Trizol method. Synthesis of cDNA was carried out with the miScript II RT kit (Qiagen).

**Results:**

Vincristine and prednisone promote apoptosis in tested leukemia cell lines in a dose-dependent manner. Both cellular and exosomal miR-181a expression was down-regulated after vincristine and prednisone exposure in all three leukemia cell lines (JM1, SUP-B15, and NALM-6). These observations demonstrate that cellular miR-181a down-regulation in the parental leukemic cells is stable and can be transferred to exosomes, confirming the concept that exosomes carry the fingerprint of parent cells.

**Conclusion:**

The anti-leukemic effect of vincristine and prednisone maybe induced by another- yet unexplored- pathway resulting in miR-181a suppression at a cellular and exosomal level, causing subsequent apoptosis of leukemic cells.

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Poster # 703

**CORRELATION OF ABSOLUTE BLAST COUNT ON DAY EIGHT OF TREATMENT WITH MINIMAL RESIDUAL DISEASE IN B-ALL**

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**Background:**

Early treatment response predicts superior outcome in B-lineage acute lymphoblastic leukemia (ALL). An absolute blast count of  $<1000/\mu\text{L}$  following prednisolone pre-phase is recognized as a favourable response criterion.

**Objectives:**

The study evaluated if a complete blast clearance was a better predictor of outcome.

**Design/Method:**

A file review of children aged  $\leq 15$  years diagnosed with B-ALL from 2014 to 2019 was performed. Modified UKALL protocol was used for risk stratification and treatment. National Cancer Institute (NCI) risk groups were used for baseline risk stratification. Hyperdiploidy and  $t(12;21)$  were considered as favourable cytogenetics. Response assessment was performed using day 8 absolute blast count (ABC), end of induction marrow morphological remission and flow cytometry based minimal residual disease (MRD).

**Results:**

ABC was available in 251 of 255 patients treated for B-ALL. The median age of the patients was 5-years (0.4 – 15 years). ABC was 0,  $< 100/\mu\text{L}$ ,  $< 500/\mu\text{L}$  and  $< 1000/\mu\text{L}$  in 141 (56%), 170 (68%), 209 (82%) and 221 (87%), respectively. The proportion of MRD negative patients was greater, when they were categorized based on an ABC cut-off of 0 (81% vs. 70%,  $P = 0.053$ ),  $< 100/\mu\text{L}$  (80% vs. 67%,  $P = 0.018$ ) and  $< 500/\mu\text{L}$  (79% vs. 62%,  $P = 0.020$ ). The proportion of MRD negative patients did not differ among patients with  $\text{ABC} < 1000/\mu\text{L}$  and  $\text{ABC} = 1000/\mu\text{L}$  (77% vs. 67%,  $P = 0.207$ ). On univariate analysis,  $\text{ABC} > 0/\mu\text{L}$  [2.447 (95% CI:1.230-4.867),  $P =$

0.011], = 100/ $\mu$ L[2.774 (95% CI:1.422-5.408), P = 0.003] and = 500/ $\mu$ L[2.108 (95% CI:0.985-4.512), P = 0.055] predicted increased risk of relapse. ABC = 1000/ $\mu$ L did not predict relapse [0.869 (95% CI:0.306-2.470), P = 0.792]. On multivariate analysis including NCI high risk, absence of favourable cytogenetics, ABC and MRD, ABC = 100 / $\mu$ L emerged as the strongest predictor of relapse (p=0.007)

**Conclusion:**

Complete clearance of blasts or an ABC < 100 / $\mu$ L were more predictive of response and outcome when compared to the conventional cut-off of ABC < 1000 / $\mu$ L.

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Poster # 704

**EXPLORING DISPARITIES AMONG AMERICAN INDIAN CHILDREN WITH CANCER**

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**Background:**

Childhood cancer is the leading cause of disease-related death among children aged 5-19 years in the US. While there have been great successes in the treatment of cancer, little information is available on disparities in access to treatment and survival among underrepresented populations, especially American Indian (AI) people. No recent studies have conducted in-depth analysis of disparities among AI children with cancer. AI children who use Indian Health Service (IHS) or tribal health clinics may have increased challenges due to the need to obtain referrals through the IHS system, which is unique to tribal healthcare and subject to funding limitations.

**Objectives:**

We aimed to evaluate the relation between race and event-free survival among AI and non-Hispanic (NH) white children diagnosed with acute lymphoblastic leukemia (ALL) prior to age 20 from 2000 to 2018.

**Design/Method:**

We partnered with a children's hospital at an academic medical center to abstract data from electronic medical records and the institution's cancer registry on cancer diagnosis, treatment, and outcomes for children with ALL. We used Fisher's Exact Test for categorical variables and Wilcoxon Rank-Sum Test for continuous variables that were not normally distributed to evaluate differences in these factors between AI and NH white children. Using Kaplan-Meier analysis with the log-rank test, we compared survival curves of time from diagnosis to recurrence, death, or end of the study period by race.

**Results:**

We identified children with ALL who were AI (n=34, 15%) or NH white (n=196, 85%) included both in medical records and the hospital's cancer registry. Of these, 44% were female, the most

common primary payers were Medicaid (47%) and private insurance (38%), and 83% were B-cell ALL. The median age of ALL diagnosis was 5.5 years, which did not differ by race (p=0.48). The median time from diagnosis to initial treatment was 1.5 days for AI children and 1 day for NH whites. However, the survival curves did not differ by race (p=0.60).

**Conclusion:**

As a next step, we will obtain electronic medical record data from the other children's hospital in the state and link our dataset with the state cancer registry to allow for a more comprehensive, population-based evaluation of cancer disparities. This project will generate important preliminary data for future studies, which will evaluate strategies to improve care coordination and incorporate cultural factors important to AI families into pediatric oncology care by tribal health and oncology providers.

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Poster # 705

**DISTANCE TO TREATMENT CENTER IS ASSOCIATED WITH OVERALL SURVIVAL IN CHILDREN AND AYAs WITH ALL**

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**Background:**

Outcomes for pediatric patients with Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) have improved with successive generations of clinical trials. For adolescent and young adults (AYAs), outcomes have historically lagged behind that of younger children. Various socioeconomic and demographic categories such as income, race, insurance status and treatment center type are associated with outcomes in acute leukemia. However, distance to treatment center (which might lead to increased strain and potential delays in care) has not been previously examined.

**Objectives:**

We aimed to determine if distance to treatment center impacts overall survival in children and AYAs with acute leukemia.

**Design/Method:**

We queried the National Cancer Database (NCDB) for patients  $\leq 39$  years of age, and diagnosed between 2004 and 2015 with AML or ALL. Data from the NCDB includes overall survival but does not contain information about disease relapse. ALL and AML were analyzed separately for overall survival. Backwards elimination procedure was used to select final multivariate Cox models.

**Results:**

In total, 12,301 AML and 22,683 ALL patients were analyzed. For both patients with AML and ALL, slightly more than 20% of patients had a distance to treatment center of >50 miles. The final multivariate model for ALL included distance to treatment center, Charlson- Deyo score,

age (<18 vs. ≥18 years), race, insurance status, and community income level. US census definitions of urban vs. rural were not statistically significant, and no interaction was seen for any included variable (including age). Compared to distances >50 miles, all other distance groups were associated with improved survival: ≤10 miles (HR 0.91, p=0.04), >10 to ≤20 miles (HR 0.86, p=0.004) and >20 to ≤50 miles (HR 0.87, p=0.005). The final model for AML included the same variables as the ALL model, except distance to treatment center, which was not statistically significant.

**Conclusion:**

For children and AYAs with ALL, distances >50 miles are associated with inferior overall survival, however no difference was seen for AML. Treatment for ALL typically continues for many years and is associated with multiple trips from home to treatment center, whereas treatment for AML is typically shorter and is mostly performed inpatient. Although it is unknown if differences in survival for ALL based on distance are driven by relapse or treatment related mortality, increased attention to adherence, supportive care and logistics for patients living >50 miles from their treatment center is warranted.

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Poster # 706

**HIGH DOSE METHOTREXATE USE IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA IN A MIDDLE INCOME COUNTRY**

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**Background:**

High dose methotrexate (HDMTX) is key component in the treatment of pediatric malignancies. Its cytotoxic effect on bone marrow and penetration of the blood brain barrier have decreased the requirement for cranial radiation and improved event-free survival in children with acute lymphoblastic leukemia (ALL). Important toxicities can occur due to the drug’s metabolism and excretion. Hyper-hydration, MTX level monitoring and carboxypeptidase use have been shown to decrease the occurrence of these toxicities. However, the cost of carboxypeptidase makes its use prohibitive in low- and middle-income countries.

**Objectives:**

To report the use of HDMTX in a developing country following hyper-hydration and increased MTX monitoring protocol.

**Design/Method:**

We performed retrospective chart review of patients 1-13 years old with high and very high risk ALL, admitted from May 2017 to May 2019 to Hospital Nacional de Niños in Costa Rica, treated according to the national protocol (CR LLA 1-16) based on COG AALL1131. Patients received high dose MTX at 5 g/m<sup>2</sup>/dose as a 24-hour infusion, every two weeks for a total of four doses. MTX infusion rate, hyper-hydration rate and leucovorin dosages were adjusted



according to MTX clearance, creatinine, cystatin-C levels and urinary pH, based on the hyper-hydration protocol provided by Texas Children's Hospital.

**Results:**

Fifty-two patients were included with a total of 207 admissions. Infusion rate adjustments occurred in 51 admissions (24.6 %). Of these, three infusions (1.4%) were modified secondary to high MTX levels at two hours post-initiation, and 48 infusions were modified due to elevated MTX levels at six hours post-initiation. Toxicities during MTX clearance up to 3 days after the infusion included: vomiting (11.6%, n=24), fever (7.3%, n=15), diarrhea (6.3%, n=13) and acute kidney injury (1.9%, n=1). A week follow-up revealed neutropenia in 24.6% (n=51), and its mean duration was 10.7 days (range: 3.0-19.0); thrombocytopenia in 9.2%, with mean duration of 10.2 days (range: 6.0-15.0), mucositis 4.8% (n=10), neurotoxicity in 1% (n=2). Neutropenia caused a delay in next cycle initiation in 7.7% (n=16) No hepatotoxicity or deaths were reported. There were no statistically significant differences in the occurrence of toxicities during MTX infusions for patients that required adjustments based on protocol, compared to those who did not.

**Conclusion:**

Real-time algorithm-based individualized HDMTX monitoring and infusion adjustments was effective without any significant high grade toxicities. To our knowledge, this is the first implementation of this type of HDMTX protocol in low-middle income countries.

Reference: 1. Foster et al., J Pediatr Hematol Oncol, 2017.

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Poster # 707

**CRITICAL STATUS AT DIAGNOSIS AFFECTS TRIAL ENROLLMENT AND OUTCOME IN PATIENTS WITH T-ALL AND T-LLy**

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**Background:**

Patients with T-cell acute lymphoblastic leukemia and lymphoma (T-ALL/LLy) more commonly present with critical features such as hyperleukocytosis (WBC>300,000/uL) and mediastinal mass which complicates the ability to complete a diagnostic and staging workup. The effect this has on clinical trial enrollment and outcome has not been evaluated.

**Objectives:**

Describe the frequency of critical features at initial presentation in patients with T-ALL/LLy and assess the effect this has on clinical trial enrollment and outcome.

**Design/Method:**

Consecutive patients newly diagnosed with T-ALL/LLy from 1999-2019 at the Children's Hospital of Philadelphia were analyzed for PICU admission, hyperleukocytosis, mediastinal

mass, dialysis, and tumor lysis syndrome (TLS); as well as clinical trial enrollment and outcome. Medical non-enrollers were defined as patients requiring emergent therapy precluding them from trial enrollment.

**Results:**

We identified 153 patients diagnosed with T-ALL (103) and T-LLy (50). Fifty-three (35%) required PICU level care within 24 hours of admission and 73 (48%) within 7 days. Forty-four (29%) presented with hyperleukocytosis, 17 (11%) underwent apheresis (WBC > 300,000) and 102 (67%) had a mediastinal mass.

Of the 104 patients diagnosed when a trial was open 33 (32%) did not enroll; 10 refused enrollment and 23 were medical non-enrollers. When trials were open, patients requiring PICU admission in the first 24 hours had a 51.3% enrollment rate; non-PICU patients had a 77.3% enrollment rate (p=0.0068). Patients enrolled on a clinical trial had a 15.5% relapse rate versus 27.3% of non-enrollers (p=0.1560).

In the total cohort 18% of patients relapsed (10% with T-LLy, 22% with T-ALL). Of those admitted to the PICU within 24 hours, 26% relapsed versus 14% of non-PICU patients (p=0.0629). If enrolled on a clinical trial the PICU cohort relapse rate was 21% versus 33% for those who did not enroll (p=0.4005).

Evaluating by individual critical feature, 30% of patients with hyperleukocytosis relapsed versus 13% without (p=0.0223). Almost half (47%) of patients who underwent apheresis relapsed versus 19% without (p=0.0011). Mediastinal mass, TLS, or dialysis did not affect relapse risk.

**Conclusion:**

Surprisingly almost half of T-ALL/T-LLy patients required PICU-level care within the first week of diagnosis, making enrollment on clinical trials more challenging. For patients who required PICU-level care, enrollment on a clinical trial predicted a better outcome. Physicians should attempt to balance maintaining eligibility with safety to offer patients all options. As well, trial requirements limiting T-ALL/T-LLy patients' ability to enroll on trials, potentially containing new agents, should be reviewed for necessity.

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Poster # 708

**MOLECULAR REARRANGEMENTS OF B-ALL AND ITS PROGNOSIS ASSOCIATED IN A MEXICAN COHORT OF PATIENTS.**

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**Background:**

B-Cell Acute Lymphoblastic Leukemia (B-ALL) is the most common cancer in childhood, with

an increased incidence in Latino patients. High-risk molecular subtypes are more common in Latino ethnicity patients treated in the United States, which may explain its worse prognosis.

**Objectives:**

To present the clinical features associated with distinct molecular subtypes of newly diagnosed B-ALL and compare the prognosis associated with each mutation.

**Design/Method:**

A prospective study, with all incident cases of B-ALL at University Children's Hospital of Torreon, Coahuila, Mexico from January 2017 to December 2019. Patients were allocated in high and standard risk groups accordingly to age, immunophenotype, Minimal Residual Disease (MRD) at 1 month, leukocyte count at diagnosis, and cytogenetics. Bone marrow samples were obtained at diagnosis and the end of induction. In-house qPCR was used to determine 3 molecular alterations in our patients: MLL-AF4, ETV6-RUNX1, and P2RY8-CRLF2. This not affect the clinical decision of physicians. Briefly, therapy is based on BFM protocols.

**Results:**

Seventeen patients were included in the present study, all of Latino ethnicity. The mean age at diagnosis was 5.06 years(1-13), female predominance was observed (70%). Leukocyte count at diagnosis was >50 000 in 35% of patients, anemia was observed in 70.6%, neutropenia in 94.1%, thrombocytopenia 76.5%, tumor lysis syndrome was diagnosed in 11.8%.

Common B-ALL was the predominant immunophenotype with 89% of cases, preB 5% and proB 5%. Hyperploidy was seen in 17.6% of patients and hypoploidy in 5.9%. The prevalence of the distinct re detected were MLL-AF4 5.9%, P2RY8-CRLF2: 11.8%, ETV6-RUNX1: 29.4%. 29% of our patients were allocated at standard-risk and 71% at high-risk according to risk factors. MRD at the end of induction was positive in 1 patient.

The median follow-up of the cohort was 17 months (1-33 months). Kaplan-Meier survival analysis determined that at 2 years, overall survival (OS) was 84%, 95% CI(58-96%); 46% of patients in the high-risk group had suffered a relapse(6/13), and none among the standard-risk group. The molecular subgroups with higher relapse rates (100%) were MLLr(1/1) and CRLF2r(2/2). ETV6-RUNX1 group had a relapse rate of 20% (1/5), similar to No-Rearrangement-Detected group with 30% relapse rate (3/10).

**Conclusion:**

At 2 years of follow-up, the OS rate in our cohort is 84%. Patients with MLLr and CRLF2r B-ALL seem to have the worst prognosis associated.

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Poster # 709

**THE ECONOMIC BURDEN IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA WITH COMMERCIAL AND MEDICAID INSURANCE**

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**Background:**

Due to recent treatment advancements, pediatric acute lymphoblastic leukemia (ALL) is now considered curable. However, there is a lack of real-world evidence regarding the economic burden of disease in this era of improved therapeutic options.

**Objectives:**

This study aimed to examine and compare healthcare resource utilization (HCRU) and costs in the first year following diagnosis in a pediatric ALL population from a Commercial and Medicaid insurance perspective.

**Design/Method:**

Administrative claims data from 2011 through 2016 were analyzed. Patients 21 and under with newly diagnosed ALL, at least 12 months of continuous enrollment, and no evidence of capitated claims were studied. Demographics, remission and relapse, and HCRU and costs were stratified by insurance type. The mean(standard deviation) HCRU and costs were reported by type of service (inpatient, emergency room (ER), non-ER outpatient, pharmacy, and total) and measured during the first year following diagnosis. Multivariable generalized linear models (GLMs) were run to compare the cost ratio of total healthcare costs in the year post-diagnosis between Commercial and Medicaid patients adjusting for age (10-21 versus 0-9) and gender.

**Results:**

A total of 803 (599 Commercial and 204 Medicaid) patients were studied. Median age was 6. Remission occurred in 94.2% of Commercial patients and 90.2% of Medicaid patients ( $p=0.0531$ ) and relapse occurred in 14.7% and 14.2% of Commercial and Medicaid patients, respectively ( $p=0.8680$ ). The average number of inpatient admissions was 6.2(3.8) and 6.0(4.6) for Commercial and Medicaid, respectively ( $p=0.6480$ ) and the average number of ER visits was 2.8(6.2) and 2.1(2.6) for Commercial and Medicaid patients ( $p=0.0444$ ). Commercial patients experienced significantly more non-ER outpatient visits (75.8(29.2) versus 57.2(33.2),  $p<0.0001$ ) and significantly less pharmacy claims (48.5(26.7) and 61.3(42.3),  $p<0.0001$ ) versus Medicaid patients. Total healthcare costs were more than double for Commercial patients compared to Medicaid patients (\$527,629.57(\$542,287.49) versus \$197,521.98(\$181,464.20),  $p<0.0001$ ) and mainly driven by inpatient costs. The average pharmacy-related costs were significantly less for Commercial patients versus Medicaid patients (\$5,983.68(\$15,767.12) versus \$13,368.88(\$18,843.85),  $p<0.0001$ ). When adjusted for age and gender, total healthcare costs in the year post-diagnosis for Commercial patients were 1.61 times the costs in patients with Medicaid.

**Conclusion:**

Pediatric ALL causes a significant economic burden in the first year following diagnosis. The largest HCRU differences between Commercial and Medicaid patients were non-ER outpatient visits and pharmacy claims. While total costs were much greater in Commercial patients compared to Medicaid patients, there was no difference in relapse events.

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Poster # 710

## NEXT-GENERATION SEQUENCING REVEALS INCREASED PREVALENCE OF PICALM-MLLT10 FUSIONS IN T-ALL AND T-LLY

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### **Background:**

The genomic landscape of pediatric and young adult T-cell acute lymphoblastic leukemia (T-ALL) has been described (Liu, Nature Medicine 2017). However, prospective sequencing of newly-diagnosed pediatric T-ALL patients has not been routinely conducted. The Aflac Precision Medicine Program (APMP) uses comprehensive tumor profiling to identify molecular targets with the aim of improving outcomes of children with de novo or recurrent high-risk tumors. The APMP targets newly-diagnosed T-ALL and T-lymphoblastic lymphoma (T-LLy) because of higher relapse rates, dismal salvage rates post-relapse, and inferior overall outcomes compared to pediatric B-ALL.

### **Objectives:**

To describe the results of prospective, comprehensive CLIA-certified tumor profiling of newly-diagnosed pediatric T-ALL/T-LLy performed at a single institution.

### **Design/Method:**

Pediatric patients with newly diagnosed T-ALL or T-LLy enrolled on the IRB-approved AflacPM1702 protocol between 5/17/2018-12/20/2019. Tumor (bone marrow, peripheral blood, soft tissue) and germline samples (saliva, peripheral blood) were analyzed using Ashion's GEM Extra Platform, including full transcriptome (RNASeq) and whole-exome (WES) sequencing coupled with germline subtraction.

### **Results:**

A total of 14 patients (Age 6y-19y/11 male, 3 female/7 black, 5 white, 2 unknown) with newly-diagnosed T-ALL or T-LLy enrolled during the study period. One patient was excluded due to inadequate sample for sequencing. Overall, the mutational landscape in de novo T-ALL/TLLy was similar to published reports, with comparable mutation rates in the JAK/STAT, NOTCH, and cell cycle regulation pathways, among others. Most interestingly, however, PICALM-MLLT10 (CALM-AF10) fusions were detected in 4/13 cases (30.8%), compared to a published rate of 5-10% (Asnafi, Blood 2003). Importantly, only 2/4 patients with PICALM-MLLT10 fusions detected had t(10;11) present on karyotype. Additionally, RAS pathway mutations were present in 4/13 cases (30.8%), compared to a published rate of 14 % (Liu, Nature Medicine 2017). There was no difference in WBC count at diagnosis, CNS status, or end-induction MRD status in patients with or without PICALM-MLLT10 fusions.

### **Conclusion:**

Our results demonstrate that prospective comprehensive tumor profiling utilizing a combination of WES and RNASeq is feasible in pediatric T-ALL and T-LLy, and that sequencing results

generally reflect the published literature. The use of RNASeq revealed an increased frequency of PICALM-MLLT10 fusions that were not detectable by karyotype. Recent data suggest that MLLT10 fusions carry an adverse prognosis in pediatric and young adult acute myeloid leukemia, regardless of fusion partner (Ries, ASH 2019). The increased prevalence of PICALM-MLLT10 fusions in our cohort provides a rationale for their further study in T-ALL and T-LLy.

The APMP is generously supported by CURE Childhood Cancer.

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Poster # 711

## **IDENTIFICATION OF A POTENTIAL ROLE FOR EPS15 IN CALM-AF10 LEUKEMOGENESIS**

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### **Background:**

CALM-AF10 leukemias, which account for ~10% of childhood T-cell acute lymphoblastic leukemia (T-ALL) and a subset of acute myeloid leukemia (AML), have a poor prognosis. These leukemias exhibit increased HOXA gene expression, which we have shown is dependent on the interaction between CALM-AF10 and the CRM1/XPO1 nuclear export receptor: interruption of the CALM/CRM1 interaction abrogates both HOXA gene activation and leukemogenesis. However, since neither CALM-AF10 nor CRM1 contains a recognized DNA binding domain, the mechanism by which CRM1 interacts with HOXA genes is not currently understood. We took advantage of a proximity based-labeling approach using a biotin ligase (BioID2) to detect candidate CALM-AF10-interacting proteins that could mediate binding to HOXA genes.

### **Objectives:**

Identify candidate proteins that interact with CALM-AF10 and potentially mediate DNA binding

### **Design/Method:**

We prepared a BioID2-CALM-AF10 expression plasmid and determined that it transcriptionally activates HOXA genes and promotes leukemogenesis, similar to CALM-AF10. Human Embryonic Kidney 293 (HEK293) cells were transiently transfected with BioID2-CALM-AF10 and grown in the presence or absence of biotin, and mass spectrometry (MS) identified candidate interacting proteins. Initial validation of candidate proteins was conformed via co-immunoprecipitation (co-IP) in HEK293 cells transiently transfected with CALM-AF10.

### **Results:**

Three independent transfections/MS experiments identified 11 biotin-labeled proteins that interact with CALM-AF10. Importantly, these included two proteins that validate our approach: DOT1L, a protein known to interact with AF10, and NUP214, a nuclear pore protein with a potential role in CALM-AF10 leukemias. Among the remaining nine proteins, we identified epidermal growth factor receptor substrate 15 (EPS15), a known CRM1 interacting protein that

is also involved in KMT2A translocations. Co-IP studies performed in triplicate showed that EPS15 directly interacts with CALM-AF10, validating a potential role for EPS15 in CALM-AF10 leukemogenesis.

**Conclusion:**

Proximity-based labeling using biotin ligase is a novel approach for identifying proteins that interact with CALM-AF10. Among the proteins identified, EPS15 is an intriguing candidate: KMT2A-EPS15 translocations (t(1;11)(p32;q23)) have been identified in both AML and ALL, and KMT2A-EPS15 is among the eight most common KMT2A-rearrangements. Since EPS15 is known to bind to CRM1 and is involved in signal transduction and transcriptional regulation, our demonstration that it also directly interacts with CALM-AF10 suggests a possible role in mediating binding to HOXA genes. EPS15 overexpression and knockdown studies in hematopoietic precursors and CALM-AF10 leukemia cells are currently underway to evaluate effects on leukemogenesis and gene expression.

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Poster # 712

**LEARN-ING ABOUT DURATION OF NEUTROPENIA IN ACUTE MYELOID LEUKEMIA**

**Tamara Porter Miller, Kelly Getz, Biniyam Demissei, Karen Rabin, Marla Daves, Philip Lupo, Michael Scheurer, Evanette Burrows, Brian Fisher, Robert Grundmeier, Judy Lee, Jennifer Wilkes, Lena Winestone, Monica Gramatges, Richard Aplenc**

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**Background:**

Children with acute myeloid leukemia (AML) experience periods of prolonged neutropenia post-chemotherapy. This is an expected adverse event, but there are minimal data describing differences in neutropenia duration by demographics and chemotherapy regimen.

**Objectives:**

This study sought to use detailed electronic health record (EHR) data to describe and compare course-specific neutropenia durations by demographic and treatment characteristics.

**Design/Method:**

The Leukemia Electronic Abstraction of Records Network (LEARN) comprises data from patients with leukemia treated at Children's Hospital of Philadelphia, Children's Healthcare of Atlanta, and Texas Children's Hospital between 2006 and 2018. Treatment data were collected manually. Absolute neutrophil counts (ANCs) and demographics were extracted from the EHR using ExtractEHR, a software package we developed which requires input of only medical record numbers and chemotherapy course dates. De-identified laboratory data were cleaned to remove erroneous results, including those that normalized within 1 hour. Neutropenia duration in each course was computed as the first day post-chemotherapy of ANC <200 cells/ $\mu$ L until the ANC was >200 cells/ $\mu$ L. Mean durations with standard deviations (SD) were calculated, and unadjusted mean differences (MD) in neutropenia duration were compared by age, sex, race,

ethnicity, and chemotherapy regimen using linear regression.

**Results:**

Laboratory results on 251 patients (825 courses) with AML were extracted; 52.2% were female, 18.4% were Hispanic, 63.6% were white, and 25.5% were black. Mean days of neutropenia varied by course (Induction I: 24.0, SD 9.7; Induction II: 21.3, SD 14.7; Intensification I: 18.5, SD 8.8; Intensification II: 21.4, SD 10.5). The largest difference by chemotherapy regimen was during Induction II: neutropenia duration was longer after mitoxantrone/cytarabine than cytarabine/daunorubicin/etoposide (25.4 vs. 16.6 days,  $p < 0.01$ ). Addition of sorafenib increased neutropenia duration irrespective of chemotherapy backbone, but adding gemtuzumab ozogamicin or bortezomib did not cause consistent differences. Compared to children aged 2-10, children aged 16-20 (MD -5.2,  $p = 0.01$ ) and children aged 0-1 (MD -3.3,  $p = 0.03$ ) had shorter neutropenia duration during Induction I, but not consistently across subsequent courses. There were no statistically significant differences in mean neutropenia duration in any course by sex, race, ethnicity, or for ages 11-15.

**Conclusion:**

LEARN provides estimates of neutropenia duration for each frontline AML chemotherapy course. Multivariable analyses and further evaluations of variability in neutropenia duration over the trajectory of frontline treatment are ongoing. These results can be used to counsel patients on risks for complications of prolonged neutropenia, project potential hospitalization duration, and provide a baseline comparison for evaluating experimental agents in future clinical trials.

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Poster # 713

**ROLE OF SETD2 MUTATIONS IN THE PROGRESSION AND CHEMORESISTANCE OF PEDIATRIC LYMPHOBLASTIC LEUKEMIA**

**Gabriel Robbins, Ashfiyah Chowdhury, Joshua Greenberg, Harry Kilberg, Lindsay Kramer, Nikki Evensen, William Carroll**

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**Background:**

Outcomes for children with relapsed B-ALL remain poor, in part due to genetic and epigenetic lesions that confer drug resistance to one or more classes of agents used in therapy. SETD2, an epigenetic modifier, commonly harbors loss of function mutations in relapsed pediatric B-ALL. Prior studies have demonstrated the tumor suppressor function of SETD2 in an AML model as well as its role in resistance to DNA damaging agents, but the role of SETD2 mutations in relapsed B-ALL is not yet understood.

**Objectives:**

Determine the role of relapse-specific SETD2 loss-of-function mutations in disease progression by measuring proliferation and drug sensitivity in isogenic B-ALL cell lines that recapitulate these mutations.



**Design/Method:**

A panel of isogenic B-ALL cell lines (697 and KOPN-8) were generated with knockout of SETD2 using the CRISPR/Cas9 system. Conversely, B-ALL cell lines already harboring SETD2 heterozygous mutations (REH and RCH) had SETD2 expression restored using an inducible vector system. Western blot analysis was used to confirm the relative expression of SETD2 and downstream markers of DNA damage response in engineered cell lines. Isogenic cell lines were plated with or without HEK 293 stromal cells and then exposed to vincristine, etoposide, cytarabine, prednisone, or mercaptopurine for 72 hours. Cell viability of cells plated without stroma was measured using CellTiter-Glo. Apoptosis of cells plated with stroma was measured using flow cytometric analysis of apoptosis markers Annexin V and 7AAD. Relative proliferation of all untreated cell lines were measured over 168 hours using an automated cell counter.

**Results:**

697 and KOPN-8 clones with either a SETD2 heterozygous mutation or compound heterozygous mutations exhibited similar rates of proliferation compared to their respective isogenic controls. The half-maximal inhibitory concentrations (IC50) of all chemotherapy agents were similar in mutant clones and their isogenic controls, regardless of the presence of stromal cells. REH and RCH with re-expression of SETD2 also had similar rates of proliferation and IC50 compared to their isogenic controls. No increase in DNA damage was observed upon knockout of SETD2.

**Conclusion:**

Loss of SETD2 expression in B-ALL cell lines does not confer increased resistance to conventional chemotherapy agents, either in isolation or when grown in a stromal microenvironment. Conversely, re-expression of SETD2 in lines that already harbored SETD2 mutations does not restore chemosensitivity. We postulate that SETD2 deletions alone may not confer a clonal advantage, but may operate in collaboration with other genetic alterations in a cell context-specific manner.

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Poster # 714

**OUTCOMES OF WEIGHT LOSS DURING INDUCTION THERAPY FOR CHILDHOOD ALL**

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**Background:**

Pediatric patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LLy) often experience significant weight gain during remission induction therapy. However, some patients experience significant weight loss instead. This population is not widely recognized which can lead to the oversight of potentially necessary interventions. Although malnutrition is reported in a general setting, there remains a scarcity of in-depth analysis regarding malnutrition and the unintended outcomes that result.

**Objectives:**

To determine whether significant weight loss during induction therapy decreased likelihood of reaching end of therapy (EOT) or increased risk of death or relapse in pediatric ALL and LLY patients.

**Design/Method:**

This was a retrospective chart review of patients aged 2-20 years diagnosed with ALL and LLY at Cook Children's Medical Center from 1/1/11 to 3/31/17. For each patient, weights at diagnosis and end of induction therapy and dates at EOT, death, and relapse were recorded. Percent weight change from diagnosis to end of induction was grouped into three categories: loss ( $\geq 5\%$  weight loss), gain ( $\geq 5\%$  weight gain), and steady ( $< 5\%$  weight loss or gain). The effects of weight loss on outcomes were examined using logistic regression analyses for whether EOT was reached and Cox regression for death and relapse.

**Results:**

There were 187 patients included. Weight-change categories were as follows: 17% loss, 39% steady, and 45% gain. Eighteen (10%) patients did not reach EOT; 10 (5%) patients died; and 22 (12%) patients relapsed. Compared to patients in the steady category, patients who lost weight were significantly less likely to reach EOT (OR=0.31, 95% CI=0.16-0.63,  $p < 0.01$ ); the odds ratio demonstrated increased risk of death (HR=3.67, 95% CI=0.81-16.52,  $p = 0.09$ ) or relapse (HR=1.83, 95% CI=0.60-5.60,  $p = 0.29$ ), but this did not reach significance. Patients in the steady and gain groups did not significantly differ in outcomes of EOT, death, or relapse ( $p > 0.05$ ).

**Conclusion:**

This research demonstrates that patients who experience malnutrition during induction therapy may be at greater risk for not completing therapy. Those in the loss group had higher mortality rates (13%) than did those in the steady or gain (4%) groups; and a larger sample may have produced a significant effect for death. Therefore, further study is necessary to determine the long-term impact of early malnutrition during therapy and if weight loss during induction therapy should be considered for additional nutritional interventions. It is our goal that this information can be used for future studies and to help develop evidence-based guidelines to modify existing treatment plans.

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Poster # 715

**IDENTIFYING RISK FACTORS FOR DRUG INDUCED LIVER INJURY IN PATIENTS WITH ALL RECEIVING CHEMOTHERAPY**

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**Background:**

Hepatotoxicity in pediatric acute lymphocytic leukemia (ALL) patients receiving chemotherapy is a critical issue for hematology and oncology divisions across the country. Despite speculation of which risk factors promote short- and long-term liver injury, current data is insufficient to

provide surveillance for at risk populations.

**Objectives:**

This study sought to 1) determine risk factors for drug-induced liver injury (DILI) during ALL treatment and 2) evaluate long-term complications using the Drug Safety Service (DSS) program at our institution.

**Design/Method:**

A retrospective cohort study was performed for newly diagnosed patients with ALL, 1-18 years of age, at our institution from 2013 to 2018. Data collection included patient age, sex, self-declared race, BMI, laboratory and imaging studies, and ALL risk classification. Multivariate regularized logistic regression was used to assess the association between risk factors at the time of diagnosis and DILI trigger events (defined by a serum ALT > 5x upper limit of normal (ULN) or serum total bilirubin (BILI)  $\geq$  2xULN). The frequency and duration of events, as well as long-term complications (including cholelithiasis, cholecystectomy, non-alcoholic steatohepatitis (NASH), portal hypertension, hepatic fibrosis and cirrhosis) were also collected for each patient.

**Results:**

In total, 132 ALL patients were analyzed, 89 (67%) of whom triggered for potential DILI event. Regression analysis indicated an increased event odds associated with: high-risk classification (OR 3.65 (CI: 1.44-9.27), p= 0.006) and the upper (4th) quartile (18.93-46.79] of BMI (OR: 7.73 (CI: 1.22-48.92), p=0.03, reference 1st quartile (11.57-15.39]). Age  $\geq$  10 years (OR: 0.57 (CI: 0.13-2.55), p=0.46) and male sex (OR: 0.6 (CI: 0.25-1.43), p=0.25) were not associated with increased risk of DILI. Compared to a Caucasian reference group, indication of either African American or Multiracial race was found to be protective (OR: 0.09 (CI 0.01-0.65), p=0.016, and OR: 0.18 (CI 0.05-0.67), p=0.011 respectively). With respect to long-term effects, chronic cholestasis, gallstones or cholecystitis requiring surgery developed in 4 patients, NASH was observed in 2 patients, and hepatic fibrosis was seen in 1 patient.

**Conclusion:**

Several diagnostic characteristics were identified as significant risk or protective factors for a DILI event during hospitalization. Despite the limited number of patients who have reached >5 years post-chemotherapy, several have experienced complications possibly related to chemotherapy-associated DILI. It is clear further study is needed to determine how DILI risk factors together with event characteristics (e.g. duration of DILI, concurrent infection, treatment phase, etc.) are associated with long-term complications.

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Poster # 716

**HYPOGAMMAGLOBULINEMIA AND THE IMPACT OF IVIG DURING TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA**

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**Background:**

Previous studies have shown that chemotherapy for acute lymphoblastic leukemia (ALL) results in hypogammaglobulinemia. This secondary hypogammaglobulinemia places patients at increased risk for life-threatening infections. While, immunoglobulin replacement therapy (IVIG) for secondary immunodeficiency is supported by numerous reports in the literature, there is a paucity of literature addressing the use of it for supportive care in children. Although several guidelines and algorithms exist to direct the appropriate use of immunoglobulin therapy in adults with malignancy, there are no studies specifically evaluating children with malignancy who are receiving immunosuppressive therapy.

**Objectives:**

To evaluate the role of IVIG in preventing infectious complications and preventing chemotherapy holds in children undergoing treatment for ALL.

**Design/Method:**

We retrospectively reviewed medical records over a 7-year period (2010-2017) to identify patients with ALL who received IVIG due to hypogammaglobulinemia during the maintenance phase of chemotherapy. Exclusion criteria included Down syndrome, administration of IVIG secondary to B-cell aplasia, or infusion of IVIG prior to cycle two of maintenance therapy. Records were reviewed to determine (1) the number of infectious complications before and after initiation of IVIG (based on pre-specified events including positive viral panels, fevers, hospital admissions due to fever) and (2) the number of episodes of neutropenia/chemotherapy holds before and after initiation of IVIG.

**Results:**

We identified 27 patients with a diagnosis of ALL with hypogammaglobulinemia for which they received monthly IVIG infusions during maintenance therapy. The average number of IVIG infusions per patient was 11. Following initiation of IVIG monthly infusions, patients had a statistically significant decrease in the number of oral chemotherapy holds during maintenance, decreasing the number by half (Wilcoxon,  $p=0.035$ ). Patients also had a two-fold decrease in the number of ED visits secondary to fever (Wilcoxon,  $p=0.0003$ ) and the number of hospital admissions secondary to fever (Wilcoxon,  $p=0.018$ ) following initiation of therapy with IVIG.

**Conclusion:**

In this small cohort, we demonstrate that administration of IVIG to correct secondary hypogammaglobulinemia in patients with ALL led to a decrease in oral chemotherapy holds during maintenance therapy. Previous studies have shown that lower adherence to oral mercaptopurine increased relapse risk. Thus, administration of IVIG and subsequent prevention of oral chemotherapy interruptions may ultimately decrease risk of relapse in patients with ALL. Additionally, it decreased infectious complications and febrile illnesses during maintenance therapy. These results offer promising insight to the benefit of IVIG administration during the treatment of pediatric ALL. (Bhatia, J Clin Onc, 2012)

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Poster # 717

## CASEIN KINASE II INHIBITORS SHOW IN VIVO EFFICACY IN AML PATIENT DERIVED XENOGRAFTS

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### **Background:**

Casein Kinase II (CK2) is emerging as a valuable therapeutic target in various diseases, including cancers. Overexpression of CK2 is seen in many malignancies including one third of Acute Myeloid Leukemia (AML), and is strongly associated with poor outcomes. CK2 promotes leukemia cell growth and proliferation via several mechanisms. Phosphorylation of Ikaros tumor suppressor in B cell leukemia leads to impaired transcriptional regulation of cell cycle progression and PI3K pathway genes.

### **Objectives:**

To establish in vivo efficacy of CK2 inhibitor CX-4945 in AML patient derived xenograft models and to determine its mechanism of action.

### **Design/Method:**

Myeloid leukemia cell lines such as U937, MOLM-13. Primary AML patient samples were used for in vitro experiments. CK2 inhibitor, CX-4945 is commercially available. Genome-wide binding studies using chromatin immunoprecipitation coupled with next-generation sequencing (ChIP-seq) of U937 cells with and without Cx-4945 treatment were done.

### **Results:**

Treatment of AML cell lines and primary cells with CX4945 show increased cytotoxicity, apoptosis, cell cycle arrest, and decreased colony formation. Treatment of patient derived xenografts of AML with CX4945 showed significant decrease in leukemia burden and prolonged survival. ChIP-seq followed by quantitative ChIP demonstrated that treatment of AML cell line with 10 uM (IC50) of CX4945 for 24-72hrs enhances binding affinity of Ikaros at the promoter regions of several target genes. Among the significantly Ikaros bound genes (more than two fold change) are anti-apoptotic genes such as BCL2A1 (B Cell Lymphoma 2 related protein A1) and Bcl-xL (B Cell Lymphoma extra-Large); and genes involved in drug metabolism such as cytidine deaminase (CDA). Furthermore, loss of function and gain of function experiments showed that inhibition of CK2 (CK2ShRNA and CX4945) enhances Ikaros-mediated repression of genes involved in apoptosis and drug metabolism.

### **Conclusion:**

CX-4945 has strong antitumor effect in leukemia PDX. Targeting CK2 is a promising therapeutic strategy in leukemia. One of the mechanisms by which CK2 inhibitors exert a therapeutic effect in AML involves enhancing Ikaros' function as a tumor suppressor. Early phase clinical trial to test safety and tolerability of CX4945 in relapsed refractory hematological malignancy are being developed.

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## A ROLE FOR THE NUP214 NUCLEAR PORE PROTEIN IN LEUKEMOGENESIS

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### **Background:**

The t(10;11) CALM-AF10 translocation is a recurrent abnormality in 5-10% of T-cell acute lymphoblastic leukemias. CALM-AF10 leukemias are associated with a poor prognosis, and display elevated HOXA gene expression. However, the mechanism by which CALM-AF10 targets and activates the HOXA locus is unclear. Our lab discovered that CALM-AF10-mediated leukemogenesis requires interaction with the CRM1/XPO1 nuclear export receptor protein, which shuttles proteins to the cytoplasm via the nuclear pore (NUP) complex. Importantly, CRM1 can substitute for CALM: our lab has shown that a CRM1-AF10 fusion activates HOXA genes and is leukemogenic in vivo. CRM1 does not contain a DNA binding domain: we therefore hypothesize that NUP214, a known binding partner for CRM1, mediates the ability of CRM1-AF10 to activate HOXA genes. NUP214 is a partner in leukemogenic translocations (SET-NUP214, DEK-NUP214) that are associated with increased HOXA expression, and NUP214 can localize to Hoxa DNA. In addition, we found that mutating CRM1 residues that mediate binding to NUP214 abrogates CRM1-AF10 leukemogenesis. Based on these observations, we hypothesize that NUP214 can substitute for CRM1, and that a NUP214-AF10 fusion will be leukemogenic.

### **Objectives:**

To determine whether a NUP214-AF10 fusion can activate HOXA gene expression and promote leukemogenesis.

### **Design/Method:**

A NUP214-AF10 fusion expression plasmid was created using overlapping PCR cloning. Expression of NUP214-AF10 protein in both transiently and stably transfected cell lines was assessed by western blot and confocal microscopy. The ability of NUP214-AF10 to activate HOX genes was measured by RT-qPCR. The self-renewal potential of NUP214-AF10-transduced hematopoietic progenitors (HPP) in vitro will be assessed using methylcellulose assays.

### **Results:**

Expression of NUP214-AF10 protein was verified in both transiently transfected HEK293 cells and stably transfected NIH3T3 cells by western blot and immunofluorescence. Using RT-qPCR, we show that NUP214-AF10 is associated with increased expression of HOXA and HOXB genes in NIH3T3 cells.

### **Conclusion:**

We have previously demonstrated that CRM1 is required for CALM-AF10 leukemogenesis, and

that NUP214's interaction with CRM1 plays an important role. Since NUP214 is involved in leukemogenic translocations, we are investigating the importance of NUP214 in CALM-AF10 leukemogenesis by directly fusing it to AF10. Here we show that the NUP214-AF10 fusion protein can be expressed in two different cell lines, and that NUP214-AF10 expression is associated with increased HOXA and HOXB gene expression, similar to CALM-AF10 and CRM1-AF10. Methylcellulose assays are underway to assess the self-renewal potential of NUP214-AF10-transduced HPP. These studies will help establish the CRM1/NUP214 interaction as a potential therapeutic target in leukemias.

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Poster # 719

## **GLUCARPIDASE USE IN CHILDHOOD ALL: A BAYESIAN ANALYSIS OF CLINICAL AND GENETIC RISK FACTORS**

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### **Background:**

Carboxypeptidase G2 (CPDG2), also known as glucarpidase, is a rescue drug for patients who develop delayed clearance or kidney injury from high-dose methotrexate (MTX). While there is evidence that Hispanic ethnicity is associated with CPDG2 use, this has not been confirmed in independent studies, and little is known about other risk factors.

### **Objectives:**

Our objective was to evaluate the role of clinical and genetic factors on CPDG2 use.

### **Design/Method:**

Cases (patients who received CPDG2) and controls were identified in a chart review of patients with ALL who received MTX doses between 1-5g/m<sup>2</sup> at Texas Children's Cancer Center during the period 10/2010-12/2018. Multivariable Bayesian logistic regression was performed to evaluate the probability of CPDG2 use given a range of variables, including self-reported ethnicity, MTX dose, body mass index (BMI), ALL subtype, and age at diagnosis. The effects of 49 genetic variants previously associated with MTX metabolism were also evaluated on a subset of patients.

### **Results:**

A total of 426 patients were identified who received 1601 doses of MTX. Of the 18 patients who received CPDG2, 17 (94%) were self-identified Hispanic. Mean age of the patients was 8.9 years (SD: 5.0). The variables that demonstrated strong associations with CPDG2 were Hispanic ethnicity (OR: 3.58; 95% compatibility interval [CI]: 1.35 – 8.06) and older age (OR of 1.81 per 1 SD increase in age; 95% CI: 1.16-2.89). Although other variables' 95% CI included the null, evaluation of the posterior predictive distribution revealed that B-ALL had an 80.6% probability of positive association with CPDG2 use compared to T-ALL and BMI >95% had an 85.0% probability compared to BMI between 10-85%. There were 177 patients in the genomic cohort,

11 of which received CPDG2. Analysis of MTX-related genotypes revealed that compared to homozygous patients with the common allele of ABCC4 rs7317112 (AA), heterozygous patients (AG) had a 93.2% probability of positive association, whereas homozygous patients with the minor allele (GG) had an 89.6% probability. Variants in three other genes (SLC19A1 rs1051266, ARID5B rs4948496, and TSG1 rs9345389) also demonstrated probabilities of association between 86-88%.

### **Conclusion:**

Our assessment indicates that self-reported Hispanic ethnicity and older age are positively associated with CPDG2 use. Examination of the posterior probability distribution indicates there is a high chance that BMI >95%, B-ALL, and heterozygosity or homozygosity for the risk allele at rs7317112 are positively associated with CPDG2 use. These results identify important risk factors for CPDG2 use and suggest promising areas of further study.

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Poster # 720

## **THE SIX1 HOMEBOX GENE IS A NOVEL THERAPEUTIC TARGET IN CALM-AF10 LEUKEMOGENESIS**

**Waitman Aumann, Catherine Lavau, Donald Tope, Amanda Conway, Samarjit Patnaik, Juan Marugan, Hengbo Zhou, Rui Zhao, Heide Ford, Dan Wechsler**

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### **Background:**

The CALM-AF10 translocation is found 5-10% of T-cell acute lymphoblastic leukemias (T-ALL), and a subset of acute myeloid leukemias (AML). CALM-AF10 leukemias are characterized by elevated expression of proleukemic HOXA genes. Since HOXA genes are difficult to target, we hypothesized that identification of non-HOXA CALM-AF10 effector genes could potentially yield novel therapeutic targets. We took advantage of our prior observation that the nuclear export factor CRM1/XPO1 tethers CALM-AF10 to HOXA genes by interacting with a nuclear export signal within CALM. Using next generation sequencing, we determined that expression of SIX1, a homeobox gene involved in embryonic development, is increased in CALM-AF10 leukemias and decreased in response to the CRM1 inhibitor, Leptomycin B (LMB). SIX1 and its cofactor EYA2 are overexpressed in numerous solid tumors, but have not previously been postulated to play a role in leukemias.

### **Objectives:**

To evaluate the role of SIX1 in CALM-AF10 leukemias.

### **Design/Method:**

RT-qPCR and Chromatin Immunoprecipitation (ChIP) were performed using bone marrow progenitors transduced with CALM-AF10 or an empty vector, with and without LMB. Methylcellulose colony assays assessed SIX1's ability to enhance self-renewal of hematopoietic progenitors. CRISPR-Cas9, with a tet-inducible Cas9, was used to silence Six1 in CALM-AF10



leukemia cells, and cell proliferation and expression of downstream Six1 targets using RT-qPCR were assessed. We also evaluated CALM-AF10 leukemia cell proliferation and downstream targets of Six1 following treatment with a pharmacologic inhibitor of the Six1/Eya2 complex (8430).

**Results:**

RT-qPCR confirmed overexpression of SIX1 in CALM-AF10 leukemias, and showed decreased SIX1 expression in the presence of LMB. CHIP showed that CALM-AF10 binds the SIX1 gene locus. Overexpression of SIX1 in murine fetal liver progenitors was sufficient to increase self-renewal potential. Six1 was successfully silenced in CALM-AF10 leukemia cells and resulted in slowed cell proliferation compared to empty vector. The 8430 inhibitor reduced cell proliferation in CALM-AF10 cells compared to cells treated with DMSO alone. Finally, downstream targets such as SLC2A1, CDK2, and CYCLINA2 were decreased in both SIX1-knockdown and 8430-treated CALM-AF10 leukemia cells.

**Conclusion:**

The SIX1 homeobox gene is highly expressed during embryogenesis with and its expression is normally silenced post-embryogenesis. We determined that Six1 is upregulated in the presence of CALM-AF10 and increases the self-renewal potential of hematopoietic progenitors. Knockdown of Six1 as well as inhibition of the Six1/Eya2 complex with 8430 slowed the growth of CALM-AF10 leukemia cells. These observations suggest that SIX1 plays a pathogenic role in leukemogenesis, and is a novel therapeutic target in CALM-AF10 leukemias.

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Poster # 721

**HYPOGAMMAGLOBULINEMIA IN ADOLESCENTS AND YOUNG ADULTS ON THERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA**

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**Background:**

Acute lymphoblastic leukemia (ALL) is a leading cause of cancer-associated deaths in adolescents and young adults (AYA; 15-39 years). The use of pediatric based intensive chemotherapy regimens is often associated with infectious complications in this age group.

**Objectives:**

To determine the incidence of hypogammaglobulinemia and infectious complications in AYA patients with de novo B and T cell ALL treated with a pediatric based protocol at our institution, and to study the impact of these findings on relapse risk and overall survival.

**Design/Method:**

A retrospective chart review was conducted. Demographic and outcome variables were compared in patients with documented hypogammaglobulinemia (serum immunoglobulin (IgG) <2 standard deviations below mean; 639 mg/dL) to those with no hypogammaglobulinemia,

using chi-square or Wilcoxon test. The Kaplan-Meier method was used to assess overall survival (OS) and recurrence free survival (RFS).

**Results:**

Of the 52 AYA patient charts reviewed, 13 (25%) had hypogammaglobulinemia documented and 7 (13.5%) did not (median IgG = 436 mg/dL vs 862 mg/dL,  $p=0.002$ , respectively). IgG levels were not obtained or checked in 32 patients (61.5%). Patients with hypogammaglobulinemia were older (median age 18.0 vs. 16.0 years,  $p=0.03$ ), had a greater number of febrile neutropenia episodes ( $p=0.02$ ) and more infectious events (median 9 vs. 5,  $p=0.06$ ), compared to patients with normal IgG levels. Ten (77%) of the patients with hypogammaglobulinemia received at least one dose of IVIG (mean number of IVIG doses =  $4.2\pm 7.5$ ). Total number of hospital admission days were not different within the two groups (median 36.5 vs. 41.0 days,  $p=0.8$ ). The 5-year RFS was 84% versus 100% for patients with and without hypogammaglobulinemia, respectively ( $p=0.3$ ). The 5-year OS was excellent (100%) for both groups.

**Conclusion:**

Hypogammaglobulinemia and febrile neutropenia occur frequently in AYA patients with ALL. However, IgG levels were not obtained in the majority of the patients, underscoring the need to incorporate testing into routine practice. Further studies are needed to confirm these findings and establish specific criteria for IVIG replacement.

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Poster # 722

**INCREASED TREATMENT-RELATED TOXICITY IN HISPANIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA**

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**Background:**

Hispanic ethnicity is associated with worse survival in childhood acute lymphoblastic leukemia (ALL). However, data is lacking for ethnicity-related disparities in the incidence and severity of treatment related toxicities (TRTs) for childhood ALL therapy.

**Objectives:**

To investigate rates of overall and specific TRTs in Hispanic vs non-Hispanic patients and their impact on EFS.

**Design/Method:**

This is a single center retrospective chart-review of 260 pediatric patients, ages 1-21, diagnosed with ALL between January 2008 and December 2013 and receiving a first therapy attempt with a Children's Oncology Group (COG)-style ALL regimen. TRTs were graded per the Common Terminology Criteria for Adverse Events version 4.0. Clinically significant TRTs included fractures, osteonecrosis, and peripheral neuropathy grade 2 or above, infections, thrombosis, pancreatitis, and hyperbilirubinemia grade 3 or above, and transaminitis grade 4 and above. The

X2 test was used to compare the proportions of Hispanic and non-Hispanic patients with and without the selected TRTs. Multivariable logistic regression models evaluated association of TRTs after controlling for known potential confounders. Univariable and multivariable Cox regression models were used to examine the association of patient demographics with EFS and time to TRT.

**Results:**

Of the 260 pediatric patients, 90% had B ALL (56% NCI Rome high-risk), 10% had T ALL, 54% were male, 20% were obese, and 77% were Hispanic. The median age at diagnosis was 7 years. The majority (n=172, 66%) of patients experienced one or more clinically significant TRT. The most common TRTs were gastrointestinal and hepatobiliary events (n=114, 66%); infectious events were the second most common (n=111, 65%). A higher proportion of Hispanic patients experienced at least one severe TRT than non-Hispanic patients (70% vs 54%, p=0.03). Logistic regression models revealed a nearly twofold increased risk of developing TRTs among Hispanic patients (odds ratio = 1.88, 95%CI 0.99-3.59, p=0.057). Hispanic ethnicity was associated with a lower 5-year EFS (77% vs 91%) (odds ratio 2.03, CI 0.80-5.17, p=0.1) but this was not affected by the presence of TRT (p>0.05).

**Conclusion:**

Ethnicity increased risk for overall severe TRT during frontline therapy for children and adolescents with ALL. In this study we confirmed in a new cohort that Hispanic patients were at higher risk for poorer EFS, but this was not mediated by TRT or implicit therapy limitations. Future studies will investigate other factors that may be affecting survival in this population such as obesity, pharmacogenetics, and biology.

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Poster # 723

**PALIFERMIN AS PRIMARY PROPHYLAXIS FOR MUCOSITIS-RELATED COMPLICATIONS FROM COPADM**

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**Background:**

Cyclophosphamide, vincristine, prednisone, doxorubicin, and high-dose methotrexate (COPADM), is frontline therapy for many pediatric and adolescent patients with Non-Hodgkin lymphoma (NHL). This regimen is associated with high rates of mucositis-related complications. Palifermin is a recombinant keratinocyte growth factor that can prevent mucositis by triggering the proliferation, differentiation, and migration of epithelial cells throughout the gastrointestinal tract. Recently, palifermin use has been reported in non-hematopoietic stem cell transplant pediatric patients for secondary prevention of chemotherapy-induced mucositis, including anthracyclines and/or high-dose methotrexate.

**Objectives:**

We aimed to describe mucositis-related complications from patients that have received COPADM at our institution and report our experience using palifermin as primary prophylaxis for mucositis in an adolescent patient with NHL that received two cycles of COPADM.

**Design/Method:**

We retrospectively evaluated patients from 2009-2019 that received at least 1 cycle of COPADM. Our primary endpoint was mucositis-related complications. Secondarily, we describe our experience with palifermin as primary prophylaxis for chemotherapy-induced mucositis. This patient received palifermin 180 mcg/kg/dose in the outpatient setting 3 days prior to two COPADM courses.

**Results:**

There were a total of 16 patients that received 36 cycles of COPADM during the study period. Readmissions related to mucositis occurred in 14 of the 16 patients, after 25 cycles of COPADM. The average inpatient stay for patients readmitted was 8 days per course. The average number of days on scheduled opioids was 6 days per course. A total of 6 patients required TPN use from mucositis-related complications. In our patient that received palifermin as primary prophylaxis for mucositis prior to COPADM readmission for mucositis, TPN use, scheduled opioids, or IV opioids after either course was not required. There were no insurance issues to obtain approval for palifermin use in the outpatient setting. The patient tolerated palifermin well and achieved a complete remission after completing their full course of therapy. Of note, the patient did not receive palifermin prophylaxis prior to high-dose methotrexate and cytarabine and developed significant mucositis.

**Conclusion:**

Mucositis is a common complication following COPADM and can lead to readmissions, prolonged hospital stays, TPN use, and need for opioid medications. In our patient, palifermin was effective as primary prophylaxis for COPAD-related mucositis. Palifermin should be considered for primary prophylaxis for patients receiving COPADM based on the high rates of mucositis and potential benefits of palifermin. More data is needed to better evaluate the impact of this preventative strategy.

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Poster # 724

**PROGNOSTIC IMPLICATION OF INTERIM PET CT IN PAEDIATRIC HODGKIN LYMPHOMA**

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**Background:**

Paediatric Hodgkin lymphoma (HL) constitutes 40% of childhood lymphomas and has a 5-year PFS of >90%. However, a significant number suffer from treatment-related morbidity and mortality. Interim PET has demonstrated to be a good predictor of prognosis in adults with HL. Childhood protocols now focus on reducing treatment-associated toxicity, while maintaining

high cure rates with response adapted therapy using interim PET CT. However, the experience is limited.

**Objectives:**

To determine the prognostic value of interim PET CT in childhood HL patients treated with response-adapted strategy.

**Design/Method:**

A retrospective study was done from September 2010–March 2016. All children <15 years at diagnoses, who received 1st line treatment, and had interim PET assessment after 2 courses of chemotherapy (ABVD or OEPA) were included. SUV > 2.5 was considered PET-positive. Demographic details, investigation results and treatment outcomes were retrieved from the hospital database. Treatment strategy was decided according to prognostic factors at diagnosis and interim PET CT. Kaplan and Meier survival curves and Cox regression were used to estimate survival and determine prognostic factors. Positive predictive value (PPV) and negative predictive value (NPV) of PET were calculated using 3-years of follow-up as the endpoint. Relapse and persistent disease were considered as treatment failure.

**Results:**

Forty-seven children (40 boys and 7 girls) with a median age of 9 years (4 -15 years) were included. Majority had  $\geq$  stage 3(70%). B symptoms were seen in 27 (57.4%), bulky disease in 21 (44.6%) and extranodal disease in 34 (74.3%). 46 children completed 1st line treatment of which 45 achieved CR and 1 had persistent disease. There were 7 treatment failures including 1 death. Interim PET scan was positive in 21 and negative in 26. Overall 3-year OS and PFS were 95.7% (SE 4.3%) and 91.4% (SE 4.1%). Mean survival was 108 months (104- 112 months). Univariate analysis failed to show the significance of interim PET as well as other prognostic factors such as age, clinical stage, B symptoms, extranodal disease, bulky disease, bulky mediastinal disease, LDH, ESR and serum albumin on survival. Three-year PFS for PET-positive and negative groups were 90.5 % (SE 6.4%), and 92.3 % (SE 5.2%); 4 out of 21 PET-positive and 3 out of 26 PET negative had treatment failure. PPV and NPV PET for predicting 3-year PFS was 19.04% and 88.46%.

**Conclusion:**

PET CT was not found to be a significant prognostic marker in our study. However, it had a high negative predictive value.

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Poster # 725

**CELL-SPECIFIC GENE EXPRESSION PROFILING OF A PEDIATRIC HODGKIN LYMPHOMA COHORT**

**Jennifer Agrusa, Elmoataz Abdel, Howard Lin, Brooks Scull, Harshal Abhyankar, Nmazuo Ozuah, Olive Eckstein, Terzah Horton, Kala Kamdar, Ken McClain, Chris Man, Rikhia Chakraborty, Carl Allen**

**Background:**

Hodgkin Reed-Sternberg (HRS) cells constitute ~1% of Hodgkin lymphoma (HL) tumors. Studies characterizing HRS gene expression have been limited in these rare cells, and the majority of existing data has focused on adult HL.

**Objectives:**

To inform underlying mechanisms of HL pathogenesis and identify cell-specific clinical biomarkers by isolating viable cells from pediatric HL tumors and defining the transcriptomes of HRS cells and infiltrating lymphocytes.

**Design/Method:**

Multi-parameter flow cytometry was used to sort HRS cells, CD4+/CD8+ T-cells, and CD20+/30+ B-cells from pediatric subjects' HL lesions and control tonsils. Purity was confirmed by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC). Affymetrix GeneChip HTA 2.0 was used to assess the gene expression profiles (GEPs) for HRS cells, HL CD4+ and CD8+ T-cells, control tonsillar CD20+, CD30+, CD4+, and CD8+ cells, and HL cell lines. Unsupervised hierarchical clustering and principal component analysis (PCA) determined relatedness, and Cibersort confirmed the phenotype of the sorted cell types. GEPs of HL cells were compared to respective controls using a univariate t-test. Significance was determined using a multivariate permutation test with the confidence level of FDR assessment at 80 percent and the maximum allowed proportion of false-positive proteins at 0.1. DEGs were analyzed through gene set enrichment analysis (GSEA) and ingenuity pathway analysis (IPA).

**Results:**

GEP comparisons were performed for HL samples: HRS vs. control tonsil CD20+/CD30+ (1934/3846 DEGs), HL CD4+ vs. control CD4+ (635 DEGs), HL CD8+ vs. control CD8+ (2 DEGs). HRS cells demonstrated over-expression of genes associated with T-cell pathways, which may reflect an innate T-cell signature rather than T-cell rosetting and contamination, as HRS cells clustered separately from T-cells in unsupervised hierarchical clustering and PCA. Cibersort analysis of HRS cells revealed a heterogeneous phenotype that may reflect aberrant differentiation. Transcriptomic analysis of HRS cells vs. control CD30+ cells revealed a 2-fold downregulation of telomere maintenance/packaging genes ( $P < .001$ ) and association with genes involved in cellular senescence. Increased expression of genes associated with EBV status and therapy response were also identified when comparing clinical characteristics within HRS cells.

**Conclusion:**

In this study, highly purified HRS cell populations were isolated from whole HL lesions in a pediatric HL cohort. The ability of this study to identify candidate clinical biomarkers within a small cohort supports additional collection and analysis of prospectively collected biological specimens in an expanded cohort to validate these findings and test these cell-specific biomarkers into the current risk stratification strategies of prospective clinical trials.

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## **CD3 T-CELL INFILTRATION AND PROGNOSIS IN PEDIATRIC PTLD POST SOLID ORGAN TRANSPLANT**

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### **Background:**

Post-transplant lymphoproliferative disease (PTLD) is a heterogeneous disease and there are competing considerations in the treatment of these complex patients. A consensus on prognostic factors to stratify patients is critical. Previous studies, involving mostly adult patients, concluded that high CD3 T-cell density in the tumor environment is associated with better outcomes.

### **Objectives:**

To determine if intratumoral CD3 T-cell density at diagnosis is prognostic of progression free survival (PFS) and overall survival (OS) in pediatric patients with polymorphic and monomorphic PTLD.

### **Design/Method:**

Cases of PTLD treated in Toronto, Canada between 2000-2017 were identified. Clinical variables and outcome data were collected through databases and chart review. The most diagnostic area from lesional tissue was identified on H&E sections. Tissue obtained with insufficient size and quality was excluded. Using corresponding slides with CD3 immunohistochemical staining, counting of CD3-positive and CD3-negative cells at 400x magnification was performed by 3 independent reviewers, including one blinded pathologist. CD3 T-cell density was expressed as CD3-positive cells per 100 cells. Counts with significant discordance (>20% difference) were recounted. Cox proportional hazard model was used to quantify the hazard ratio of clinically selected variables for censored data analysis. ROC was performed to determine an optimal break-point for CD3.

### **Results:**

Thirty-six cases of polymorphic and monomorphic PTLD were included. Median age at PTLD diagnosis was 9.1 years (range 0-17 years). Patients had received heart (n=13), lung (n=8), liver (n=7), kidney (n=6), or multiple-visceral organs (n=2) transplants and 19 recipients were EBV-seronegative and received organs from EBV-seropositive donors. Median time from transplant to PTLD was 17 months (range 3 - 123 months). Histology subtypes included polymorphic (n=8) and monomorphic (n=28). Stages at diagnosis were 1 (n=5), 2 (n=3), 3 (n=24) and 4 (n=4).

Six cases required recounting due to significant discordance of initial CD3 T-cell density between reviewers. A higher CD3 T-cell infiltration was not predictive of PFS or OS. ROC area under the curve was 0.5 thus no optimal break-point could be identified. Stage 4 disease was identified to be significant by univariate analysis with respect to OS (HR 4.09, p=0.04). Factors deemed to not be significant to PFS or OS were EBV recipient/donor mismatch, time from transplant and histological type.

**Conclusion:**

Intratumoral CD3 T-cell density is not prognostic in this study. The methodology attempted to address PTLD histologic variation by identifying the most relevant lesional tissue to assess CD3 T-cell infiltration.

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Poster # 727

**STUDY ON ADHERENCE TO IMATINIB THERAPY AMONG CHILDREN WITH CHRONIC MYELOID LEUKAEMIA**

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**Background:**

Adherence to oral imatinib over very long periods is of utmost importance for optimal outcomes in Chronic Myeloid Leukaemia (CML). The ability of the treating physician to recognize non-adherence is difficult during busy outpatient visits. Measurement of adherence among children and adolescence is particularly challenging.

**Objectives:**

To assess adherence to Imatinib therapy in children with CML and find out the factors for non-adherence.

**Design/Method:**

It was a prospective questionnaire and interview-based study over a period of 2 years on children with CML attending outpatient clinic. We used, patient reported compliance measurement known as Child Drug adherence Questionnaire, a validated questionnaire developed indigenously to evaluate adherence to oral Imatinib therapy in children with CML. Score  $\geq 3$  was considered as non-adherent and  $< 3$  adherent. We also used a pill diary and pill count to assess adherence. All patients included received health education emphasizing the importance of adherence to treatment.

**Results:**

Total children included were 39 (Male=23 and female=16). The median age was 15 years (5-30). The nonadherence rate as per our scored questionnaire was 28.2%. Intentional missing of taking Imatinib was seen in 5%. Relationship between the variables- age, gender, fathers' occupation, mother's occupation, parental status, family type, patient's occupation and duration of treatment to adherence scores were studied. Patients attending school were more adherent than others ( $p=0.05$ ). Lower adherence was seen when the duration of therapy was longer ( $p=0.01$ ). Poor adherence was also related to poor disease control ( $p=0.001$ ). Non-adherence was in 37.5% in girls and 21.7% in boys ( $p=0.28$ ). Adherence measured with pill diary and questionnaire scores showed a high degree of correlation ( $p=0.01$ ). Pill count tallied with the pill diary maintained.



**Conclusion:**

Our study showed that adherence to Imatinib therapy is still far from optimal. The use of more than one method is recommended to identify nonadherence. Those who are post-school-age, female gender and those who had been on Imatinib for a longer duration showed higher nonadherence. Special attention needs to be paid to these patient populations to reinforce adherence. The questionnaire and the pill diary are good tools to measure adherence in children on long term Imatinib treatment. More research needs to be done to complement these indirect tools with direct measures like plasma Imatinib levels.

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Poster # 728

**ABERRANT MATURE MYELOID CELL CD56 EXPRESSION IN DOWN SYNDROME IS NOT LINKED TO LEUKEMOGENESIS**

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**Background:**

Transient myeloproliferative disorder (TMD) is frequently seen in neonates with Down syndrome (DS). Although greatly a self-limited disorder, a quarter of the survivors later develop acute myeloid leukemia (AML), predominantly megakaryoblastic phenotype. Expression of neuronal cell adhesion molecule, CD56 is seen in some DS-AML cases and has been proposed as a promoter of AML development overall. Furthermore, expression of CD56, has been observed on non-leukemic myeloid cells in some DS cases, which could be a reflection of dysplastic myelopoiesis.

**Objectives:**

To investigate the associations between mature myelo-monocytic CD56 expression patterns in TMD, non-TMD and leukemia cases with DS.

**Design/Method:**

In this retrospective study, patients with DS who had peripheral blood flow cytometric study performed along with infants without DS who had thrombocytopenia serving as controls were analyzed. Flow cytometry was used to investigate for possible TMD or leukemia in these cases, which presented with thrombocytopenia or leukocytosis among others. Student's t test and Pearson's correlation analysis were performed for assessment of statistical significance.

**Results:**

Flow cytometric data was reviewed in DS infants, mostly newborns, 19 with and 22 without TMD, and 4 DS children with AML and 3 with ALL and 10 control cases. Compared with non-TMD DS patients, DS-TMD cases had greater CD45-dim populations (25% vs. 2%; P=0.007) with higher CD41/61-positive, immature megakaryoblastic cells (9.5 vs. 0.05; P=0.036) reflective of TMD process. There was no significant difference in granulocyte and monocyte

expression of surface markers analyzed, including CD56 between TMD and non-TMD DS groups. Both groups separately showed increased granulocyte and monocyte CD56 expression in comparison with control cases ( $P < 0.001$ ). There were positive correlations in CD56 expression between granulocyte and monocyte populations ( $P = 0.031$ ) when these cases were grouped together,; a positive correlation between granulocyte CD56 expression and lymphocyte CD4/CD8 ratio ( $P = 0.026$ ), and a negative correlation between granulocyte CD56 and CD13 expression ( $P < 0.001$ ). In 7 cases of leukemia, expression of granulocyte and monocyte CD56 were similar to other DS groups. In 8 DS-TMD cases, follow up testing in a median of 15 months (6 – 36) revealed similar CD56 expression patterns in granulocytes and monocytes with age-appropriate mean corpuscular volume values and decreased CD4 lymphocytes ( $P = 0.016$ ).

**Conclusion:**

Granulocyte and monocyte aberrant/dysplastic CD56 expression is an inherent characteristic of some DS patients irrespective of presence of TMD or leukemia. Interestingly, decreased granulocyte CD13 expression was observed as well as higher lymphocyte CD4/CD8 ratio trend in DS cases with dysplasia.

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Poster # 729

**DISCREPANCIES BETWEEN F-18-FDG PET/CT AND CONVENTIONAL IMAGING IN PEDIATRIC PATIENTS WITH LCH**

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**Background:**

Accurate risk stratification of LCH is essential as treatment can range from conservative management in single system disease, low-risk for CNS involvement lesions, to intensive chemotherapy for multi-system or high-risk disease. Additionally, being able to differentiate active from inactive lesions is essential for both prognostic reasons and to avoid potentially unnecessary treatment.

**Objectives:**

To show that F-18-FDG PET/CT is a necessary imaging modality for the diagnosis of LCH and monitoring response to treatment.

**Design/Method:**

A retrospective review was performed on all patients with histopathology confirmed LCH at CCHMC between 2009 and 2019. PET/CT's at either the time of diagnosis or the first available scan were compared to other imaging modalities performed within 1 month as long as no major medical or surgical intervention had taken place in the interim.

**Results:**

101 PET/CT's were included in the review. A discrepancy between PET/CT and conventional

imaging occurred on 41 occasions. On 14 occasions, increased uptake was observed on PET in an area with no identifiable lesion on conventional imaging. On 27 occasions, lesions were found on conventional imaging where no increased uptake was observed on PET.

On 7 skeletal surveys, 1 radiograph, 6 diagnostic CT's, 1 MRI, and 5 CT portions of the PET/CT, no lesion was identified in an area with increased F-18-FDG uptake. This occurred on 12 instances in bone and 1 in the thymus.

On 10 skeletal surveys, 3 diagnostic CT's, 13 MRI's, 2 bone scans, and 3 CT portions of the PET/CT, a lesion was identified in a location without increased F-18-FDG uptake. This occurred on 24 instances in bone, 6 in the CNS, and 1 in the lungs.

**Conclusion:**

F-18-FDG PET/CT is vital in the evaluation of LCH lesions given its ability to detect LCH lesions not detectable on conventional imaging modalities, as well as its ability to distinguish active from inactive disease. MRI and diagnostic CT are still useful adjunctive tests for identification of CNS and lung lesions.

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Poster # 730

**TREATMENT OF REFRACTORY ROSAI-DORFMAN DISEASE WITH THE MEK INHIBITOR TRAMETINIB**

**Clinton Carroll, Amy Greer, Misty Evans, Kathryn Bruce, Cheryl Edens, Ketsia Pierre, Jennifer Domm, Haydar Frangoul**

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**Background:**

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is a non-Langerhans cell histiocytosis that classically presents with markedly enlarged cervical lymphadenopathy. Treatment has historically ranged from observation only to systemic steroids to clofarabine, but new treatment strategies are emerging. The mitogen-activated protein kinase (MAPK) pathway is aberrant in certain histiocytic disorders, and targeting this pathway is an emerging therapeutic strategy. MEK inhibition is increasingly being used to mitigate the side-effects of BRAF inhibitors in Langerhans cell histiocytosis and as an independent means of treating histiocytoses with KRAS mutations. An adult patient with Rosai-Dorfman disease and KRAS mutation has been successfully managed with the MEK inhibitor cobimetinib.

**Objectives:**

We report the case of a pediatric patient with refractory Rosai-Dorfman disease who progressed despite steroids, clofarabine, and a combination of methotrexate and mercaptopurine, but then responded to the MEK inhibitor trametinib.

**Design/Method:**

This is a case report.

**Results:**

A 2 year old male child was referred to our clinic for evaluation of cervical lymphadenopathy after failing to respond to antibiotics. Exam and imaging revealed massively enlarged cervical lymph nodes with no other adenopathy in the chest, abdomen, or pelvis. Biopsy of one of the enlarged cervical nodes showed an abundance of CD68+ S100+ histiocytes with emperipolesis and scant eosinophils, all consistent with a diagnosis of Rosai-Dorfman disease. The child was started on prednisone (2 mg/kg/day) but soon developed worsening night sweats and weight loss with progressive adenopathy. He next received two cycles of clofarabine (each cycle consisting of five 25 mg/m<sup>2</sup> doses) but progressed and was transitioned to leukemia-like maintenance therapy with mercaptopurine (75 mg/m<sup>2</sup>/day) and methotrexate (20 mg/m<sup>2</sup>/week). These were stopped after several months due to poor response and he was ultimately started on the MEK inhibitor trametinib (0.025 mg/kg/day) after NextGen sequencing of his original biopsy revealed a KRAS mutation (KRAS K117N). Trametinib was obtained through a Novartis compassionate use trial. Clinically he had significant decrease in the cervical lymphadenopathy and more than 50% decrease in the SUV activity by PET. He has been on trametinib now for approximately 16 months with no progression and has tolerated the drug well with easily controlled nausea being the only side-effect.

**Conclusion:**

To our knowledge this is the first report of a child with Rosai-Dorfman disease managed with the MEK inhibitor trametinib. MEK inhibition should be considered in pediatric patients with refractory Rosai-Dorfman disease and KRAS mutations.

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Poster # 731

**VIRAL- ASSOCIATED HEMOPHAGOCYtic LYMPHOHISTIOCYTOSIS:  
EXPERIENCE IN OMAN**

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**Background:**

Familial hemophagocytic lymphohistiocytosis (HLH) is relatively common in Oman. It usually presents early in life, and requires hematopoietic stem cell transplantation (HSCT) as a curative therapy after induction immunosuppressive treatment. Secondary HLH is often triggered by infection, malignancy, autoimmune or metabolic disorders. Herpes viruses are the most commonly reported infectious trigger for HLH in both primary and secondary HLH. Little is known on epidemiology, optimum treatment and outcome of viral-associated HLH in Oman.

**Objectives:**

To study clinical and laboratory characteristics, treatment and outcome of viral- associated HLH in Omani children.

**Design/Method:**

This is a retrospective descriptive study looking at Omani children managed for viral-associated HLH between January 2013 and December 2019. Diagnosis of HLH was based on HLH 2004 criteria. Laboratory data and patient medical records were used to describe their demographic data, clinical features, management, complications and outcome.

**Results:**

Eleven children were managed for viral-associated HLH during the study period. Median age at presentation was 6 years (3 months- 12 years). Fever, cytopenia, hyperferritinemia and evidence of hemophagocytosis in bone marrow were the most consistent findings.

All the patients who developed viral-associated HLH have either genetic predisposition or underlying comorbidities. Four patients had genetic predisposition to HLH (Chediak-Higashi syndrome, Griscelli syndrome and XIAP). One patient had familial HLH associated with perforin deficiency. Of the six children who had underlying disease, two had Acute lymphoblastic leukemia (ALL), two were post-HSCT, one had Hodgkin lymphoma and one had isovaleric acidemia.

Viral screening confirmed EBV in four patients, CMV in four, parainfluenza in two, and adenovirus in one patient.

Treatment of HLH was tailored for each case. Immunosuppressive therapy (dexamethasone + etoposide ± Cyclosporine) ± antiviral therapy, followed by HSCT was the treatment approach for patients with genetic predisposition to HLH. Antiviral therapy was used for 4 patients (3 with CMV infection and 1 with adenovirus). Rituximab was given to two patients with EBV associated HLH. Complete resolution of HLH was reported in 9 patients (82%). Two patients died secondary to HLH complications, one patient with isoveoremic academia died with multi-organ system failure and one patient with perforin deficiency died with respiratory failure.

**Conclusion:**

Viral associated HLH is more likely to be encountered in children with genetic predisposition to HLH or children with underlying comorbidities. The outcome is overall good with appropriate used of immunosuppressant medications, antiviral therapy and good supportive care.

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Poster # 732

**LANGERHANS CELL HISTIOCYTOSIS IN PEDIATRIC PATIENTS AT THE HOSPITAL NACIONAL DE NIÑOS, COSTA RICA.**

**Carolina Orduz Illidge, Karla Chaves Herrera, Kathia Valverde Muñoz**

*National Children's Hospital of Costa Rica Dr. Carlos Saenz Herrera, San Jose, San Jose, Costa Rica*

**Background:**

Langerhans Cell Histiocytosis (HCL) is a rare disease characterized by clonal proliferation of

CD1a + / CD207 + myeloid dendritic cells, which occurs in all age groups, with varying degrees of systemic involvement. In the latest reviews, it has been defined as a myeloid neoplasm with a significant inflammatory component, finding recurrent mutations of the MAPK pathway in genetic studies. This study was designed to evaluate the descriptive epidemiology of LCH in Costa Rica, using data from population at the National Children's Hospital.

**Objectives:**

Describe the incidence, epidemiological clinical characteristics, evolution, management and response to treatment of children under 13 years of age with a diagnosis of Langerhans Cell Histiocytosis and its variants (Rosai Dorfman), assessed at the National Children's Hospital of Costa Rica from January 2009 to December 2017.

**Design/Method:**

This study is observational, descriptive, retrospective, based on the review of physical and electronic clinical records. 69 patients were identified in the National Children's Hospital statistical registry with the diagnosis of LCH, of which 16 patients were excluded; leaving for analysis 53 cases. Three of the patients were diagnosed with Rosai Dorfman disease, leaving 50 cases with a diagnosis of HCL.

**Results:**

The annual incidence rate was 4.9/million per year children aged less than 13 years. Bone and skin were the most commonly involved organs at diagnosis, of which 52.5% were multifocal. The classification of the disease was: Single systemic in 76% of cases, 28% multisystemic without risk organs (MS RO-) and 10% multisystemic with risk organs (MS RO +). The patients were treated according to the protocol standard arm LCH II / III from the Histiocyte society. There was complete remission in 80% of cases and 20% of patients presented reactivation. Three patients died during the study period, (one due to MS RO+, another one for sepsis, and the third one from concomitant Acute lymphoblastic leukemia), which corresponded to 6%. The overall survival rate was 93.3%.

**Conclusion:**

This study evidenced the main features of LCH incidence in the overall population of Costa Rica and was consistent with previous studies reported in other parts of the world, including high income countries.

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Poster # 733

**PREDICTIVE PHARMACOKINETIC MODEL OF EMAPALUMAB PLASMA CONCENTRATIONS IN HEALTHY VOLUNTEERS**

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**Background:**

Emapalumab is a fully human anti-interferon (IFN)-gamma monoclonal antibody (mAb) that binds to and neutralizes IFN-gamma. Emapalumab is approved by the FDA for the treatment of adult and pediatric patients with primary HLH with refractory, recurrent or progressive disease or intolerance to conventional HLH therapy.

**Objectives:**

Develop and qualify a population pharmacokinetic (popPK) model to characterize the pharmacokinetics of emapalumab using data from a randomized, placebo-controlled, phase I trial (NCT01459562) in healthy adult volunteers.

**Design/Method:**

The analysis included 196 pharmacokinetic samples from 14 healthy trial participants who had received single escalating intravenous infusions of emapalumab (0.01, 0.1, 1, or 3 mg/kg) at the Phase I Units of ICON Development Solutions (Manchester, UK) and Hammersmith Medicines Research (London, UK). Exploratory data analysis methods and the nonlinear mixed-effects modeling (NONMEM® 7.3) program were used to obtain the final popPK model. The predictive performance of the popPK model was qualified through a visual predictive check by using the model to simulate concentration-time profiles, which were then compared with the observed data.

**Results:**

A two-compartment model best described emapalumab concentration-time profiles. In healthy volunteers at a dose of 1 mg/kg, emapalumab had the typical pharmacokinetic profile expected for a monoclonal antibody, with low central and peripheral volumes of distribution (3.02 L and 2.83 L, respectively), slow clearance (0.00712 L/h) and long distribution and terminal half-lives (1.55 and 25.4 days, respectively). Emapalumab dose was found to significantly influence the central volume of distribution (V1): i.e. when dose increases, V1 decreases. This observation could be interpreted as a sign of target-mediated drug disposition (TMDD). However, no TMDD model could be fitted to the data, probably because IFN-gamma production in healthy volunteers was minimal. A visual predictive check of the final popPK model showed that almost all the observed concentrations fell within the 95% confidence interval of the simulated data.

**Conclusion:**

The popPK model reliably predicted the individual emapalumab concentration values for healthy volunteers, which is in line with what would be expected for a monoclonal antibody. This model, together with information on (i) the neutralization of IFN-gamma by emapalumab in vitro and (ii) IFN-gamma production in HLH patients from the literature, was successfully used to select the dose for the first clinical study of emapalumab in patients with primary HLH and which formed the basis for the FDA approval in this indication.

This research was funded by Sobi (formerly Novimmune).

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Poster # 734

**HEMATOGONE HYPERPLASIA MASQUERADING AS ACUTE LYMPHOBLASTIC LEUKEMIA IN AN INFANT WITH NEUTROPENIA**

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**Background:**

Hematogones (HGs) are benign, physiologic bone marrow B-cell progenitors that are likely to be seen more in the bone marrow of children. They often increase in non-neoplastic disease, such as autoimmune disorders (idiopathic thrombocytopenic purpura and autoimmune or other blood cytopenias), congenital bone marrow disorders, AIDS, following CMV infection and in neoplastic diseases, such as lymphomas, as well as in marrow regenerative states following chemotherapy or bone marrow transplantation. As they show morphological similarities to leukemic cells, accurate differentiation from acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma is crucial.

**Objectives:**

To differentiate chronic benign neutropenia and ALL by detailed medical history, cell morphologic features, and a result of flow cytometry (FCM) of bone marrow.

**Design/Method:**

Case Report

**Results:**

We evaluated an 11-month-old girl with chronic neutropenia, complicated by febrile neutropenia. Antineutrophil antibody was negative. Cell morphology, FCM, ALL chimera screening, and G-banding of her bone marrow were investigated. Bone marrow examination showed 50% lymphoblastic-like cells (highly condensed, uniform nuclear chromatin and scant cytoplasm). FCM showed strongly positive CD19, CD10, and HLA-DR, with negative myeloid antigens. G-banding showed normal karyotype and ALL chimera screening was negative. We planned to treat her for B-cell precursor acute lymphoblastic leukemia (BCP-ALL), but hematogone hyperplasia came up in an alternative diagnosis as she had previously unknown chronic neutropenic history with no recurrent severe infectious history. As commercial FCM inspection doesn't cover CD38 or CD58 in Japan, we requested an additional examination at one of the main medical institutions. It showed strongly positive CD38, negative CD58, with no apparent abnormal antigens. Therefore, we diagnosed that she had chronic neutropenia with stage 2 hematogone hyperplasia. After natural recovery of her neutrophil counts, she was discharged on day 8 of hospitalization. Genetic examination for confirmed diagnosis including ELA2 or Gfi1 mutation hasn't been done as we couldn't get consent from the family.

**Conclusion:**

We experienced an infant with chronic neutropenia with hematogone hyperplasia. Though HGs and BCP-ALL can be differentiated by evaluating antigenicity and expression level of specific cell surface antigens, commercial FCM inspection usually doesn't include evaluation of CD38 or CD58, which suggests unnecessary ALL treatment might have been done among children with HGs in Japan. We suggest CD38 and CD58 inspection should be included in screening test



items. Also, careful clinical follow-up is needed to prevent further fatal courses and to identify potential mechanisms for the malignant transformation of HGs.

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Poster # 735

## **A RARE CASE OF ALL RELAPSE: GRANULOCYTIC SARCOMA CAUSING BRACHIAL PLEXOPATHY IN A PEDIATRIC PATIENT**

**Jamie Pruitt, Seth Rotz**

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### **Background:**

The overall incidence of extra medullary relapse in pediatric Acute Lymphoblastic Leukemia (ALL) is approximately 20%. KMT2A gene rearrangements are common in patients with infantile ALL. Granulocytic sarcomas (GS), traditionally termed “chloromas”, are rare tumors composed of a collection of immature acute leukemic cells. When GS occurs, it typically involves the bone or skin. Exceptionally uncommon, GS can invade the peripheral nervous system (PNS), a phenomenon termed “Neuroleukemiosis”.

### **Objectives:**

To describe an unusual case of a patient with ALL relapse that presented as a left arm palsy due to a KMT2A rearranged leukemic GS found to be invading the brachial plexus and to discuss the implications and role, if any, of KMT2A in the formation of GS.

### **Design/Method:**

Information including pertinent history, physical exam findings, labs and imaging were gathered via the electronic health record (EHR). Literature research was performed via PubMed.

### **Results:**

A 6 year old female with history of infantile B-cell ALL with CNS involvement and MLL KMT2A rearrangement diagnosed at 4 months of age. She was originally treated per COG AALL0631. During continuation therapy, she developed a scalp mass that was confirmed to be a leukemic relapse. She underwent re-induction chemotherapy followed by Blinatumomab with subsequent remission, and later received MUD allogenic hematopoietic cell transplant (HCT). Three years following HCT, she presented with a left arm palsy and was found to have a GS of the brachial plexus with CNS disease, a relapse of her previously diagnosed neoplasm. She went on to receive Tisagenlecleucel after bridging therapy and is now in remission. A literature search revealed that GS presenting as a relapse in the peripheral nervous system (PNS) of a pediatric ALL patient is almost unprecedented, with only one other case report documented in the literature. Three case reports were published involving GS occurring in the PNS as either a primary presentation or relapse of ALL. In pediatric AML patients with KMT2A rearrangements, 3.8% develop GS at some point during therapy. No publications report on the incidence of GS in ALL patients with KMT2A rearrangements.

### **Conclusion:**

GS occurring in ALL are rare. A KMT2A gene rearrangement may have led to the unusual presentation of relapse in this patient. A nerve palsy/neuropathy presenting acutely in a patient with previous ALL diagnosis should prompt further work up to rule out neuroleukemiosis, with special attention paid to patients with KMT2A rearrangements as they may be at higher risk for developing GS.

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Poster # 736

## **NAVIGATING THERAPY OF ACUTE LYMPHOBLASTIC LEUKEMIA IN A PATIENT WITH ALAGILLE SYNDROME**

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### **Background:**

Alagille syndrome is a complex genetic disorder of the Notch signaling pathway that affects multiple organ systems, known in particular for intra-hepatic bile duct paucity. Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children, with some genetic conditions incurring predisposition to development of ALL. Alagille syndrome is not known to be a genetic predisposition syndrome to ALL, and there have been very few cases described in the literature of patients with Alagille syndrome and ALL.

### **Objectives:**

The objective of this case report is to inform pediatric oncologists on the difficulties encountered in a patient with underlying biliary and liver dysfunction, who is undergoing treatment for ALL.

### **Design/Method:**

We describe a two-year-old male patient with Alagille syndrome diagnosed with ALL, and the challenges faced by the oncologists during the treatment process.

### **Results:**

The patient is a two-year-old male with Alagille syndrome, who initially presented to the emergency department after two weeks of worsening fatigue and jaundice, found to have blasts on peripheral blood smear. He was diagnosed with National Cancer Institute standard risk pre-B-cell ALL, CNS2b. He was initially treated as per Children's Oncology Group (COG) protocol AALL0932 for Induction chemotherapy with modified and delayed vincristine (25% of total dose) due to hyperbilirubinemia. Epoietin alpha was started to minimize blood transfusions due to the marked increase in bilirubin with repeated transfusions. Peripheral blood minimal residual disease was positive on Day 8 of therapy at 2.44%, and Day 29 end-of-Induction bone marrow MRD was negative. He was therefore transitioned to COG AALL1131 for post-Induction therapy. Induction was complicated by vincristine-induced peripheral neurotoxicity, and hypertriglyceride-induced hyponatremia. During consolidation, he developed bacteremia and an elevated ferritin >34,000 and levels trended downward over a several-week period. Normal range ferritin levels in Alagille are not known. Consolidation was delayed for 4-weeks due to prolonged neutropenia, thrombocytopenia, as well as an opportunistic invasive Trichophyton

fungal infection of his left facial cheek. He is currently receiving interim-maintenance chemotherapy, per Capizzi (escalating) methotrexate regimen, given concern for poor clearance of high-dose methotrexate with his underlying liver dysfunction. Following the first two doses of methotrexate (100 mg/m<sup>2</sup>), daily Methotrexate levels were monitored until levels were less than < 0.1, which took 48 and 24 hours, respectively.

**Conclusion:**

Alagille syndrome is a complex disease process involving multiple organ systems. Risk-benefit ratio of all decisions must be considered in the context of a multidisciplinary team, when determining the treatment course for ALL.

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Poster # 737

**MEDICAL PARADOX: AUTOIMMUNE ENCEPHALITIS IN AN IMMUNOCOMPROMISED PATIENT UNDERGOING ALL CHEMOTHERAPY**

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**Background:**

Encephalopathy in pediatric patients with acute lymphoblastic leukemia (ALL) without CNS involvement is often linked to methotrexate (MTX). Development of autoimmune encephalitis (AIE) during high-intensity immunosuppressive chemotherapy seems paradoxical.

**Objectives:**

We describe a patient with high risk pre-B ALL developing rapidly progressive leukoencephalopathy during post-induction high-intensity chemotherapy, and discuss differential diagnosis and management.

**Design/Method:**

Case Report/ PubMed & Cochrane Literature Review

**Results:**

The patient is a 5-year-old boy with high risk pre-B ALL in remission, treated as per COG AALL1131. Nineteen days following intrathecal MTX (day 56 of the delayed intensification cycle) the patient presented with progressively worsening agitation, irritability and regression of speech. Brain MRI revealed restricted diffusion in bifrontal convexities without enhancement; CSF analysis was negative for evidence of CNS leukemia or infection; and EEG showed generalized slowing without epileptiform discharges. This temporal presentation was initially attributed to MTX toxicity, and hence the patient received therapy with Dextromethorphan, Leucovorin and Aminophylline to abort presumably MTX-related neurological deterioration [modified Rankin Scale (mRS) score 4]. As a result, the patient demonstrated clinical improvement with mRS score 2-3.

Three weeks later, the patient presented with a new onset progressively worsening apraxia, truncal ataxia, myoclonic jerks and intention tremor (mRS score 4). MRI demonstrated stable

restricted diffusion but worsening parenchymal atrophy with changes concerning for AIE. Hence, immunotherapy with IVIG, high dose methylprednisolone was initiated. Subsequent therapy consisted of five cycles of plasma exchange and IVIG, which resulted in small but measurable clinical improvement (mRS score 3). The CSF AIE panel and infectious encephalitis work-up were unrevealing. Concurrently performed brain PET demonstrated a pattern characteristic of anti-NMDA receptor autoantibody encephalitis. As further immunotherapy for antibody negative AIE, the patient received consolidation therapy with four weekly doses of Rituximab and high dose Dexamethasone. Ongoing follow-up demonstrated a fluctuating clinical performance status with mRS scores ranging 2-3, while MRI revealed involvement of whole brain white matter and progressively severe parenchymal volume loss.

**Conclusion:**

Progressive leukoencephalopathy in pediatric ALL warrants a broad differential beyond the purview of chemotherapy induced neurotoxicity. AIE has not previously been described in the setting of ongoing multi-agent chemotherapy. However, given the sudden onset and rapid progression of symptoms, longitudinally evolving clinical signs, and existence of antibody negative AIE the early recognition and treatment defined by objective clinical and radiological approach is important. Other etiologies for leukoencephalopathy including toxic, metabolic and genetic causes need to be taken into account.

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Poster # 738

**HODGKIN LYMPHOMA FOLLOWING ACUTE LYMPHOBLASTIC LEUKEMIA IN A PEDIATRIC PATIENT POST THERAPY**

**Mithra Lakshmi Narasimhan, Ganesh Maniam, Samer Zaid-Kaylani, Smita Bhaskaran**

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**Background:**

Pediatric hematologic malignancies have an excellent prognosis with treatment, but a major long-term toxicity includes the development of second malignant neoplasm due to a variety of etiologies. Secondary malignancies among cancer survivors account for 6-10% of all cancers in the United States and this is mostly seen in the fourth or fifth decade of life.

**Objectives:**

To discuss the unique case of development of Hodgkin lymphoma following Acute Lymphoblastic Leukemia (ALL) in a pediatric patient in complete remission, thereby emphasizing the importance of attentive surveillance and symptom recognition in pediatric cancer survivors.

**Design/Method:**

Case report and PubMed review of literature (September 1983-November 2018). Data was collected retrospectively by analyzing the patient's hospital records.

**Results:**

A 4-year-old boy presented with intermittent leg pain, fevers and generalized malaise for one month. He was diagnosed with pre-B cell ALL following bone marrow biopsy, further supported by flow cytometry, co-expressing CD19, CD20, CD10 and CD34. He was CNS1 at presentation. He was treated according to Children's Oncology Group protocol AALL0932 and was randomized to Maintenance therapy Arm LR-C (Vincristine and Dexamethasone pulses every 12 weeks, 20 mg/m<sup>2</sup> of weekly oral Methotrexate). He did not receive any radiation therapy. Approximately 3 years after chemotherapy completion (7 years from the initial diagnosis), his routine labs demonstrated normocytic anemia with elevated ESR - consistent with anemia of chronic disease. Subsequently, he developed fatigue, intermittent fevers and lymphadenopathy and underwent a lymph node biopsy which revealed atypical lymphoid infiltrate of numerous enlarged, pleomorphic malignant cells and Reed Sternberg cells. Immunostaining was positive for CD15, CD30 and EBER. Patient was diagnosed with Nodular Sclerosing Hodgkin lymphoma, Stage IIA and was treated according to German protocol GPOH-HD 2002 - OEPA regimen (Vincristine, Etoposide, Prednisone, Doxorubicin). p53 gene mutation testing was negative. Following completion, CBC and ESR normalized, CT scan showed lymph node resolution and PET scan was negative. The patient is in remission post treatment completion.

### **Conclusion:**

Overall, this case suggests that pediatric patients with a primary childhood malignancy are at increased risk of development of second malignant neoplasm, post completion of therapy. The etiology is not completely understood – which may be due to their genetic predisposition, or the carcinogenic and immunosuppressive effects of therapy for primary malignancies. Regardless, clinicians should follow these patients with attentive surveillance for the development of second malignant neoplasms.

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Poster # 739

## **DAY 8 MINIMAL RESIDUAL DISEASE OF 67% IN A CHILD WITH STANDARD RISK ACUTE LYMPHOBLASTIC LEUKEMIA**

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### **Background:**

Minimal residual disease (MRD) assessment at the end of Induction has been shown to be a significant predictor of relapse for pediatric patients with newly-diagnosed pre-B acute lymphoblastic leukemia (ALL). Recent Children's Oncology Group (COG) protocols for standard-risk (SR) ALL incorporate MRD measurement in the peripheral blood (PB) at Induction day 8 in planning post-Induction chemotherapy. COG protocol AALL08B1 utilized a threshold of Day 8 PB-MRD of >1% to move SR ALL patients to high-risk (HR) therapy at end-Induction.

### **Objectives:**

We report a child with newly-diagnosed SR ALL who was found to have extremely high day 8 PB-MRD level.

**Design/Method:**

Case Report

**Results:**

A 5-year old boy was diagnosed with pre-B ALL after presenting with pancytopenia; his initial WBC was  $10.4 \times 10^3/\mu\text{L}$  with 54% blasts. Bone marrow blast flow cytometry revealed CD19, CD22, CD10, CD34, CD38 (dim), and HLA-DR positivity. Cerebrospinal fluid was negative for ALL. He began 3-drug Induction chemotherapy for SR ALL. Cytogenetics showed hyperdiploidy (53 XY). FISH testing was negative for targeted favorable/unfavorable changes. He had persistence of peripheral blood blasts through Induction day 7 (WBC 1.5 with 32% blasts). Day 8 PB-MRD (Johns Hopkins Medical Laboratories) was 67%. Next-generation sequencing for targeted genomic changes (FoundationOne Heme) was not indicative of Philadelphia-like ALL. He completed 3-drug Induction; his end of Induction bone marrow MRD was  $<0.01\%$ . His post-Induction treatment was augmented to HR ALL therapy. He remains in continuous remission at 21 months post-Induction.

**Conclusion:**

Pediatric ALL studies have shown that day 8 PB-MRD  $> 0.01\%$  is a risk factor for relapse; outcomes are worse as the MRD level increases. Analysis of P9900 patients across NCI risk groups (Borowitz et al, Blood 111:5477-85, 2008) showed that patients with day 8 PB-MRD  $> 10\%$  had a 5-year event-free survival (EFS) of 54%. COG AALL08B1 used a cutoff of day 8 PB-MRD  $> 1\%$  for augmentation to HR post-Induction therapy. Our patient had elevation of day 8 PB-MRD to a level not previously reported (67%). It was of great concern; however, given the lack of additional adverse features and bone marrow MRD negativity, he was re-classified as HR at end-Induction. This case illustrates that SR ALL patients who demonstrate a very slow early response to therapy as manifested by extremely high day 8 PB-MRD may achieve BM-MRD negativity at day 29 and may be successfully treated with high-risk therapy, avoiding the toxicity of stem cell transplant for poor-prognosis ALL.

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Poster # 740

**USING NOVEL AGENTS TO TREAT A RARE CASE OF CLL/SLL IN AN ADOLESCENT PATIENT**

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**Background:**

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common cancer in adults with a median age at diagnosis of 72 years. Rare occurrence of CLL/SLL in adolescents (with only a few cases reported in the literature over the past 10 years) makes the diagnosis and treatment planning challenging for young patients. Furthermore, in the previous two decades, the management of the disease has undergone dramatic changes with the development of novel targeted therapeutic agents. Here we describe the use of such agents to treat a rare case of CLL/SLL in an 18 year old female patient.

**Objectives:**

To report a rare case of CLL/SLL in an adolescent patient and describe the use of novel agents as treatment.

**Design/Method:**

Patient chart review and review of the literature.

**Results:**

An 18 year old female presented with a year and a half history of painful neck lymphadenopathy, progressive fatigue and new onset night sweats. Labs were significant for leukocytosis and thrombocytopenia. A PET CT revealed hypermetabolic lymphadenopathy in her neck, bilateral axilla, mediastinum, retroperitoneum, bilateral iliac chain and inguinal region. A cervical node biopsy was positive for small lymphocytic lymphoma. Chromosomal microarray revealed an ATM and POUF2AF1 deletion (both on 11q). ATM is an intermediate to high risk genetic lesion and POUF2AF1 is not well characterized in CLL/SLL. She was started on venetoclax and obinutuzumab with minimal reported side effects. After completion of cycle one therapy, the patient has had resolution of her leukocytosis, significant improvement in her lymphadenopathy and subsiding fatigue.

**Conclusion:**

The combination of venetoclax and obinutuzumab is currently one frontline therapy for patients with CLL/SLL demonstrating an 88% progression free survival at 24 months when used in combination. The treatment duration of 12 months and low side effect profile made this combination an ideal treatment option for our adolescent patient. To our knowledge, this is the first reported case of CLL/SLL in an adolescent patient treated with novel therapeutic agents. Our preliminary findings suggest efficacy and tolerability and hopefully long-term disease control. Continued treatment and long term follow up is necessary.

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Poster # 741

**CML AS SECOND MALIGNANCY IN A PATIENT PREVIOUSLY DIAGNOSED WITH ALL**

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**Background:**

CML is a myeloproliferative malignancy characterized by a BCR-ABL translocation. The incidence of CML is 1-2 per 100,000 adults but is rarely seen in children. CML in blast crisis can mimic the much more common ALL in children and adolescents; this highlights the importance of identification of the BCR-ABL translocation for diagnostic and treatment purposes.

**Objectives:**

We report the case of a young man who developed CML as a second malignancy after treatment

for ALL. To our knowledge, there have been two other case reports of a patient in remission from ALL found to have CML, both of whom were discovered during routine surveillance. From this case, we pose the clinical question if this case of CML is a second malignancy versus a recurrent primary malignancy unmasked (i.e. Did this patient initially have CML in blast crisis but was misdiagnosed with ALL).

**Design/Method:**

Single subject case report

**Results:**

A 25-year-old male developed CML 18 months after completion of therapy for precursor B-cell ALL. The initial diagnosis of ALL was negative for BCR-ABL by FISH and routine cytogenetics. The patient was treated with standard chemotherapy for ALL and then presented in follow-up with an incidental finding of asymptomatic leukocytosis (WBC=58,800 cells/microliter). Bone marrow examination confirmed CML with standard BCR-ABL translocation at p210. Patient is currently receiving tyrosine kinase inhibitor therapy.

**Conclusion:**

This case report highlights an interesting case of CML as a second malignancy only 18 months following completion of therapy for ALL where the ALL was not associated with a BCR-ABL translocation. As the initial diagnosis of ALL was BCR-ABL negative, it would seem this is a second malignancy rather than a recurrence of CML that was initially misdiagnosed as ALL.

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Poster # 742

**BREAST MASS AS INITIAL PRESENTATION OF ACUTE LYMPHOBLASTIC LEUKEMIA IN A MALE PEDIATRIC PATIENT**

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**Background:**

The majority of acute lymphoblastic leukemia (ALL) cases presenting as a breast mass are in female patients. Leukemic and lymphoid involvement of breast tissue constitutes only 0.25% of all breast tumors. Breast involvement is also more commonly seen in acute myeloid leukemia (AML) rather than ALL. A review of breast mass cases associated with AML or ALL showed approximately 31% of the cases were primary ALL masses, and only 5% of these cases were in male patients. Fine needle aspiration of leukemic breast masses exhibit common cytologic morphology; 90% of these breast masses are T-cell neoplasms and the remaining 10% are of B-cell origin. We report a rare case of an adolescent male who presented with lymphadenopathy and a breast mass and was subsequently diagnosed with high risk B-ALL.

**Objectives:**

We seek to discuss the presentation of a breast mass as an initial presentation for B-ALL in a male pediatric patient.



**Design/Method:**

Single subject case report

**Results:**

A 12 year old male first presented to his primary care physician (PCP) complaining of fatigue and lymphadenopathy behind his right ear. One month prior to this visit, he was found to have two lymph nodes around his right ear by a physician in Lebanon. Blood work at the time was normal, except for a low white blood count (WBC) at  $1.5 \times 10^9/L$ . Viral panels (toxoplasma, cytomegalovirus and Epstein Barr virus) were also negative. Repeat blood work showed leukopenia with neutropenia (WBC  $1.3 \times 10^9/L$ , absolute neutrophils  $330 \times 10^9/L$ ), prompting referral to hematology/oncology. At this visit, the patient complained of swollen but painless lymph nodes on neck, bilaterally, with one under his axilla. On physical exam, the lymph nodes were nontender, soft, mobile, and nonerythematous. A course of Augmentin did not reduce the lymphadenopathy, prompting re-evaluation. At this time, a 2 cm firm mass under his right areola was identified which was non-tender with deep palpation and mobile. Breast and axillary lymph node biopsy revealed ALL. Microarray analysis showed double trisomies of 4 and 10 and hyperdiploid status with no adverse prognostic indicators. He initiated treatment per the COG AALL1131 protocol.

**Conclusion:**

Breast mass is a rare but well-reported presentation of leukemia and lymphoma primarily in adult female patients. This case is unique in that it reveals a young male patient presenting with a breast mass later diagnosed as ALL. Leukemic cancers should be considered as a rare differential for pediatric patients presenting with lymphadenopathy and breast mass.

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Poster # 743

**SINGLE CELL RNA SEQUENCING IDENTIFIES TUMOR HETEROGENEITY IN PEDIATRIC T-CELL ALL**

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**Background:**

Pediatric T-cell acute lymphoblastic leukemia (T-ALL) comprises 10-15% of all ALL diagnoses in children. Recurring genetic alterations include activating sequence mutations of NOTCH1, loss-of-function alterations in hematopoietic transcription factor genes, and overexpression of oncogenic transcription factors, commonly through chromosomal rearrangement.

**Objectives:**

Here, we examine gene expression differences across individual cells in three pediatric T-ALL samples using single cell RNA sequencing (scRNA-seq). We hypothesized that scRNA-seq data would reveal tumor heterogeneity within T-ALL samples and identify additional genes involved in the pathogenesis of pediatric T-ALL.

**Design/Method:**

Cryopreserved samples of three pediatric T-ALL cases at initial diagnosis - one case of Gamma-Delta T-ALL, one case of T-ALL with no further subtype specification, and one T/Myeloid mixed phenotypic acute leukemia case—were thawed and checked for viability (>90% of cells viable) using trypan blue staining. Paired blood and bone marrow specimens were tested for the first two cases. Samples were multiplexed and processed for scRNA-seq using the Chromium Single Cell 3' Library Kit (v2) and Chromium controller per manufacturer's instructions (10x Genomics, Pleasanton, CA). Single cell libraries were converted to cDNA and sequenced on an Illumina NovaSeq instrument. Transcript alignment and counting were performed using the Cell Ranger pipeline (10x Genomics, default settings, Version 2.2.0, GRCh37 reference). Quality control, normalization, gene expression analysis, and unsupervised clustering were performed using the Seurat R package (Version 3.0). Cases were compared to pediatric B-ALL and acute myeloid leukemia (AML) cases previously run for scRNA-seq. Dimensionality reduction and visualization were performed with the UMAP algorithm.

**Results:**

Data analysis revealed 9 distinct clusters of immature/precursor type cells across the three T-ALL samples. Some of these cell clusters were unique to a given sample, while others were shared across all samples tested. Comparative analysis of clusters identified genes more highly expressed in T-ALL cells compared to B-ALL and AML cells, such as: NGFRAP1, BIN1, NUCB2, CAPG, LGALS1, SPINK2, TUBB, HMGB2, PPDPF, and CTSB. Comparative analysis of clusters within individual samples also identified interesting expression differences. For example, within the second T-ALL case, cell clusters were found to have significant expression differences of histone subunit genes (e.g. H3F3A and H3F3B), as well as unexpected genes such as NPM1, a known gene involved in the development of cytogenetically normal AML but not known to be implicated in T-ALL.

**Conclusion:**

scRNA-seq can reveal heterogeneity of gene expression in pediatric T-ALL and identify genes potentially involved in disease pathogenesis.

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Poster # 744

**MLL1 REARRANGEMENT AND LINEAGE SWITCHING IN PRECURSOR B-ALL: THE CLINICAL OUTCOMES OF TWO PATIENTS**

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**Background:**

Approximately 10% of leukemias harbor an MLL1 rearrangement (MLL-r). The two major patient populations that comprise the majority of cases are infants and young and middle aged adults. Outcomes for patients with MLL-r are generally poorer than patients with leukemia who lack MLL-r. A lineage switch has been considered an uncommon type of mixed leukemia with a

frequency between 6–9% of the cases in relapse. Here we report two cases, one infant and one young adult with MLL-r precursor B-ALL. Both patients had lineage switching to acute myeloid leukemia (AML).

**Objectives:**

To report the molecular characteristics, clinical features, and treatment outcomes of one infant and one young adult with MLL-r precursor B-ALL and evidence of lineage switching.

**Design/Method:**

We report two clinical cases from our center and have conducted a review of the literature from the PubMed database.

**Results:**

Patient 1: A 2 month old female presented to the ED with seizure like activity. Brain MRI showed a right parietal middle cerebral artery infarct. CBC showed a white blood cell count of 352,000. Peripheral blood flow cytometry revealed precursor B-ALL with lymphoid markers. Cytogenetics showed MLL rearrangement t(v;11q23). She was started on Induction chemotherapy per COG Protocol AALL15P1. Bone marrow done at the end of Induction showed persistent disease. T-cells were collected to harvest for CAR-T-cell therapy. Despite bridge therapy with Fludarabine, Cytarabine and G-CSF (FLAG)-Idarubicin and Blinatumumab, she was found to have evidence of lineage switching with an active circulating blast population expressing myeloid markers. She died due to complications of therapy and multiple infections. Patient 2: A 20 year old male presented to the ED with hematuria. Due to leukocytosis, peripheral blood was sent for flow cytometry which showed precursor B-ALL. He started chemotherapy according to the very high risk arm of COG AALL1131. Cytogenetics showed MLL rearrangement t(v;11q23). His end of Induction Minimal Residual Disease (MRD) negative. During his 4th cycle of maintenance chemotherapy, he began experiencing right upper quadrant pain and circulating blasts. Bone marrow evaluation revealed Promonocytic leukemia (AML). Flow cytometry showed an abnormal myeloid blast population. Despite aggressive management, the patient died due to complications of newly diagnosed AML.

**Conclusion:**

Despite tremendous progress in the knowledge of the pathogenesis of MLL-r leukemias, much remains to be addressed about the mechanisms driving lineage switching at relapse or with refractory disease. Clinical trials are needed to accelerate treatment options including novel targeted therapies for this unique group of patients.

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Poster # 745

**MONOSOMY 7 MUTATION ACUTE LYMPHOBLASTIC LEUKEMIA**

**Kisha Beg, Teresa Scordino, David Crawford, Hanumantha Pokala**

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**Background:**

Monosomy 7 is a cytogenetic abnormality usually associated with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Monosomy 7 occurs in about 1% of ALL, is associated with a poor prognosis and may evolve to AML.

**Objectives:**

We describe a rare case of ALL with monosomy 7 and an innovative approach to treatment.

**Design/Method:**

Case report

**Results:**

A 3 year old male with short stature and speech delay was referred for evaluation of pancytopenia and one week of fever. The initial bone marrow aspirate showed mild hypocellularity without malignancy or dysplasia. Continued pancytopenia and fevers prompted a bone marrow biopsy two months later which demonstrated normocellular marrow with clusters of TdT+ and CD19+ cells and co-expression of CD34. This was suggestive of early involvement with precursor B-ALL (19% blasts). Cytogenetics revealed monosomy 7 (85% of cells). Testing for bone marrow failure syndrome was negative except a heterozygous mutation of PALB2. Although this gene has been implicated in Fanconi anemia increased chromosomal breakage was absent. The patient also had a microdeletion of 5q that was shared with his healthy father. Anticipating potentially poor response to typical induction therapy, the patient started treatment with Blinatumumab to reduce toxicity prior to bone marrow transplant. On day 15, 1% peripheral blasts were noted by morphology in a blood smear. Flow cytometry on a marrow aspirate revealed a small population of blasts (0.5% of events) that had converted to CD19-negativity, suggesting resistance to blinatumumab. Therapy was changed to standard 3 drug induction and patient achieved MRD-negative status on day 29. He received oral mercaptopurine, weekly vincristine with monthly IT chemotherapy until he underwent a 10/10 HLA-matched unrelated bone marrow transplant. His post-transplant course was complicated by stage 1 gut graft-versus-host disease and sinusoidal obstruction syndrome that were treated with steroids and Defibrotide. Patient remains disease free with no active transplant-related complications at day +145.

**Conclusion:**

We report a rare case of monosomy 7 with ALL in a patient. The high risk of induction failure, risk of early relapse, the potential evolution to AML reported in these patients, and the rapid conversion to CD-19 negative blasts in our patient justified an innovative approach to therapy including initial targeted therapy and bone marrow transplant in first remission.

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Poster # 746

**IRON OVERLOAD DURING ACTIVE TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA**

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**Background:**

Acute lymphoblastic leukemia (ALL) treatment includes intensive chemotherapy with resultant myelosuppression requiring supportive care with packed red blood cell (PRBC) transfusions. However, repeated transfusions can lead to iron overload (IO) and organ dysfunction. Currently, iron status surveillance is not a routine part of pediatric ALL treatment. IO is described in the hematopoietic stem cell transplantation and survivorship literature, but less is known about the screening, diagnosis, and treatment of IO during active leukemia treatment.

**Objectives:**

To describe two cases of IO during active leukemia treatment.

**Design/Method:**

Case Series

**Results:**

Patient 1 is a 13yo girl who was initially diagnosed with ALL, treated on AALL1131. She had end of induction positive MRD and found to have a Ph-like chromosomal abnormality. Her course was complicated by necrotizing pancreatitis secondary to asparaginase with resultant insulin dependent diabetes. During maintenance she was found to have CNS disease. She was enrolled on AALL1331 for treatment of relapsed ALL, low risk. This course has been complicated by intermittent transaminitis and hyperbilirubinemia. During maintenance she was admitted with abdominal pain and fever, MRI abdomen was significant for iron deposition in the liver and spleen, which were not present on MRI one year prior. Her Ferritin was 3324ng/mL and MRI T2\* was significant for cardiac 1-22ms and liver 217 umol/gm. Since starting initial treatment she had been transfused 37units of PRBCs, approximately 240ml/kg.

Patient 2 is a 19yo young man diagnosed with ALL with Ph-like chromosome, treated on AALL1131. His past medical history before diagnosis included obesity and pre-diabetes. End of induction MRD was 0.57%, end of consolidation MRD was 0%. His course was complicated during induction by hyperbilirubinemia, elevated ammonia, and hypertension. During interim maintenance II, he was admitted for abdominal pain and CT showed fatty liver and iron deposits in liver. Ferritin was checked and found to be 3400ng/mL. MRI for iron deposition showed liver iron content of 222 umol/gm. He has been transfused 29units of PRBCs, approximately 99ml/kg.

**Conclusion:**

These cases highlight two patients who developed significant IO which was diagnosed after MRI abdomen obtained as part of their GI workup. Of note both of our described patients are of Hispanic descent, raising the question of ethnic predisposition IO during treatment. These cases represent a need for further investigation into the rates of IO in pediatric ALL patients actively receiving treatment and development of screening guidelines.

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Poster # 747

**CASE SERIES OF AML PATIENTS WITH ACUTE HEART FAILURE DURING CHEMOTHERAPY**

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**Background:**

Anthracyclines are essential chemotherapy in treating pediatric acute myeloid leukemia (AML) and have contributed to significant improvement in survival. Cardiotoxicity is a well-known side effect of anthracyclines and the literature has been focused on their dose-dependent late effects among cancer survivors prompting cumulative dose limitation, routine surveillance echocardiograms and more recently, use of prophylactic dexrazoxane.

**Objectives:**

Here, we review three very similar cases of acute-onset heart failure in children with AML who received anthracycline for induction therapy without prior evidence of endocarditis or cardiomyopathy in an effort to identify potential screening tools and management strategies for patients who are at risk for developing heart failure.

**Design/Method:**

Chart review of three patients with AML who developed acute-onset heart failure after receiving anthracycline for induction therapy.

**Results:**

All three children received the same cumulative dose of anthracycline (300 mg/m<sup>2</sup>), were diagnosed with recent strep viridans bacteremia, had persistent tachycardia prior to acute-onset heart failure with near-complete resolution within weeks. Heart failure in all three cases was evidenced by significant decline in shortening fraction and ejection fraction on echocardiogram, and additionally, markedly elevated BNP that decreased by the time of discharge.

**Conclusion:**

We hypothesize their acute heart failure was secondary to sepsis-induced cardiomyopathy with anthracycline-induced cardiac myocyte damage as a predisposing factor. Sepsis-induced cardiomyopathy is characterized by left ventricular dilation, decreased ejection fraction, and recovery within a few weeks. There seems to be some overlap in mechanisms of cardiac myocyte damage between anthracycline and sepsis-induced cardiomyopathy such as mitochondrial dysfunction and oxidative stress. As all children with AML receive anthracyclines and are at increased risk for bacteremia, especially with strep viridans, we suggest possible prophylaxis (dexrazoxane, beta-blockers, ACE inhibitor) and the means of early detection (BNP, echocardiogram, strain analysis, cardiac MRI) when patients are persistently tachycardic to prevent acute heart failure. These cases also may provide important insights not just for pediatric AML patients, but for any pediatric oncology patient who receives anthracyclines.

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Poster # 748

**PEDIATRIC ACUTE MYELOID LEUKEMIA PRESENTING WITH PROFOUND BONE MARROW NECROSIS**

**Michell Lozano Chinga, Lauren Draper, Tracy George, Archana Agarwal, Dave Dansie, Luke Maese**

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**Background:**

Bone marrow necrosis (BMN), defined as the death of the medullary stroma with conservation of the cortical bone, is a rarely reported finding in the pediatric population. Etiologies for BMN include medications, radiation, infection, autoimmunity, and malignancy. Ninety percent of cases of BMN are associated with malignancies. It is present in 5.6% at the initial diagnosis of leukemia and more commonly seen in adults. BMN contributes to a challenging diagnostic process and its effect on prognosis remains unknown.

**Objectives:**

We describe the case of a 15-year-old female who presented with significant BMN, later diagnosed with acute myeloid leukemia (AML), who achieved remission with cytotoxic chemotherapy.

**Design/Method:**

Case report and review of the literature.

**Results:**

A 15-year-old female presented with a 1-month history of back, knee and hip arthralgia along with a 6-kilogram unintentional weight loss and night sweats without report of fevers or joint swelling. Initial workup included unremarkable peripheral blood counts and radiographs. As symptoms persisted despite conservative management a pelvis MRI was completed demonstrating extensive signal abnormality in the lumbosacral spine, pelvis and proximal femurs concerning for an infiltrative process. Repeat CBC at that time was consistent with mild anemia, leukopenia, and neutropenia with elevated ESR, uric acid and LDH. Bilateral iliac crests bone marrow aspiration (BMA) and biopsy demonstrated >95% tumor necrosis, no flow cytometric evidence of malignancy, and a suboptimal mitotic index on chromosome analysis. Whole-body PET-CT showed increased uptake in the bone marrow of axial and proximal appendicular skeleton without evidence of solid tumor. Expanded infectious and autoimmune workup revealed no other etiology. One month later repeat bilateral iliac crest BMA and biopsy was performed again with >95% necrosis without other evidence of malignancy. Suspicion for hematopoietic malignancy remained high leading to a third BMA and biopsy several weeks later at right humerus and tibia that did not show evidence of necrosis on imaging. Marrow was diagnostic for AML, demonstrating 83% myeloid blasts with a KMT2A-MLLT3 rearrangement. Patient was treated with five cycles of chemotherapy per AAML1031 with remission after the first induction cycle and has now been off therapy for 1 year without evidence of recurrence.

**Conclusion:**

High suspicion for malignancy should be maintained in cases of BMN. Diagnosis is difficult due to lack of viable tissue obtained with bone marrow biopsies. BMN has been associated with poor

outcomes in adults, however, its effects on outcomes in pediatric malignancies are unknown and deserve further investigation.

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Poster # 749

## **V2 THERAPY: VENETOCLAX WITH VYXEOS (CPX-351) FOR ACUTE MYELOID LEUKEMIAS IN YOUNG PATIENTS**

**Laura Agresta, Jennifer Young, Erin Breese, Christine Phillips, Karen Burns, Benjamin Mizukawa, Lynn Lee, Robin Norris, Maureen O'Brien, John Perentesis, Michael Absalon**

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### **Background:**

Despite significant advances in AML therapy, 30-40% of all young patients with AML will suffer a relapse, after which achieving long-term disease-free survival remains challenging. Historically, initial response rates to salvage therapy were limited. Recently, a COG Phase II study of CPX-351 (liposomal cytarabine:daunorubicin) in pediatric patients with AML in first relapse demonstrated an 81.3% CR/CRp/CRi rate. Separately, we presented data from our first-in-pediatrics CPX-351 Phase I trial showing 48% M1 marrow response in patients with multiply relapsed and refractory (R/R) AML. We also obtained single cell RNA sequencing on study patients' peripheral blasts before, during, and after CPX-351 treatment. Preliminary data showed CPX-351 differentially impacts p53 targets within blast clusters, with an enrichment for genes regulating apoptosis (e.g.: FAS, BAX), suggesting these blasts may be primed for apoptosis following CPX-351 treatment. Venetoclax is an orally bioavailable, small molecule inhibitor of anti-apoptotic protein BCL-2, which is frequently overexpressed in leukemias. Based on published preclinical data and sequencing data from our CPX-351 trial, we developed a Phase I study to investigate venetoclax combined with CPX-351 for young patients with R/R acute leukemias. Concurrently, some patients who did not meet eligibility criteria or who presented when the trial was not accruing have been treated with venetoclax and CPX-351 outside of the prospective trial.

### **Objectives:**

To describe the safety profile and treatment outcomes of patients treated with CPX-351 and venetoclax in a “real world” setting at our institution.

### **Design/Method:**

We performed a retrospective chart review to describe the safety profile and treatment outcomes of young patients with acute leukemias treated with venetoclax combined with CPX-351.

### **Results:**

Venetoclax combined with CPX-351 was generally well tolerated by 7 young patients with relapsed/refractory AML. Ages ranged from 8 months to 22 years. Patients received CPX-351 100 units/m<sup>2</sup> on Days 1, 3, 5, and venetoclax allometrically scaled from the FDA approved adult doses. Median time to neutrophil recovery was 35 days (range: 30-51). Median time to platelet recovery was 36.5 days (range: 30-51). The most common Grade 3-4 adverse effects were febrile



neutropenia (100%) and infections (43%). One patient with multiply refractory AML died of overwhelming infection. Five patients (71%) achieved CR/CRi after one therapy course; all five were MRD negative. Six patients (86%) achieved adequate disease control to proceed to HSCT.

**Conclusion:**

This case series provides promising evidence that the addition of venetoclax to CPX-351 may provide a safe and highly effective therapy for young patients with relapsed/refractory AML.

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Poster # 750

**SPONTANEOUS HEMATOLOGICAL REMISSION OF ACUTE MEGAKARYOBLASTIC LEUKEMIA IN A CHILD.**

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**Background:**

Besides transient myeloproliferative disorder (TMD) of Down syndrome, t(8;16)(p11;p13) is the other known acute myeloid leukemia (AML) in neonates that shows recurrent self-limiting cases.

**Objectives:**

We hereby report a child with initial bone marrow biopsy confirming the diagnosis of acute megakaryoblastic leukemia. During hospitalization, we observed that the child's pancytopenia to spontaneously resolve.

**Design/Method:**

PubMed search was done with search for terminology including "AKML" and "spontaneous remission". Relevant papers were selected for literature review.

**Results:**

A 20-month-old male presented with one week of fever and upper respiratory tract infection symptoms. Physical exam was notable for petechiae. Routine blood analysis showed severe pancytopenia. Initial bone marrow biopsy yielded severe myelofibrosis and proliferation of large dysplastic megakaryocytes concerning for AML-M7 with no cytogenetic abnormalities or myeloid molecular abnormalities by next generation sequencing. Bone marrow biopsy was reviewed at two additional laboratories agreed that findings were consistent with AML-M7. Extensive infectious work up were negative. A second bone marrow examination showed absence of leukemia. During hospitalization, his pancytopenia recovered without any further intervention. One month later, the child presented with bruises and profound thrombocytopenia in the setting of recent viral upper respiratory infection. An additional bone marrow procedure displayed regenerative bone marrow with remarkable megakaryopoiesis and absence of leukemia. The diagnosis of immune thrombocytopenic purpura (ITP) was made and the patient received intravenous immunoglobulins with a good rise of the platelets count.

**Conclusion:**

Watch-and-wait approach was applied to our patient who could potentially showed spontaneous resolution of AML. The occurrence of ITP one month later could be a coincidence. Close long-term monitoring is required to ensure long-term spontaneous hematologic remission.

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Poster # 751

**IMATINIB MONOTHERAPY IN A CHILD WITH BLAST PHASE FIP1L1-PDGFR A MYELOID NEOPLASM WITH EOSINOPHILIA**

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**Background:**

Hypereosinophilic syndromes in children are rare and the differential is broad. In 2008, the WHO created a new major category as a secondary cause of hypereosinophilia labeled "myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1". This is a rare occurrence in the pediatric population with only five cases described in the literature, all presenting as a chronic eosinophilic leukemia in chronic phase. Imatinib is the preferred therapy as it is well tolerated with good efficacy and has a low risk for resistance. Imatinib targets the chimeric oncoprotein encoded by FIP1L1-PDGFR A fusion, in which the autoinhibitory juxtamembrane domain of PDGFRA is disrupted, resulting in constitutive activation of the tyrosine kinase. High rates of molecular remission have been reported with imatinib doses of 100-400mg/day, even in adults who presented in blast phase.

**Objectives:**

We report the first pediatric case of a myeloid neoplasm with eosinophilia with FIP1L1-PDGFR A fusion that presented in blast phase and has achieved remission with imatinib monotherapy alone.

**Design/Method:**

Single subject case report and literature review

**Results:**

Our patient is a previously healthy 7-year-old male who presented with fever x 2 days, mild periorbital edema and rhinorrhea. CBC showed a WBC of 26K, with 39% eosinophils, 20.5% blasts, anemia and thrombocytopenia. Exam showed massive splenomegaly. Bone marrow evaluation showed a myeloid leukemia with 23% blasts. Given the associated eosinophilia, FISH analysis was done and demonstrated the intrachromosomal deletion of CHIC2 in chromosome 4 resulting in the FIP1L1-PDGFR A fusion. A diagnosis of FIP1L1-PDGFR A associated myeloid neoplasm with eosinophilia in blast phase was made. Based on adult literature, and in consultation with experts, we chose to start the patient on low-dose imatinib monotherapy (100mg daily = ~100mg/m<sup>2</sup>) and hold off intensive chemotherapy. The patient had an excellent response to therapy, achieving hematological remission after 6 weeks, cytogenetic remission

after 3 months, and molecular remission after 4.5 months. He has now remained in molecular remission 16 months post his initial diagnosis. Current management includes continuing imatinib 100mg daily with monitoring every three months.

**Conclusion:**

It is important to recognize and work-up hypereosinophilia in the setting of a possible neoplasm. Prompt recognition of the PDGFRA-rearrangement resulted in us avoiding myeloid-directed toxic high-dose chemotherapy, while successfully achieving molecular remission with low-dose imatinib. We plan to continue imatinib monotherapy indefinitely at this time. If resistance develops, we can potentially switch to another tyrosine kinase inhibitor and discuss allogeneic HSCT.

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Poster # 752

**PEDIATRIC AML SUBTYPE WITH APL FEATURES AND RAR B TRANSLOCATION**

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**Background:**

Acute promyelocytic leukemia (APL) is a rare subtype of acute myeloid leukemia (AML) accounting for 5%-10% of cases. About 98% of cases of APL are associated with the t(15;17)(q24;q21) translocation that creates a rearrangement between the promyelocytic leukemia (PML) and retinoic acid receptor RARA. Leukemia cells carrying the PML-RARA fusion are sensitive to the combination of trans-retinoic acid (ATRA) and arsenic trioxide. Conversely, leukemia cells carrying fusions involving the PML gene and RARB or RARG, the two other RARs, although sharing some of the same morphological features of typical APL, are less responsive to ATRA. Therefore, it is critically important to distinguish between atypical and typical APL to proper management.

**Objectives:**

To describe the clinical, laboratory features and response to therapy of a patient with relapsed atypical APL.

**Design/Method:**

Case report

**Results:**

In November-2014, at age of 2 years, the patient presented to the local hospital with left knee pain and coagulopathy. Due to the morphological features of the leukemia cells and coagulopathy, APL was suspected. Therefore, she was treated with ATRA/idarubicin. Quantitative-RT-PCR assay did not disclose the PML-RARA fusion, her therapy was changed to idarubicin/cytarabine. Measurement of residual disease at end-of-induction was negative. Post-induction chemotherapy consisted of daunorubicin (3 daily doses) and continuous cytarabine for 7 days followed by two courses of high-dose cytarabine. In November-2019, during laboratory

follow-up, pancytopenia with peripheral myeloblasts were noted. Bone marrow examination revealed myeloblasts with cytomorphological features like those at diagnosis of the leukemia. The patient was referred to St. Jude Children's Research Hospital for management, the patient presented with fever, knee pain, and refused to walk. WBC and hemoglobin were normal. CRP was 17.9. The peripheral blood smear stain revealed hypo-granular leukemia cells with bilobed-nucleus without Auer-rods. Cytochemical staining for myeloperoxidase was positive. Immunophenotyping revealed blasts with extremely high side scatter and CD45-dim to negative as well as CD33(subset),CD13,CD56,CD4(subset),CD123 and was negative for CD19,cyCD3,CD11c,CD64,CD14,CD34,CD117 and HLA-DR. Targeted-RNA-seq identified a TBL1XR1-RARB fusion transcript consistent with the karyotype t(3;3)(p24;q26.2). The patient was treated with fludarabine,cytarabine,G-CSF,and idarubicin(FLAG-Ida) with an excellent response. She is currently awaiting haploidentical hematopoietic stem cell transplant.

### **Conclusion:**

This case illustrated the clinical course of a very rare subtype of AML, classified as atypical promyelocytic leukemia with an RARB rearrangement. Although there was a durable response after conventional AML treatment strategy, the disease eventually relapsed. Although there is a paucity of similar cases reported, we suggest that children with atypical APL with RARB should be considered for transplant in first remission.

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Poster # 753

## **SUCCESSFUL INDUCTION THERAPY IN A PREGNANT PEDIATRIC FEMALE WITH ACUTE PROMYELOCYTIC LEUKEMIA**

**Maritza Ruiz, Maki Okada, Laurel Truscott, Jacqueline Casillas**

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### **Background:**

Acute promyelocytic leukemia (APL) is a rare subtype of acute myeloid leukemia (AML) characterized by t(15;17)(q22;q12), resulting in the fusion transcript oncogene PML-RARA. APL treatment with all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) has dramatically improved survival. Both drugs are teratogenic during pregnancy, however, there are several case reports of successful treatment of APL in pregnant adults using ATRA alone or in combination with cytarabine and/or anthracycline. There are no published cases on treatment of APL in a pediatric patient during pregnancy.

### **Objectives:**

To describe a case of APL in a pediatric pregnant patient treated with induction monotherapy ATRA during her second and third trimesters of pregnancy.

### **Design/Method:**

A review of medical records and literature on APL treatment in pregnancy was completed.

### **Results:**

A 16-year old, G2P0010, previously healthy Hispanic female, presented at 27w2d gestational age with pancytopenia during routine OB care. She presented to emergency care for a prolonged episode of epistaxis and was transferred to a high-risk obstetric center where she was found to have: WBC 1.1k/ $\mu$ L, ANC 297, Hgb 8.9 g/dL, Platelet 31k/ $\mu$ L, normal LDH, uric acid, PT/INR, PTT, fibrinogen, and elevated d-dimer >20,000ng/mL. Peripheral blood smear review showed 5-10% blasts with bilobed and reniform nuclei and Auer rods consistent with APL. PCR for PML-RARA from the peripheral blood confirmed the presence of t(15;17). Diagnostic bone marrow evaluation was obtained but diagnostic lumbar puncture was deferred due to the absence of neurologic symptoms. Induction therapy was started with oral ATRA monotherapy (adult dose of 45mg/m<sup>2</sup>/day divided twice a day). Anthracycline was avoided due to her low-risk classification. Platelet transfusions were given to maintain a platelet count > 50k/ $\mu$ L during her entire pregnancy. She was prophylactically treated with oral prednisone to prevent differentiation syndrome (DS), and this was changed to dexamethasone on Day 13 of treatment for symptoms of DS. Her blood counts normalized by Day 33 of ATRA therapy and a repeat bone marrow evaluation after delivery (Day 68) confirmed morphologic and molecular remission. Patient proceeded to Consolidation therapy with ATRA and ATO therapy two weeks after delivery.

**Conclusion:**

This is a case report of a pediatric patient treated with induction ATRA monotherapy during her second and third trimesters of pregnancy. She achieved morphologic and molecular remission and successfully carried her pregnancy to 36w6d and delivered vaginally with no complications after a planned induction.

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Poster # 754

**CASE SERIES OF DIMINISHED CARDIAC FUNCTION FOLLOWING GEMTUZUMAB OZOGAMICIN**

**Kevin McNerney, Richard Aplenc**

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**Background:**

Gemtuzumab ozogamicin is an anti-CD33 antibody tumor antibiotic conjugate used in the treatment of pediatric AML. Although there have been several trials including gemtuzumab in pediatric patients, different schedules have been used and presently there is no optimal dose in pediatric patients. Although bilirubin increase and veno-occlusive disease are described as dose-dependent adverse effects of Gemtuzumab, cardiac toxicity is not a commonly described side effect.

**Objectives:**

To describe the clinical course of 2 patients at one major academic institution who developed a significant decrease in left ventricular ejection fraction following receipt of gemtuzumab and to review the literature of gemtuzumab-induced toxicities.

**Design/Method:**

Summary of 2 pediatric patient cases that developed moderate to severe decreased left ventricular ejection fraction following receipt of gemtuzumab as re-induction therapy for relapsed acute myeloid leukemia (AML)

**Results:**

Patient 1: A 23 month old patient with relapsed AML presented to care after having been refractory to FLAG-idarubicin therapy and had received a total of 400mg/m<sup>2</sup> of anthracycline. She received 6 doses of fractionated gemtuzumab at 3mg/m<sup>2</sup>/dose for a total of 18mg/m<sup>2</sup> in a span of 21 days. Prior to initiation of gemtuzumab, an ECHO was obtained showing a left ventricular ejection fraction (LV EF) of 52%, considered low normal. Following completion of Gemtuzumab, a bone marrow biopsy was done showing MRD-negative remission, however, a surveillance ECHO was done showing moderate-severe diminished LV EF of 40% and a dilated left ventricle, and a max BNP of 1592. After 4 cycles of azacytadine and venetoclax, LVEF improved to 56% and she was able to undergo URD BMT with stable cardiac function and is now in an MRD negative remission now 2 months after transplant.

A 3 yo male with a history of CD33+ FLT3- AML relapsed with 35% bone marrow blasts and a facial chloroma presented having received a cumulative anthracycline dose of 600mg/2. He received 5 total doses of 3mg/m<sup>2</sup> of gemtuzumab for a total of 15mg/m<sup>2</sup>. An ECHO done prior showed a LV EF of 60% while an ECHO performed following Gemtuzumab showed a severely diminished LV EF of approximately 20%.

**Conclusion:**

The two patients presented illustrate an acute diminishment in left ventricular cardiac function with after receiving doses of gemtuzumab. Both patients had significant prior anthracycline exposure but had low normal or normal left ventricular function prior to the receipt of gemtuzumab, and then exhibited recovery of LVEF following gemtuzumab.

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Poster # 755

**PRIMARY BONE MARROW DLBCL MASQUERADING AS COLD AGGLUTININ HEMOLYTIC ANEMIA**

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**Background:**

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma in adults, accounting for about 25% of non-Hodgkin's lymphomas. Mean age at diagnosis is 66, and rates increase dramatically over 50. NHL in general, and DLBCL specifically, are much less common in the pediatric population: accounting for about 7% of cancers in patients under the age of 20, with the rate of DLBCL alone being 1.4%. The typical presentation of DLBCL involves a rapidly enlarging, symptomatic mass, usually in the neck, abdomen, or mediastinum, often accompanied by B symptoms. While bone marrow involvement of DLBCL is not uncommon, primary bone marrow disease is quite unique. Cold agglutinin hemolytic anemia

(CAHA) is also exceedingly rare in children, usually occurring in the seventh decade of life. It often signifies an underlying lymphoproliferative disorder, such as DLBCL.

**Objectives:**

To highlight an unusual presentation of DLBCL manifesting as CAHA in a pediatric patient.

**Design/Method:**

Case Report

**Results:**

Our patient is a 17-year old girl with a complex medical history, including an unnamed genetic syndrome, vesicoureteric reflux with bilateral ureteral reimplantation, dysmenorrhea, myopia, hypertelorism, and talipes equinovarus who presented to the ED for evaluation of symptomatic anemia, with an initial hemoglobin of 5.2 g/dL. Labs were suggestive of a hemolytic process with a positive direct Coombs. Anti-CD3 IgM antibodies were positive, suggesting cold agglutinin disease. She returned multiple times over the next two weeks for ongoing hemolysis despite aggressive treatment with PRBC transfusions, prednisone, IVIG, Rituximab, and plasmapheresis. Her hemolysis slowed, but never resolved. CT showed an enlarged spleen with scattered infarcts but no focus of malignancy. Bone marrow biopsy revealed a hypercellular marrow with infiltration by nodular aggregates of large atypical cells with prominent nucleoli. Immunophenotyping demonstrated a monoclonal, kappa light chain restricted B-cell population expressing CD19, CD20, BCL-2, MUM-1 with EBER, CD5, CD10, and CD138 negativity, consistent with DLBCL. She was treated per ANHL1131 and achieved clinical remission with resolution of her CAHA. She experienced several complications including myelopathy with incontinence and lower extremity paralysis. She underwent months of intensive rehabilitation. She is currently 6 months post-treatment and doing well.

**Conclusion:**

CAHA as the initial symptom of DLBCL is rare. To our knowledge, our patient is the first reported pediatric patient with CAHA as the presenting symptom for underlying DLBCL of the bone marrow. While our patient's underlying genetic syndrome may have contributed to the development of these conditions, we cannot be certain.

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Poster # 756

**PRALATREXATE-BASED THERAPY INDUCED RESPONSE IN AN ADOLESCENT WITH REFRACTORY HSTL**

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**Background:**

Hepatosplenic T-cell lymphoma (HSTL) is a rare and aggressive subtype of mature T-cell lymphoma. Poorly responsive to chemotherapy, the estimated 5-year overall survival of pediatric patients with HSTL is < 10% in the US.[1] Patients are usually treated with platinum- or non-

platinum-based chemotherapy with the goal of achieving a maximum response prior to allogeneic stem cell transplant (Allo-SCT). Pralatrexate is a potent antimetabolite drug currently approved by the US Food and Drug Administration (FDA) to be used in adult patients with relapsed/refractory peripheral T-cell lymphoma, including HSTL.[2]

**Objectives:**

To describe the case of an adolescent with refractory HSTL who achieved partial response after 2 cycles of pralatrexate-containing chemotherapy.

**Design/Method:**

Case Report.

**Results:**

A 17-year-old female of Hispanic origin presented with few weeks of drenching night sweats, fever and unintentional weight loss. Physical exam was remarkable for massive splenomegaly. Initial laboratory work-up revealed pancytopenia, normal lactate dehydrogenase, and uric acid. Bone marrow was hypercellular with trilineage hematopoiesis and presence of an infiltrate of nondescript cells with medium size nuclei, a scant to moderate amount of cytoplasm, and inconspicuous nucleoli. Immunostains highlighted an extensive infiltrate of T-cells positive for CD2/CD3/CD7/CD56 expression, negative for CD4/CD8/granzyme B. Gene rearrangement studies demonstrated clonal  $\gamma$ - $\delta$  T-cell receptor pattern, consistent with HSTL. Due to significant transfusion requirements and abdominal discomfort, patient underwent splenectomy, with improvement but not complete resolution of cytopenias. Splenic tissue pathology confirmed HSTL. Spleen cytogenetic studies showed trisomy 7q; genomic findings included KRAS, SETD2, and STAT5B alterations (FoundationOne®). Additional staging with PET/CT scan showed diffuse uptake throughout the osseous structures (stage IV per Revised International Pediatric Non-Hodgkin Lymphoma Staging System [IPNHLSS])[3]. She initially received 2 cycles of ifosfamide, carboplatin, etoposide with disease progression. Then she received 2 cycles of pralatrexate 30 mg/m<sup>2</sup>/dose weekly x 3 doses in combination with cyclophosphamide, doxorubicin, prednisone (PRX-CHP) with resolution of cytopenias and significant reduction in bone marrow involvement by HSTL (partial response per International Pediatric Non-Hodgkin Lymphoma Response Criteria [IPNHLRC])[4]. Patient experienced one episode of grade 4 mucositis during PRX-CHP therapy. Support of care included vitamin B12 and folic acid supplementation, G-CSF use, in addition to hospitalization during chemotherapy-induced neutropenia phase. She is currently undergoing preparation for a matched sibling Allo-SCT.

**Conclusion:**

Pralatrexate-containing chemotherapy induces response in pediatric patients with refractory HSTL.

References:

- 1.Sorge, Xavier, Cairo. Br J Haematol, 2019.
- 2.O'Connor, Pro, Pinter-Brown. J Clin Oncol, 2011.
- 3.Rosolen, Perkins, Pinkerton. J Clin Oncol, 2015.
- 4.Sandlund, Guillerman, Perkins. J Clin Oncol, 2015.



## **A RARE CASE OF EXTRANODAL MARGINAL ZONE LYMPHOMA IN A CHILD SUCCESSFULLY TREATED WITH RITUXIMAB**

**Yevgeniya Bamme, Smita Dandekar**

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### **Background:**

Extranodal marginal zone lymphoma (ENMZL) of mucosa-associated lymphoid tissue (MALT) is a unique subset of indolent B cell lymphomas that are rarely seen in children, and constitute only 8% of all non-Hodgkin lymphomas. They typically arise in the setting of chronic autoimmune or antigenic stimulation in areas that are devoid of lymphoid tissue, such as the stomach, salivary glands, and lungs. We describe a unique case driven by Epstein - Barr virus (EBV) that responded completely to treatment with only rituximab.

### **Objectives:**

To describe our experience treating a medically complex child with ENMZL of bilateral parotid glands and achieving complete remission with eight infusions of single agent rituximab.

### **Design/Method:**

Case Review

### **Results:**

A 17 year old male with a complex past medical history, most notable for common variable immune deficiency (CVID), chronic kidney disease (CKD), juvenile idiopathic arthritis, hypothyroidism, and insulin dependent diabetes mellitus, presented with 2-3 months of progressively enlarging painful protuberances on both cheeks. Ultrasound evaluation showed multiple lymph nodes adjacent to the right parotid gland, within both parotid glands, and within the left submandibular gland. A biopsy of the left parotid node revealed lymphoid proliferation resembling ENMZL of mucosa-associated tissue, with numerous cells positive for EBER1, consistent with an EBV driven malignancy. Additional tissue testing revealed CD20 positivity but no rearrangements in MALT1 (18q21). Staging with PET/CT revealed numerous intensely FDG avid lymph nodes within the parotid glands bilaterally, many mildly FDG avid retroperitoneal nodes and diffuse uptake throughout the bone marrow. Sampling of retroperitoneal nodes and bilateral bone marrow aspirates and biopsies showed no evidence of disease. Patient was classified as Stage IIE per Ann Arbor staging. Due to his numerous comorbidities, especially CKD, conventional chemotherapy was deferred, and instead we elected to treat with single agent rituximab per the International Extranodal Lymphoma Study Group-19 trial\*. Our patient received four weekly infusions at a dose of 375mg/m<sup>2</sup>. Follow up PET scan after four weeks showed a good partial response, with greater than 50% metabolic and volumetric reduction, and the patient then continued with four additional monthly infusions of rituximab at the same dose. An end of therapy PET scan confirmed complete response, and the patient has remained in remission since.

**Conclusion:**

ENMZL is exceedingly rare in children. Our case demonstrated that an EBV-driven MALT lymphoma in the setting of immunodeficiency and CKD can be successfully treated with single agent rituximab.

Reference: \*Zucca E, J Clin Oncol. 2017 Jun 10

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Poster # 758

**GASTRIC BURKITT LYMPHOMA DIAGNOSED AFTER WORK UP FOR SEVERE IRON DEFICIENCY ANEMIA: A CASE REPORT**

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**Background:**

Burkitt lymphoma is an aggressive non-Hodgkin lymphoma and comprises approximately 30% of pediatric lymphomas. In the United States, Burkitt lymphoma typically presents as an intraabdominal mass, and primary gastric Burkitt lymphoma is rare. Moreover, while there have been few case studies demonstrating concomitant *Helicobacter pylori* (*H. Pylori*) infection the association between primary gastric Burkitt lymphoma and *H. Pylori* is not fully delineated.

**Objectives:**

To describe a case of severe, refractory iron deficiency anemia and biopsy proven *H. Pylori* infection eventually diagnosed with gastric Burkitt lymphoma

**Design/Method:**

Case report

**Results:**

A 16-year-old female was initially evaluated for fatigue, pallor and headaches. She was found to have a hemoglobin of 5.7 gm/dL with reticulocytosis and ferritin of 11 ng/ml. She received a packed red blood cell transfusion (pRBC) and was treated for iron deficiency secondary to suspected menorrhagia with oral ferrous sulfate and menstrual suppression. Due to continued severe anemia two-weeks after presentation she received intravenous ferric carboxymaltose infusions and further investigation for occult gastrointestinal bleeding was initiated. She was found to have positive fecal occult testing and underwent an upper GI endoscopy (EGD) and colonoscopy. The EGD showed a large gastric ulcer with *H. Pylori* infection by biopsy. She was started on triple antibiotic therapy; however, she continued to have symptomatic anemia, weight loss and poor tolerance of oral antimicrobial treatment. Approximately four-weeks later she required another pRBC transfusion and a new abdominal mass was palpated on exam. Computerized tomography (CT) scan of the abdomen and pelvis demonstrated mass-like enlargement of the stomach as well as hepatosplenomegaly, perigastric and cardiophrenic

adenopathy and mesenteric and omental implants. Using endoscopic ultrasound, fine needle aspirates and cold forceps biopsies were obtained; findings were consistent with Burkitt lymphoma. Bone marrow biopsies and cerebrospinal fluid analysis were negative for disease. She received treatment according to ANHL1131, Group B high-risk therapy and was recently upstaged to Group C1 therapy due to inadequate response. She has completed two rounds of treatment for H. Pylori. Clinical course has been complicated by tumor lysis as well as gastric perforation after initiation of chemotherapy.

**Conclusion:**

We thus demonstrate a patient with large gastric Burkitt lymphoma in the setting of severe, refractory iron deficiency anemia and recently diagnosed H. Pylori infection. This case highlights the importance of continued investigation of causes of severe non-responsive anemia even in the presence of a plausible explanation such as biopsy proven H. Pylori.

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Poster # 759

**EARLY RELAPSES OF ANAPLASTIC LARGE CELL LYMPHOMA SUCCESSFULLY TREATED WITH BRENTUXIMAB AND HSCT**

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**Background:**

Anaplastic large cell lymphoma (ALCL) accounts for approximately 10-15 % of childhood non-Hodgkin lymphoma. It commonly presents as advanced systemic disease and long-term event free survival is around 70%. Patients that relapse, tend to have disease recurrence within 6 months of completing treatment. Patients with relapsed ALCL have poorer prognosis with 40-70% chance of survival. Treatment of relapsed pediatric patients can result in severe long-term toxicities including cardiotoxicity, secondary cancers and infertility.

Brentuximab vedotin is a CD30 targeted antibody-drug conjugate. It selectively induces apoptosis in CD30 positive cells by inducing cell cycle arrest after lysosomal internalization of the drug and subsequent release of the microtubule disrupting agent monomethyl auristatin E (MMAE).. It is approved in adults for relapsed or refractory systemic ALCL following failure of at least one previous chemotherapy regimen. Data on safety and efficacy of Brentuximab vedotin for pediatric ALCL is limited to phase 2 trials.

**Objectives:**

To describe the characteristics and clinical course of three children with early relapse of ALCL who rapidly achieved a second complete remission after treatment with Brentuximab vedotin and proceeded to consolidation with allogeneic hematopoietic stem cell transplantation (HSCT).

**Design/Method:**

Case series

**Results:**

Three patients (4-year-old boy, 7-year-old girl and 14-year-old boy) were diagnosed between 2013 to 2019 with ALK positive ALCL. One patient had bone marrow involvement and one patient was positive for CD3. All patients received chemotherapy per ALCL99 and were in remission when therapy was completed. Time to relapse was 2 weeks, 2 months and 3 months from completion of therapy. All patients achieved complete remission after 2 doses of Brentuximab vedotin. After an additional 1-2 doses to bridge to transplant, all patients received a HSCT. Toxicity from Brentuximab vedotin was minimal with one patient experiencing grade 4 neutropenia and no neuropathy. All 3 patients remain alive and disease free 6 years, 3 years and 3 weeks from HSCT.

**Conclusion:**

Brentuximab vedotin is a safe and effective treatment for children who experience an early relapse of ALCL and was successful at getting patients to HSCT with minimal adverse events.

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Poster # 760

**PRIMARY MEDIASTINAL B-CELL LYMPHOMA WITH A MATERNALLY INHERITED GERMLINE CHEK2 MUTATION**

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**Background:**

The checkpoint kinase 2 (CHEK2) gene codes for the CHK2 protein, an important mediator of the DNA damage response pathway. CHEK2 pathogenic variants cause a "Li-Fraumeni-like" syndrome. While this syndrome is incompletely defined, the most notable cancer risks are for breast and colon cancer, though many other cancers have been reported in CHEK2 families. We report a case of primary mediastinal B cell lymphoma (PMBCL) in a pediatric patient with a maternally inherited germline CHEK2 mutation and maternal family history of lymphoma. We also discuss the limitations to screening in their kindreds.

**Objectives:**

To describe a case of PMBCL in a pediatric patient with a germline CHEK2 mutation and discuss counseling for families with CHEK2 mutations.

**Design/Method:**

We collected data on medical and family history, therapy received, and survival.

**Results:**

The patient was a previously healthy male diagnosed at age 17 with PMBCL after presenting to a local ED with chest pain. Family history was notable for his mother, who was diagnosed with DLBCL at the age of 32. In addition, his maternal great aunt was diagnosed with rectal cancer, another maternal great aunt had colon and breast cancer in her 60s, and lastly, maternal great grandmother was diagnosed with melanoma in her 60s. He ultimately underwent genetic testing

via a comprehensive hereditary lymphoma/immunodeficiency panel, which revealed a CHEK2 c.470T>C missense mutation. The mutation was confirmed in his mother but was absent in his healthy brother. He was treated with six cycles of DA-EPOCH-R and is disease free 20 months from diagnosis.

**Conclusion:**

Here we report a case of PMBCL in a patient with a maternally inherited germline CHEK2 mutation with a maternal history of lymphoma. Germline CHEK2 mutations affecting protein coding sequences increase the risk of NHL and are associated with a worse prognosis (1,2). However, in one series, the CHEK2 c.470T>C mutation did not confer an increased risk of NHL. As such, lifetime risk estimates are not well-defined for individuals with CHEK2 mutations (1). Screening recommendations, particularly in the pediatric period, are even less clear. Currently, women with CHEK2 pathogenic mutations should consider increased breast screening beginning at age 40. Both men and women should consider colonoscopy by age 40. There are no specific recommendations regarding lymphomas.

This case report contributes to the limited literature to help to further describe the presentation of lymphoma in pediatric patients with CHEK2 mutations.

Tort et al. Blood. 2002

Havranek et al. PLoS One. 2015

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Poster # 761

**HODGKIN LYMPHOMA RELATED VANISHING BILE DUCT SYNDROME  
CHOLESTASIS RESOLVED AFTER CHEMOTHERAPY**

**Rafael Gonzalez, Pooja Parmar, Steve Hardee, Brian Pugmire, Christine Chang-Halpenny, Ruetima Titapiwatanakun, Wendy Tcheng, Karla Au Yeung, Karen Fernandez**

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**Background:**

Vanishing bile duct syndrome (VBDS) is a rare disease defined by loss of intra-hepatic bile ducts leading to ductopenia and cholestasis. Rarely, Hodgkin lymphoma (HL) cells can infiltrate portal tracts and release cytokines that destroy bile ducts resulting in HL related VBDS (HL-VBDS). This entity is rarely seen in adults and even rarer in children. HL-VBDS is associated with high mortality.

**Objectives:**

To report the clinical course of an adolescent with HL-VBDS.

**Design/Method:**

Case report.

**Results:**

A 17 year old Hispanic female presented with 2 month history of right sided neck mass, 24-pound weight loss and itching. Physical exam showed an obese adolescent (BMI 47.3 kg/m<sup>2</sup>), scleral icterus, large nontender mass in the right neck with multiple submental and supraclavicular lymph nodes, jaundice and acanthosis nigricans. Laboratory evaluation revealed ESR 5 mm/hr, CRP 6.5 mg/L, Total/conjugated bilirubin 10.1/7.8 mg/dL, AST/ALT 67/61 U/L. A CT scan of chest-abdomen-pelvis showed bulky adenopathy in the right cervical, supraclavicular, paratracheal, mediastinal, and mesenteric regions and a splenic lesion. Lymph node biopsy confirmed diagnosis of classical HL nodular sclerosis subtype. FDG- PET/CT scan confirmed stage IIIB. Work up for cholestasis included, liver and coagulation panel, alpha-1-antitrypsin, ceruloplasmin, triglycerides, cholesterol, ammonia, urea, infectious testing; however, no etiologies were identified. An MRCP showed large gallstones and ERCP evidence of thick granular sludge. A liver biopsy showed canalicular cholestasis and bile duct damage with focal duct loss consisting with HL-VBDS.

The patient received treatment with modified ABVE- PC (Adriamycin, Bleomycin, Vincristin, Etoposide, Prednisone, Cyclophosphamide) regimen. Vincristine was omitted, prednisone was given at 100% dosing and all other agents at 50%. An attempt to increase dosing to 75% resulted in increased toxicity and extended hospitalizations. Her chemotherapy was given on a 4-5 week schedule due to toxicities, including increasing levels of Total/conjugated bilirubin up to 30/21 mg/dL. Cycle 5 was omitted. Radiation therapy to involved bulky sites was given with 30 Gy. Four weeks after radiation bilirubin level normalized. Patient is alive and doing well 10 months after completing treatment.

**Conclusion:**

HL-VBDS imposes challenges to the administration of chemotherapy. HL-VBDS is associated to increased chemotherapy related toxicity as well as morbidity from intrinsic hepatobiliary disease. HL-VBDS typically has a poor prognosis. The majority of reported pediatric cases either suffer from or die of liver failure. Our patient is an example of a rare case in which HL-VBDS cholestasis resolved after chemotherapy and radiation. Patient is doing well 12 months after completing treatment.

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Poster # 762

**A SUPRAGLOTTIC MASS IN A PEDIATRIC PATIENT: AN UNUSUAL PRESENTATION OF LYMPHOMA**

**Paloma Perez, Wesley McIlwain, James Winters, Mary Dhesi, Derek Rogers**

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**Background:**

A 13 year old male patient presented with a rapidly enlarging right neck mass. Work up of the neck mass included a computed tomography scan of the neck with contrast. This revealed a 2.5 cm right neck mass and an asymmetric lobulated soft tissue mass in the right pyriform sinus of the supraglottic larynx.

**Objectives:**

To present a case of primary laryngeal lymphoma in a pediatric patient and perform a literature review of this rare entity.

**Design/Method:**

The patient underwent excisions biopsy of the right supraglottis mass. Once his diagnosis was confirmed he was treated with a standard lymphoma protocol consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone.

**Results:**

Intraoperative frozen analysis revealed a small blue cell tumor. The decision was made to not pursue an excisional biopsy of the neck mass, as this was felt to be likely related to probably lymphoma. Final pathology demonstrate diffuse large B-cell lymphoma of the germinal center B-cell subtype. The patient underwent treatment with primary chemotherapy 12 days after his original procedure. Twelve months after completion of treatment the patient remains disease free.

**Conclusion:**

This is an unusual presentation of lymphoma, without evidence of disease outside of the larynx and neck. There is limited literature of primary laryngeal lymphoma in a child. With appropriate treatment, the five year disease free survival remains excellent for germinal center - diffuse Large B-cell lymphoma.

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Poster # 763

**RESIDUAL DISEASE DETECTED BY PET/MRI IN CNS RELAPSE OF PRIMARY MEDIASTINAL B CELL LYMPHOMA**

**Amy Moskop, Richard Tower, Paul Harker-Murray**

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**Background:**

Functional imaging tests are an important component of diagnostic staging and evaluating response to therapy in pediatric lymphoma. 18F-FDG PET/CT is frequently used and modern scanners can detect tumors down to ~4 mm in size, have a high sensitivity and specificity in lymphoma but have lower resolution images. 18F-FDG PET/MRI is increasingly being used in staging and response assessment of lymphomas and offers similar accuracy, lower radiation exposure, and higher resolution images compared to PET/CT.

Central nervous system (CNS) relapse of primary mediastinal B cell lymphoma (PMBCL) is extremely rare. Studies have reported using PET/CT in primary and secondary CNS lymphoma both in the diagnosis and response assessment, however MRI provides superior anatomic visualization. PET/MRI might offer a better method to both visualize CNS disease and provide a functional assessment of abnormal MRI findings.

**Objectives:**

To describe the use of PET/MRI to identify residual disease in isolated CNS lymphoma

**Design/Method:**

A 15-year-old with PMBCL was treated with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab, and achieved complete metabolic remission at the end of treatment based on PET/CT. Three months off therapy he presented with vomiting and left facial nerve palsy. An MRI showed a 5.6 x 3.8 x 5.2 cm mass within the right basal ganglia. This location prohibited a biopsy and was presumed a CNS relapse. He received CNS directed chemotherapy (high-dose methotrexate, cytarabine, brentuximab, cytarabine, and etoposide) but had disease progression. He then received focal CNS radiation and pembrolizumab, a programmed death-1 inhibitor antibody, with the goal of proceeding with consolidative therapy (transplantation versus chimeric antigen receptor T cell therapy) if he achieved CNS remission. He was monitored with PET/MRI performed on an integrated 3-Tesla scanner (SIGNA PET/MR, GE Healthcare, Milwaukee, USA).

**Results:**

Following radiation and pembrolizumab there was a small residual mass with abnormal PET activity. During ongoing pembrolizumab therapy, the mass continued to decrease in size (2.4 x 1.2 cm) but PET avidity remained abnormal (SUV max 6.4). Three months later, he presented with progression of his CNS disease and leptomeningeal spread. He went on to receive craniospinal irradiation with pembrolizumab and PET/MRI showed a residual basal ganglia mass but resolution of leptomeningeal disease and abnormal PET activity.

**Conclusion:**

PET/MRI identified a small CNS lesion that was decreasing in size but with increased PET activity that ultimately progressed. PET/MRI technology offers functional imaging with the benefit of higher resolution images that can improve disease monitoring in CNS lymphoma .

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Poster # 764

**RARE CASE OF CNS-PREDOMINANT METASTATIC PERIPHERAL T-CELL LYMPHOMA IN A PEDIATRIC PATIENT**

**John Norko, Natalie Bezler**

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**Background:**

Pediatric peripheral T-lymphocyte lymphoma is rare and to involve the CNS is even rarer. To date, only three case reports have been published describing this type of tumor in a pediatric patient. This is the first patient described with metastatic disease. There is no standardized treatment protocol and a prospective study of this cohort is improbable due to rarity of the tumor.

**Objectives:**

To describe the unique presentation of a rare tumor and our therapeutic approach



**Design/Method:**

Case Report

**Results:**

The patient is an eleven-year-old male who presented with a two-week history of worsening headaches, fatigue, and fevers and a 48-hour history of mid-thoracic back pain, ambulation difficulties, and paresthesias. An MRI demonstrated a 6.5 cm thoracic lesion spanning T5-T8 and causing cord compression. Additionally, extensive intradural disease extending from T11 to the sacral levels was noted. Emergent debulking of the tumor was performed. Additional sites of disease identified by PET imaging included scalp, sphenoid sinus, spine, bone marrow, pancreas, lymph nodes, and testicles. Cell morphology was consistent with T-cell non-Hodgkin lymphoma and positive for mature T-cell antigens.

The patient was initially treated with a Children's Oncology Group (COG) T-cell acute lymphoblastic leukemia (T-ALL) induction regimen plus additional doses of intrathecal (IT) cytarabine. Repeat imaging following induction demonstrated significant improvement in active tumor burden, but persistent spinal disease. Given the favorable response, a COG T-ALL consolidation regimen was initiated. Following consolidation, there was persistent spinal column enhancement on MRI but no PET avidity. He then received cycles of EPOCH with mid-cycle high dose methotrexate and intrathecal methotrexate, cytarabine, and hydrocortisone. He then received an autologous bone marrow transplant, conditioned with thiotepa, busulfan, and cyclophosphamide.

**Conclusion:**

This is the first reported case of metastatic CNS-predominant peripheral T-cell lymphoma in a pediatric patient. Limited retrospective studies describe treatment regimens utilizing either B-cell NHL/ALL therapies or T-cell ALL/lymphoblastic lymphoma therapies. Multi-drug regimens that included HD-MTX and cytarabine appear most effective. Several factors contributed to our therapeutic approach. A more intensive T-ALL based regimen was utilized upfront due to the patient's neurologic compromise. Subsequently, we sought to optimize CNS coverage with frequent IT therapy and systemic chemotherapeutics with a high degree of CNS penetrance. Our patient is now nine months from initial diagnosis with excellent response evidenced by no appreciable disease on PET scan. He tolerated therapy well and had vast improvement in ambulation since diagnosis.

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Poster # 765

**RELAPSED HODGKIN LYMPHOMA SUCCESSFULLY TREATED WITH TARGETED IMMUNOTHERAPY AND CHEMOTHERAPY**

**Amy Moskop, Paul Harker-Murray**

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**Background:**

High-dose chemotherapy followed by autologous stem cell transplant (HDCT/ASCT) is standard

for most relapses of Hodgkin lymphoma (HL), however, the acute and late effects of radiation therapy and HDCT/ASCT remain a concern in relapsed HL and highlight the need for novel, less toxic approaches. A subset of pediatric patients with relapsed HL can be cured without HDCT/ASCT, however, in North America, there are no established inclusion criteria for this group, nor is there a standard treatment approach.

Several agents are highly active in relapsed and refractory HL and have the potential for decreased late effects. These include Brentuximab vedotin, an antibody drug conjugate targeting CD30, nivolumab, an antibody that inhibits programmed death-1 (PD-1), and bendamustine, a bifunctional alkylating agent. The use of immunotherapy and targeted agents in combination with conventional chemotherapy is a primary area of study in relapsed HL.

**Objectives:**

To describe the successful management of a patient with relapsed HL with targeted immunotherapy and chemotherapy and without HDCT/ASCT.

**Design/Method:**

A 15-year-old with stage IIA HL was treated upfront with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) therapy. He presented at 23-years-old with lymphadenopathy and rash and was diagnosed with recurrent, stage IIA, non-bulky HL. He was enrolled on an open clinical trial, COG AHOD1721, a risk-stratified, response-adapted trial which incorporates nivolumab and brentuximab (BvN) and subsequent brentuximab and bendamustine (BvB) for a subset of patients with suboptimal response. All patients in the low risk group with complete metabolic remission (CMR) received involved site radiation therapy (ISRT).

**Results:**

The patient met criteria for the low risk relapse based on stage (IIA), absence of B symptoms, and > 12 months from end of therapy to relapse. He achieved CMR after 2 cycles of BvN and completed a total of 6 cycles. The patient refused to undergo ISRT so an additional 2 cycles of BvB was recommended off study to consolidate his remission. He had no complications during this therapy. He remains in complete remission 1.5 years off therapy.

**Conclusion:**

This case offers an alternative consolidative approach to late relapse HL sparing a select group of patients the long-term side effects of both radiation therapy and HDCT/ASCT. The prospective cooperative group trial, AHOD1721, may provide an effective approach to relapsed HL while minimizing toxicity.

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Poster # 766

**SPORADIC BURKITT LYMPHOMA PRESENTING WITH SPHENOID BONE  
INVASION AND ACUTE PANCREATITIS IN A CHILD**

**Tal Dror, Virginia Donovan, Naomi Strubel, Sucharita Bhaumik**

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**Background:**

Acute pancreatitis in children is most often due to infection, trauma, or anatomical abnormalities and is rarely due to obstruction from malignancy. Burkitt lymphoma (BL) is an aggressive non-Hodgkin B-cell lymphoma. The sporadic variant seen in the United States usually involves the bowel or pelvis, with isolated cases presenting as acute pancreatitis.

**Objectives:**

To present a case of sporadic BL in a 12 year-old boy with acute pancreatitis, obstructive jaundice, and a facial mass invading the sphenoid bone.

**Design/Method:**

A previously healthy 12 year-old male presented to the emergency room with abdominal pain, jaundice, and a right-sided facial mass. Labs were suggestive of pancreatitis, jaundice, and transaminitis with signs of biliary obstruction. Lactate dehydrogenase and inflammatory markers were elevated. Abdominal ultrasound showed a distended gallbladder with sludge and stones and a dilated common bile duct (CBD) measuring 21mm in diameter, nearly ten times the upper limit for age. Facial computed tomography (CT) revealed an abnormal right sphenoid bone wing with lytic changes, destruction, and a mass in the right middle cranial fossa with displacement of the right temporalis muscle and widening of the temporomandibular joint. Brain magnetic resonance imaging (MRI) reported a right temporal mass with a second one adjacent to an irregularly shaped right sphenoid wing. Prominent left retropharyngeal and posterior neck nodules were also visualized.

**Results:**

CT-guided right middle fossa soft-tissue biopsy displayed a small blue cell tumor, suggestive of lymphoma. Subsequent imaging showed a pancreatic mass, a 3mm distal biliary stricture and CBD dilation without cholelithiasis. Biliary sphincterotomy with metal stent placement followed, draining biliary sludge. The pancreatic mass and multiple gastric lesions were biopsied during the procedure, with pathology showing diffuse infiltration of lamina propria by atypical CD20+ lymphoid cells with crypt involvement. This was all consistent with metastatic stage 4 BL due to intracranial involvement. Bone marrow and cerebrospinal fluid showed no disease. The patient showed rapid response to intense chemotherapy.

**Conclusion:**

Early recognition of BL is essential for survival given the rapidly progressing nature of this disease. This case illustrates the importance of ruling-out malignancy in a child with acute pancreatitis and obstructive jaundice, especially in the presence of multi-system involvement. It is distinct from other isolated reports of pediatric BL presenting with acute pancreatitis, as there was widespread disease with intracranial and bony components without bowel or pelvic involvement, reinforcing the need for a multidisciplinary team.

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Poster # 767

**BILATERAL TESTICULAR HIGH GRADE B-CELL LYMPHOMA PRESENTING IN A PATIENT WITH COMPLETE SITUS INVERSUS**

**Adriana Trabal, Branko Cuglievan, Cesar Nunez, Jie Xu, Ajaykumary Morani**

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**Background:**

Non-Hodgkin's lymphoma includes subtypes that can vary in aggressiveness and location. Primary testicular lymphoma is an uncommon presentation in the pediatric population. We present the case of a 17-year-old male with situs inversus who presented with bilateral testicular enlargement and intermittent fever. Labs showed negligible B-hCG and decreased testosterone level. PET CT demonstrated FDG avidity in testicles and bilateral retroperitoneal lymphadenopathy. Biopsy revealed high grade B-cell lymphoma. The patient was treated as per COGANHL1131. After two cycles, the patient's clinical and radiological response was suboptimal. Repeat testicular biopsy revealed fibrotic tissue. Further hemato-pathological markers revealed no evidence of disease. The patient currently remains on chemotherapy and undergoing genetic testing for this rare association between situs inversus and testicular lymphoma.

**Objectives:**

We describe the case of a patient with primary presentation of high grade B-cell lymphoma as bilateral testicular masses. Imaging demonstrated patient had complete situs inversus with dextrocardia.

**Design/Method:**

PubMed search was done with search for terminology including "high grade lymphoma", "situs inversus", and "primary testicular lymphoma". Relevant articles were selected for literature review.

**Results:**

A 17-year-old male patient, previously healthy, presented with a one-month history of worsening bilateral testicular enlargement. Patient was initially treated for orchitis. Given no improvement, patient sought a second opinion. Testing done was negative for b-hCG and alpha-fetoprotein. Patient referred intermittent fever over the past month. Otherwise denied weight loss and night sweats. Physical exam showed bilateral indurated testicles with erythema and mild tenderness. CT of chest/abdomen was ordered and was remarkable for complete situs inversus and dextrocardia. Family had no previous knowledge of this diagnosis. Patient was then referred to our institution. CT of abdomen/pelvis showed the left testis measured 8.5 X 5.5 X 7cm and the right testis 5.7 X 5.2 X 8.7cm. PET confirmed increased FDG uptake in both testicles as well as bilateral retroperitoneal lymphadenopathy. Testicular biopsy confirmed High grade B cell lymphoma, suggestive of Burkitt's lymphoma. However, final FISH report was negative MYC gene rearrangement. Flow cytometry was positive for CD 10, CD19, CD20, CD22, CD38, CD43, CD79b, and Kappa. Patient was started on treatment as per ANHL1131.

**Conclusion:**

Our case opens the door to considering high grade lymphoma diagnosis in a pediatric patient

presenting with rapid testicular enlargement. Monitoring of this patient's treatment response should be further documented for patients with similar presentations.

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Poster # 768

## **AN UNUSUAL PRESENTATION OF HODGKIN LYMPHOMA IN A 12-YEAR-OLD MALE WITH ABDOMINAL PAIN**

**Minelys Alicea, Maria Español, Jennifer Lim, Corey Falcon, Justin Farge**

*LSU HSC, New Orleans, Louisiana, United States*

### **Background:**

Classic Hodgkin lymphoma (CHL) is a lymphoid malignancy characterized by the presence of clonal multinucleated Reed-Sternberg cells (RS) and mononucleated Hodgkin cells. It comprises 6% of pediatric cancers, and occurs more commonly in males under 15 years of age. CHL commonly presents with cervical and/or mediastinal lymphadenopathy along with systemic symptoms such as fatigue, and weight loss. Parenchymal lung lesions are rare in children with HL.

### **Objectives:**

To depict an interesting case of Classic Hodgkin Lymphoma in a 12-year-old male presenting with cough, weight loss and abdominal pain, in addition to extensive nodular pulmonary lesions on chest imaging.

### **Design/Method:**

Case Report

### **Results:**

A 12-year-old African-American male with no significant past medical history presented to an outside Emergency Department with 3 days of intermittent right upper quadrant, poorly characterized abdominal pain not associated with nausea, emesis, dysuria, constipation or diarrhea. Physical examination revealed an anxious child with tachycardia, tachypnea, bilateral crackles in pulmonary bases and diffuse abdominal pain. Initial laboratory work-up was concerning for a WBC count of  $65.6 \times 10^3/\mu\text{L}$ . and a chest X-ray showing extensive nodular pulmonary lesions. Further evaluation with computed tomography (CT) of the chest showed innumerable pulmonary nodules of varying size from several millimeters to 1.5 cm, with areas of confluence and mass-like consolidation in the middle lobe, and one small cavitary nodule in the RLL. Abdominal and pelvic CT were negative. The patient was transferred to our tertiary care center for additional testing and treatment. A comprehensive infectious workup was non-diagnostic. Biopsy of a peripheral lung lesion was consistent with Classic Hodgkin lymphoma, nodular sclerosis subtype. Bilateral bone marrow biopsies were negative for disease. Positron emission tomography-computed tomography (PET-CT) demonstrated hypermetabolic diffuse adenopathy, with diffusely positive lymphomatous involvement of the lungs and spleen. The patient was subsequently diagnosed with Stage IV CHL and began treatment with COG protocol AHOD1331. After 6 months of treatment, he achieved a 75% reduction in the extensive

mediastinal and pulmonary parenchymal disease, showing marked and rapid improvement.

**Conclusion:**

Pulmonary involvement is rare in pediatric Hodgkin lymphoma, and it typically arises from lymphatic extension of mediastinal lymphadenopathy. This presentation was unusual in that the distinct innumerable nodular lesions likely arose via hematogenous spread. As this case shows, Hodgkin lymphoma should be considered in the differential diagnosis of a patient with extensive nodular pulmonary lesions.

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Poster # 769

**THE USE OF EMAPALUMAB AS TREATMENT FOR A CRITICALLY ILL PATIENT WITH FAMILIAL HLH**

**Amanda Scheuermann, Rachel Phelan, David Margolis, Miranda Gries, Julie Talano**

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**Background:**

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease characterized by impaired natural killer and cytotoxic T cell function. Patients present with signs of systemic inflammation and have the potential to progress to multi-system organ failure. The treatment has historically included steroids and etoposide as a bridge to curative hemopoietic stem cell transplant (HSCT). Emapalumab is an interferon gamma blocking antibody that was approved by the FDA in November 2018 following a multicenter clinical trial. The trial showed that 63 percent of patients experienced a response and 70 percent were able to proceed to HSCT. It is currently approved for the treatment of children with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

**Objectives:**

We present a 10-year-old male diagnosed with familial HLH, UNC13D mutation, with initial presentation of focal neurologic deficits and cerebellar lesions. He was initiated on HLH 94 treatment with weekly intrathecal methotrexate and hydrocortisone. Two weeks into HLH therapy, he developed bloody diarrhea positive for shiga toxin E Coli, treated with eculizumab. He rapidly developed hemolytic uremic syndrome (HUS), renal failure and severe neurologic involvement requiring veno-venous hemofiltration and mechanical ventilation. He developed multiple areas of bowel perforation with erosion into an artery requiring a diverting colostomy and open abdominal wound healing by secondary intention. Despite the use of Emapalumab to treat patients with refractory/progressive HLH, it was unclear to our team if it would be effective in our critically ill patient. In addition, one of the most commonly reported adverse reactions is infection. We hypothesized that this would be the best option given its targeted nature.

**Design/Method:**

Due to his neutropenia and bowel perforation, he was unable to receive etoposide. Emapalumab was initiated in addition to dexamethasone. He was started on 1 mg/kg IV every 72 hours and dose escalated up to 3 mg/kg IV every 72 hours.

**Results:**

Following initiation of Emapalumab, his dexamethasone was weaned to ~1 mg/m<sup>2</sup>/day to aid with healing of his abdominal wound. He required dialysis for 2 months and then had recovery of his renal function. His HLH remains in remission and we plan to proceed to HSCT in the coming months.

**Conclusion:**

In our patient with life threatening complications due to shiga toxin induced HUS, Emapalumab treated his HLH to allow recovery of his organ function. Given our experience, this medication appears to be an excellent option for the treatment of HLH, even in patients with significant comorbidities.

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Poster # 770

**CONGENITAL SELF-HEALING RETICULOHISTIOCYTOSIS: A CASE SERIES**

**Richard Suarez, Megan Murphy, Andie O'Laughlin, Michael Hardiman, Rafat Ahmed**

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**Background:**

Congenital self-healing reticulohistiocytosis (CSHR) is a benign form of Langerhan cell histiocytosis (LCH) that typically presents at birth or early within the neonatal period with skin involvement. CSHR, like all forms of LCH, show microscopic evidence of histiocytes that are positive for S100 and CD1a on immunohistochemical staining. CSHR rarely demonstrates, recurrence or multiorgan involvement and typically presents with benign skin lesions. Patients usually have long term follow up through lab work and imaging modalities to evaluate for systemic involvement.

**Objectives:**

To present two cases, presenting with CSHR, a rare type of LCH, showing resolution of skin symptoms, one with treatment and one without treatment.

**Design/Method:**

The study is a case series. Patients who were admitted at Cooper University Hospital. Patient A, a two-day old term male infant born via spontaneous vaginal delivery presented from an OSH for evaluation of a pustular rash all over his body. Biopsy of skin lesion was consistent with CHSR. Patient A was on Vancomycin and Acyclovir on arrival which were discontinued, and lesions were treated with triamcinolone acetonide ointment. Patient B, a 33 weeks old twin Premie, born via spontaneous vaginal delivery, presented at day 20 with a yellow-red papule on his left calf and shoulder. On clinical monitoring by 5 weeks patient two of the skin lesion grew and were crusted. At 7 weeks, a skin biopsy, revealed CSHR. His skin lesions resolved without treatment.

**Results:**

Both patients were found to be positive for CD1a and S100 on immunohistochemical staining. Patient A's skin biopsy showed prominent Langerhans cell proliferation with associated ulceration. Skin lesions were successfully treated with triamcinolone acetonide ointment twice a day. Patient B's biopsy showed similar findings. Blood work and imaging of both patients showed no indication of other organ involvement.

**Conclusion:**

We found two patients with similar skin lesions to have CSHR with resolution of symptoms one with and one without treatment. At latest follow up, at six months of age, patient one is healthy and has no new lesions. Patient two's most recent follow, at one year of age, also shows no new lesions and is healthy.

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Poster # 771

**PULMONARY LANGERHANS CELL HISTIOCYTOSIS IN AN ADOLESCENT WITH CHRONIC MARIJUANA USE**

**Maggie Seblani, Joanna Weinstein**

*Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, United States*

**Background:**

Langerhans cell histiocytosis (LCH) is an entity with varied presentation and clinical course. Pulmonary LCH rarely occurs in pediatric patients, with lung involvement more commonly seen in children with multi-system disease. Isolated pulmonary LCH in adults has a strong association with smoking, with initial management focused on cessation. Smoking induces inflammation, oxidative stress and stimulates cytokine production leading to recruitment and differentiation of dendritic cells. Corticosteroids and agents such as cytarabine and cladribine have been used for progressive pulmonary disease in adults but have not been well-studied in the pediatric population.

**Objectives:**

With this case report we demonstrate the occurrence of isolated pulmonary LCH in a pediatric patient in the context of chronic marijuana use.

**Design/Method:**

Our patient is a 17 year old previously healthy male with a two to three year history of daily marijuana smoking who initially presented with a spontaneous pneumothorax in setting of several weeks of worsening cough. His unilateral pneumothorax improved with thoracotomy however within one week, he again became symptomatic with chest pain and dyspnea and found to have bilateral pneumothoraces, requiring thoracotomy. Computed tomography (CT) of the chest identified innumerable thin-walled cysts throughout the lung parenchyma with subpleural and bi-basilar predominance and honeycombing appearance. He underwent video-assisted thoracoscopy with wedge resection of right lung. Histology demonstrated large cells with abundant eosinophilic cytoplasm and irregular convoluted nuclei and grooves around cystic spaces positive for CD1a. With findings consistent with pulmonary LCH, our patient underwent



subsequent assessment for multisystem involvement. Magnetic resonance imaging of brain and pituitary and skeletal survey were both negative for lesions and thyroid studies, serum and urine electrolytes were all within normal limits. Testing for BRAF (V600E) mutation of lung tissue was negative.

**Results:**

For our patient with single-system pulmonary LCH, we pursued strict smoking cessation and avoidance of secondary exposure with close clinical follow up and serial CT imaging. He has overall remained asymptomatic and with interval improvement in radiographic findings of his pulmonary LCH without use of systemic therapies.

**Conclusion:**

Pulmonary LCH is a rare interstitial lung disease found in adult smokers typically in the third and fourth decades, isolated involvement in children is rare and lung disease often accompanies multisystem involvement. While previously described in adults with a strong smoking history, there have not been published reports of pediatric patients developing pulmonary LCH with marijuana use. Our patient has demonstrated clinical and radiographic improvement with cessation and avoidance of exposures.

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Poster # 772

**SUCCESSFUL TREATMENT OF LCH-LIKE BRAIN LESIONS WITH ANTI-METABOLITE THERAPY**

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**Background:**

Langerhans cell histiocytosis is a rare clonal malignancy. Clinical presentation varies depending on site and extent of involvement. LCH is a disease diagnosed through molecular analysis as well as histochemistry.

**Objectives:**

To report to report the excellent response of LCH-like CNS lesions to antimetabolite therapy despite difficulty reaching a final diagnosis and treatment plan.

**Design/Method:**

Case report

**Results:**

Our patient presented at 10 years old with several years of headaches and development of a skull vault mass that was excised. Pathology was consistent with classic LCH. Skull mass was significant for BRAF V600E mutation. Skeletal survey and labs were negative for additional lesions. No additional treatment was required for the diagnosis of unifocal LCH. After 5 years, headaches worsened and he developed tremors. MRI demonstrated multiple T2

and FLAIR hyperintense lesions within the cerebral hemispheres. Treatment with cytarabine (150 mg/m<sup>2</sup>/dose daily x5 days every 28 days) was instituted with resolution of symptoms and regression of CNS lesions on imaging. He was stable for 2 years before he had a recurrence of headache, tremors, and development of right-sided hemiparesis. MRI revealed new multifocal supratentorial lesions, with brain biopsy suggestive of CNS LCH. BRAF V600E mutation was not identified in the brain biopsy or peripheral blood. The lack of the BRAF mutation raises the question of whether these CNS lesions were more consistent with an immune mediated process such as multiple sclerosis (MS), and second pathology opinion is pending. Treatment with clofarabine (25 mg/m<sup>2</sup>/dose daily x5 days every 28 days) as for CNS LCH was started. After 6 cycles, he had resolution of CNS symptoms and near complete regression of lesions on MRI.

**Conclusion:**

Despite some uncertainty over the diagnosis of CNS LCH vs immune mediated injury such as seen in MS, antimetabolite therapy was very effective for our patient. While antimetabolites are a major component of LCH therapy, they are not first-line therapy for MS and clofarabine has not been reported for use in MS. This case represents both a diagnostic and treatment dilemma with differing final diagnoses and treatments recommended depending on the subspecialty. This may be an area for future study and collaboration with our neurology colleagues.

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Poster # 773

**MICROBIAL CELL-FREE DNA SEQUENCING FOR EVALUATION OF ANTIBIOTIC-RESPONSE IN PATIENTS WITH LEUKEMIA**

**Joshua Wolf, Kathryn Goggin, Amanda Griffen, Christina Kohler, Kim Allison, Yuki Inaba, Asim Ahmed, Desiree Hollemon, Brenner Abigail, Gabriela Maron, John Choi, Jeffrey Rubnitz, Veronica Gonzalez-Pena, Charles Gawad, Ellie Margolis**

*St. Jude Children's Research Hospital, Memphis, Tennessee, United States*

**Background:**

In patients with bloodstream infection (BSI), true eradication of infection takes longer than blood culture clearance. Therefore, optimal treatment duration, especially in immunocompromised hosts, is unknown. A sensitive test of microbiological response to treatment could improve care by indicating a time for safe antibiotic discontinuation. Microbial cell-free DNA sequencing (mcfDNA-seq) is a sensitive predictor of BSI, and we hypothesize that it might also be useful to measure response to treatment.

**Objectives:**

To describe the kinetics of DNA decay after initiation of appropriate therapy for bloodstream infection in patients with leukemia and evaluate the association with response to antibiotic treatment.

**Design/Method:**

Eligible participants were <25 years of age being treated for relapsed or refractory leukemia. Remnant plasma samples were collected as part of a prospective study (PREDESEQ), and

underwent mcfDNA-seq by Karius Inc. in a CLIA/CAP-accredited laboratory. Pathogen DNA was reported in molecules per microliter (MPM). Testing was batched and blinded. Available samples from Day 1 through Day 7 after onset of bacterial BSI were included. We evaluated decay of the BSI pathogen DNA after initiation of effective antibiotic therapy, from the peak to last available sample, and compared episodes with slow ( $<0.5 \log_{10}$  MPM/day) vs. rapid DNA decay.

**Results:**

There were 13 evaluable BSI episodes in 9 participants, including 10 Gram positive and 3 Gram negative bacteria; 7 had slow DNA decay. Persistence of bacteremia or fever  $\geq 1$  day after initiation of effective antibiotics occurred in 9/13 episodes (7/7 slow decay and 2/6 rapid decay;  $P = 0.02$ ). Slow decay persisted beyond resolution of bacteremia and fever in 3/7 of these cases.

**Conclusion:**

In this small sample of patients with leukemia, slow mcfDNA-seq DNA decay correlated with persistent fever or bacteremia. Post-BSI mcfDNA-seq monitoring should be investigated with the goal of decreasing inappropriate antibiotic therapy and preventing treatment failure.

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Poster # 774

**RARE PRESENTATION OF RELAPSED LANGERHANS CELL HISTIOCYTOSIS OF THE FINGERNAILS**

**Kyle Randolph, Amy Cruickshank**

*University of New Mexico Health Sciences Center, Albuquerque, New Mexico, United States*

**Background:**

Langerhans Cell Histiocytosis is an extremely rare diagnosis with approximately 24% of patients relapsing when there is skin involvement at initial diagnosis<sup>1</sup>. We present a rare case of single system relapsed LCH initially isolated to the fingernails followed by the scalp.

**Objectives:**

Present a rare case of isolated fingernail LCH relapse with photographs of progression and resolution of disease.

**Design/Method:**

This is a case of a 17 year old girl with relapsed Langerhans cell histiocytosis (LCH). She was initially diagnosed with multisystem LCH with skin and CNS involvement 3 years ago. She completed a year of prednisone and vinblastine. Her skin involvement resolved within a month of treatment. She remained in remission for one year when she noticed bruises at the base of a couple of her nails. She previously had artificial fingernails in place. After removal, the bruises were present and one nail was peeling. Initially, this was thought to be due to the artificial nails. At the next 6 month follow up, she developed nail involvement of all 10 fingernails. She was referred to dermatology, and she had developed a scalp rash in the interim. A biopsy of the scalp was positive for LCH. Staging was otherwise negative. She was started on hydroxyurea with

improvement in her nail and scalp disease.

**Results:**

This is a case of a 17 year old girl with single system relapsed LCH presenting with fingernail involvement who is being treated with hydroxyurea with positive results.

**Conclusion:**

Patients with multisystem LCH are at risk for skin relapse and can present as fingernail only disease. We present a case with multiple time points of the nail disease to show progression and regression.

1. Zinn, Blood, 2016

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Poster # 775

**NEONATAL PRESENTATION OF RAS-ASSOCIATED AUTOIMMUNE LEUKOPROLIFERATIVE DISORDER**

**Ashley Bui, Samuel John**

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**Background:**

RAS-associated autoimmune leukoproliferative disorder (RALD) is a rare chronic lymphoproliferative syndrome characterized by splenomegaly, leukocytosis with B-lymphocytosis and monocytosis, and immune dysregulation. Previously classified as autoimmune lymphoproliferative syndrome type IV, it is now considered a separate entity driven by somatic RAS mutation resulting in increased proliferation, defective apoptosis, and subsequent accumulation of non-malignant T-lymphocytes.

**Objectives:**

We present the youngest reported patient with RALD, along with diagnostic and therapeutic challenges.

**Design/Method:**

Case report

**Results:**

A one-day-old full term male was admitted to the NICU with respiratory distress. Work up revealed platelet count of 13 thousand/mm<sup>3</sup>. He received platelet transfusions and IVIG for presumed neonatal alloimmune thrombocytopenia.

He presented to hematology clinic on day 18 of life, clinically well without focal exam findings. Labs demonstrated continued thrombocytopenia and WBC count 32.1 thousand/mm<sup>3</sup> with significant absolute monocytosis and 4% peripheral blasts. Direct Coombs was positive.

Shortly after, he presented with new splenomegaly, rising WBC count, persistent peripheral blasts, and worsening thrombocytopenia. Workup for infectious etiology, Down and Noonan syndromes was negative. Bone marrow evaluation showed somatic KRAS G12S mutation, normal cytogenetics, and hematogone hyperplasia. No evidence of acute leukemia or MLL gene rearrangement.

He then developed acute respiratory failure secondary to massive hepatosplenomegaly. He was started on dexamethasone followed by 6-mercaptopurine with minimal response. He transitioned to sirolimus with improvement in both blood counts and spleen size.

**Conclusion:**

We present a case of RALD with disease manifestations in the neonatal period. This diagnosis should be considered in patients with splenomegaly, autoimmunity, and/or blood count abnormalities such as persistent monocytosis and hematogone hyperplasia which may serve as disease markers. Diagnosis is made with bone marrow evaluation and confirmation of somatic RAS mutation. However, there is substantial overlap between RALD and juvenile myelomonocytic leukemia (JMML). RALD patients often meet the diagnostic criteria for JMML but follow a more indolent course. Additional cytogenetic abnormalities (i.e. monosomy 7) are the most definitive feature favoring JMML over RALD.

Given the rarity of this diagnosis, a standard of care has not been established. Steroids or 6-mercaptopurine may aid in cytoreduction. Sirolimus, an inhibitor of mTOR which is downstream of RAS, has been shown to induce apoptosis of normal and abnormal lymphocytes and has proven effective in this patient. It is unknown if this patient's early disease progression portends a more severe clinical course. Increasing use of novel RAS/RAF/MEK/ERK pathway inhibitors in other clinical settings suggests potential therapeutic benefit in RALD as well.

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Poster # 776

**SUCCESSFUL TREATMENT OF RELAPSED, REFRACTORY HLH WITH IFN $\gamma$  INHIBITION IN PATIENTS WITH TRISOMY 21**

**Jordan Fritch, Adam Reinhardt, Melissa Acquazzino, Sachit Patel**

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**Background:**

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition of immune dysregulation thought to be driven by IFN $\gamma$ . IFN $\gamma$  is also thought to play a role in the autoimmunity of Trisomy 21. HLH is a familial and sporadic disorder associated with infection, malignancy and rheumatologic disorders. Conventional treatment aims to control the immune dysregulation with chemotherapy and steroids as a bridge to hematopoietic stem cell transplant. Emapalumab (anti-IFN $\gamma$  antibody) was FDA-approved in 2018 for refractory, recurrent or progressive primary-HLH. Its role in secondary HLH is yet to be determined.

**Objectives:**

Describe the first reported cases of relapsed, refractory HLH in patients with Trisomy 21 successfully treated with emapalumab and subsequently maintained on oral baricitinib (JAK inhibitor) without the need for long-term steroids.

**Design/Method:**

Case series established by retrospective review of the electronic medical record.

**Results:**

Case 1: A 17 month-old male with Trisomy 21 presented with persistent rash, fevers, thrombocytopenia, anemia, hepatosplenomegaly and elevated ferritin and was initially treated with corticosteroids, anakinra and canakinumab (IL-1 inhibitor) for a systemic juvenile idiopathic arthritis (JIA)-like picture. However, he continued to have frequent admissions for fevers and thrombocytopenia following infections. A diagnosis of HLH was ultimately made during an admission at 34 months of age based on hyperferritinemia, elevated CXCL9 and sIL-2R, elevated liver enzymes, leukocytosis, thrombocytopenia with disseminated intravascular coagulation and acute kidney injury. Due to refractory disease, he was induced with emapalumab and methylprednisolone pulses and then transitioned to baricitinib with resolution of his flare. Case 2: A 1 year-old female with Trisomy 21 presented with recurrent thrombocytopenia and rash. She was diagnosed with a form of steroid dependent HLH when she was admitted for acute liver failure at 15 months of age with work-up showing hyperferritinemia, elevated CXCL9 and sIL-2R and thrombocytopenia. At 3 years of age, after repeated admissions for steroid dependent and IL-1 refractory HLH flares, she was initiated on emapalumab with methylprednisolone pulses and transitioned to baricitinib for maintenance.

**Conclusion:**

These are the first reported cases of relapsed, refractory HLH in patients with Trisomy 21 successfully treated with emapalumab and transitioned to a steroid sparing regimen with oral baricitinib for maintenance. Trisomy 21 autoimmunity and HLH are both thought to be driven by IFN $\gamma$ . Further investigation is needed to determine if Trisomy 21 may predispose to the development of HLH given this common pathway.

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Poster # 777

**ACCURACY OF HIGH-DOSE METHOTREXATE ADMINISTRATION IN MANAGEMENT OF PEDIATRIC PATIENTS WITH ALL**

**Angela Liang, Stacy Cooper**

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**Background:**

High-dose methotrexate (HDMTX) is an important chemotherapy agent for many pediatric cancers, including acute lymphoblastic leukemia (ALL). Its narrow therapeutic window and individual pharmacogenetic differences require a nuanced understanding of its administration. However, standard of care for management of HDMTX on Children’s Oncology Group protocols relies on a complex flowchart. Confusion in using the flowchart may result in

increased toxicity, medication errors, preventable readmissions, and added healthcare costs.

**Objectives:**

This study aimed to evaluate the accuracy of HDMTX management by providers relative to standard of care, to identify areas for improvement.

**Design/Method:**

Pediatric patients with ALL who received HDMTX between July 2016 and June 2019 at a single academic medical center were identified through pharmacy records. Twenty points in the standard flowchart were identified for analysis. These included timing related to methotrexate levels, creatinine levels, and leucovorin administration at 24, 36, 42, and 48 hours, and the frequency of urine pH measurement. Also included were dosing related to hydration and leucovorin at 24, 36, 42, and 48 hours; any administration of bicarbonate and glucarpidase; and the timing of discharge. Data were obtained by retrospective review of electronic medical records.

**Results:**

Thirty-five patients collectively received 112 doses of HDMTX. Out of 2,240 points for analysis, there was a total of 448 errors for an overall accuracy of 80%, and there was an average of 3.27 errors per treatment (range: 0-10). There were more errors related to dosing (54%) than timing (46%). In terms of timing, the lowest accuracies were associated with measuring methotrexate (39%) and creatinine (39%) at 36 hours, and with measuring urine pH (21%) during treatment. In terms of dosing, the lowest accuracies were associated with bicarbonate administration (6%), and the dosing of hydration at 42 (54%) and 48 hours (64%). The highest accuracies were related to the timing (97%) and dosing (100%) of leucovorin at 42 and 48 hours; the timing of methotrexate (96-98%) and creatinine (89-90%) at 24 and 48 hours; and the timing of discharge based on methotrexate levels (95%).

**Conclusion:**

This study highlights specific points in the standard of care for HDMTX management that could be improved to enhance patient care. In particular, methotrexate and creatinine levels are often not measured when indicated, which may affect hydration dosing, and urine pH is often not measured during treatment, which may affect bicarbonate administration. These findings are valuable in informing educational or technological efforts to facilitate more accurate HDMTX management.

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Poster # 801

**EVALUATING DIET QUALITY IN CHILDHOOD CANCER SURVIVORS**

**Matthew Nagy, Komeisha Rose, Phyllis Harbor, Seth Rotz**

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**Background:**

Childhood cancer survivors (CCS) are at greater risk of suffering from metabolic syndrome. Although the root of this predisposition is likely multifactorial, it is important to identify modifiable risk factors that may contribute to metabolic syndrome development.

**Objectives:**

We aimed to observe the overall diet quality of CCS, and explore the relationship between diet quality and various markers of metabolic health.

**Design/Method:**

Participants were recruited from the Cleveland Clinic Children's CCS Program. We measured diet quality using the Rapid Eating Assessment in Patients – Short Version (REAP-S), a validated tool, which inquires about the frequency of specific dietary behaviors (“rarely/never”, “sometime”, “usually/often”). A diet quality sum score was calculated (range = 13-39) with a higher score representing a higher diet quality. Willingness to change diet behaviors was measured on a scale of 1 (not at all willing) to 5 (very willing). Metabolic measures (HbA1c, HDL, LDL, Adiponectin, Leptin) were collected from serum. Blood pressure was measured using an automated cuff, and weight status was classified as healthy weight or overweight/obese by BMI >25 (if ≥18years) or BMI percentile > 85 (if <18 years).

**Results:**

Participants included sixty CCS (22±8 years, 50% female). Primary malignancies included brain tumors (11.7%), hematologic malignancies (48.3%), and other solid tumors (40.0%). The median time since completion of therapy was 10 years. The most frequently reported unhealthy behaviors were “usually/often” skipping breakfast (40%) and eating high fat snacks (regular potato chips, nachos, etc) (33%). The least frequently reported unhealthy behaviors were “usually/often” drinking 16 ounces or more of sugary drinks daily (8%) and eating sweets (cake, cookies, etc) more than twice daily (10%). In general, participants were willing to change their eating behaviors (4.1±0.8 out of 5). Overall reported diet score was 28.5±4.7. Compared to two previously published studies in healthy young adults, our participants had a lower REAP-S score than a cohort of 81 college students (33.6±3.1, p<0.001) and a cohort of 50 young males (30.7±3.5, p=0.09). REAP-S score was not statistically significantly associated with any of the metabolic measures.

**Conclusion:**

While many CCS reported infrequent consumption of high sugar foods and drinks, overall dietary quality was inferior to cohorts of similar age participants. Nutritional counseling regarding diet quality may be a valuable asset to survivorship clinics. Interestingly, there was no relationship between diet quality and any of the measured markers of metabolic health, which may reflect the relatively young age of the patients included.

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Poster # 802

**PROVIDER DOCUMENTATION OF TINNITUS IN CHILDHOOD CANCER SURVIVORS**



**Natalie Macaruso, Kristen Campbell, Carrye Cost, Jenna Sopfe**

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**Background:**

Tinnitus is a common complication of ototoxic therapies used to treat childhood cancer, affecting between 3-60% of survivors. In the largest ongoing follow-up cohort, the Childhood Cancer Survivor Study (CCSS), prevalence of tinnitus among all survivors was 5.6%. Tinnitus has been associated with significant distress and reduced quality of life in adults. In children, it may affect education and social development. Because children may not independently volunteer tinnitus as a symptom, clinicians must maintain a high index of suspicion. Children's Oncology Group clinical practice guidelines recommend annual surveillance by history for tinnitus in survivors who received cisplatin, myeloablative doses of carboplatin, or head/brain irradiation  $\geq 30$  Gy. No data exists to describe how often childhood cancer survivors (CCS) are screened for tinnitus in accordance with these guidelines.

**Objectives:**

This study aims to quantify clinical documenting practices of tinnitus at a single institution as a correlate for routine screening of tinnitus in CCS.

**Design/Method:**

We are performing a retrospective cohort study of CCS who received survivorship care at Children's Hospital Colorado (Aurora, CO) between January 1, 2017 and July 31, 2019 (n=624). Eligible diagnoses were those included in the CCSS: leukemia (n=199), kidney tumor (n=33), bone tumor (n=35), soft tissue sarcoma (n=19), neuroblastoma (n=29), Hodgkin disease (n=20), non-Hodgkin lymphoma (n=23), and primary central nervous system malignancy (n=240). Additionally, CCS with retinoblastoma (n=8), hepatoblastoma (n=12), and germ-cell tumor (n=6) were included due to high likelihood of receiving ototoxic therapy. The primary outcome is the rate of documented tinnitus by providers. We will compare the prevalence of documented positive screening for tinnitus with the previously reported prevalence for tinnitus in the CCSS cohort by one-sample t-test. Secondary analyses stratifying documentation rates for tinnitus by age, diagnosis, and ototoxic exposure will evaluate for screening variation by Fisher's exact test.

**Results:**

Median age at diagnosis was 4 years (range 0-18). CCS were followed for a median of 8 years (range 5-23). Median age at follow-up was 15 years (range 5-24). No CCS had tinnitus prior to treatment. The primary analyses are forthcoming. We hypothesize that prevalence of documented tinnitus is significantly lower than patient-reported prevalence of tinnitus in the CCSS cohort, but prevalence of documented tinnitus is higher among higher risk populations and older CCS.

**Conclusion:**

Tinnitus remains an underrecognized long-term effect of childhood cancer treatment, potentially due to inadequate screening. Development of a validated screening instrument for pediatric tinnitus would facilitate recognition and treatment of this complication.

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## **IMPROVING KNOWLEDGE OF FOLLOW-UP CARE AND LATE EFFECTS IN SURVIVORS: A QUALITY IMPROVEMENT PROJECT**

**Shiley Aguilar, Kellen Gandy, M. Fatih Okcu, Kiranmye Reddy**

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### **Background:**

More than 400,000 pediatric cancer survivors are living in the United States today. Greater than 60% of these will experience a treatment-related late effect. The majority of survivors (>50%) do not receive long term follow-up care. Our center has a dedicated long-term follow-up clinic designed to provide lifelong risk-based survivorship care for patients at all ages.

### **Objectives:**

To improve knowledge for the need of long-term follow-up care and potential late effects in pediatric leukemia survivors by 20%.

### **Design/Method:**

A quality improvement project was conducted among off-therapy pediatric acute lymphoblastic leukemia survivors within two years from completion of treatment. In the first Plan-Do-Study-Act (PDSA) cycle, we surveyed parents and patients older than 13 the following 3 questions: 1- How long do you think you or your child will need follow-up at our center?; 2- Why?; 3- What are some of the late effects /health problems you or your child might develop due to cancer treatment? The oncology provider reviewed correct answers (life-long, risk for late effects, and patient specific side effects, respectively) and gave an informational brochure. The same questions were surveyed at the next appointment. The main outcome measures were the percent of accurate responses for questions 1 and 3 (two or more correctly identified late effects listed in the brochure

### **Results:**

We completed 3 PDSA cycles with a total of 13 patients. For PDSA cycles 1, 2, and 3, the percent of accurate responses for follow-up duration increased from 0% to 60%, 50 to 75%, and 25 to 50% respectively. The proportion of patients who identified at least two late effects correctly before and after the intervention were 60% and 40%, 50 and 75%, and, 75 and 50% respectively for each PDSA cycle. We made a minor change in the survey after the first PDSA cycle (identification and relationship to patient) to account for different caregivers at visits. We expanded from 3 providers to 5 after the second PDSA cycle.

### **Conclusion:**

Our results demonstrate a critical need for improving knowledge of follow-up care among pediatric leukemia survivors. We showed with a simple educational intervention we can increase short-term knowledge regarding need for lifelong follow-up in survivors. Whether this information is retained long-term is unknown. Our pilot intervention provides a framework for increasing knowledge of importance of follow-up in these patients. Further implementation of

these processes is anticipated to ultimately improve follow-up adherence in pediatric cancer survivors.

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Poster # 804

## **CONFIDENCE IN KNOWLEDGE OF SURVIVORSHIP CARE PLANS IN PEDIATRIC CANCER SURVIVORS**

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### **Background:**

Comprehensive cancer care has increased the 5-year survival of children with cancer to >80%. With over 400,000 childhood cancer survivors in the US, structured follow-up care is essential. Survivorship Care Plans (SCP), which detail treatment history and recommended follow-up, are provided to childhood cancer survivors to help them navigate physical and psychosocial challenges that they face after cancer care. Confidence in knowledge about SCP by caregivers may impact utilization and health outcomes.

### **Objectives:**

To compare confidence in SCP knowledge in caregivers of childhood cancer survivors by socio-demographics, language, health literacy (HL), acculturation (if Hispanic), cancer type, treatment type, and recall of receiving SCP, with particular focus on Hispanics.

### **Design/Method:**

English or Spanish-speaking caregivers of childhood cancer survivors (>2 years from end-of-therapy) aged 2-24 years from Rady Children's Hospital survivorship clinic were recruited to participate in the study. Caregivers completed surveys to assess the variables of interest. Outcomes were analyzed using t-tests, Chi-Square tests, or Mann-Whitney U tests.

### **Results:**

Two hundred-sixty caregivers (56% female, 56.4% Hispanic) of pediatric cancer survivors were enrolled. Hispanic caregivers were younger, with less education, and lower socioeconomic status. Compared to non-Hispanic caregivers, a higher proportion of Hispanics reported high confidence in SCP knowledge ( $p=0.022$ ). Caregivers with lower education ( $p=0.015$ ), and limited English proficiency (LEP) [ $p=0.010$ ] also reported higher confidence. Patients in the higher confidence group had lower objective HL: TOFHLA ( $p=0.003$ ) and NVS ( $p<0.001$ ), yet higher subjective HL: CRI ( $p=0.002$ ). A higher percentage of caregivers in the high confidence group recalled receiving the SCP (42% vs 21.6%,  $p=0.001$ ) compared to those in the low confidence group. A higher percentage of patients in the high confidence group underwent complex treatment (surgery, radiation, and/or bone marrow transplant±chemotherapy) versus chemotherapy alone (69.6% vs 55.8%,  $p=0.046$ ).

### **Conclusion:**

Unexpectedly, high confidence in SCP knowledge was associated with Hispanic ethnicity, lower objective HL, higher subjective HL, lower education, and LEP. Consistent with our findings, low disease knowledge may correlate with overconfidence in one's perception of medical information, as reported in some underserved populations. Therefore, high confidence alone is unlikely to predict utilization of SCP. It is important to identify caregivers with objectively low HL, LEP, and low education as appropriate individualization of the SCP and tailored education to the individual's language and HL may improve SCP utilization. Future research should evaluate which factors predict SCP utilization and design interventions to improve health outcomes.

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Poster # 805

## **KNOWLEDGE GAPS IN SURVEILLANCE FOLLOW-UP TESTING AMONG YOUNG ADULT SURVIVORS OF CHILDHOOD CANCERS**

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### **Background:**

Young adult (YA) survivors of childhood cancer take on increasing independence in illness self-management when transitioning from pediatric to adult care. This requires knowledge of treatment modalities received, risk for late effects, and future testing requirements, so that survivors can communicate this information to their primary care provider (PCP). Current guidelines recommend that survivors receive treatment summaries, annual follow-up visits, and risk-adapted surveillance testing. There is little known about factors influencing survivors' knowledge of these recommendations.

### **Objectives:**

The current study aimed to assess demographic, disease, and psychosocial factors associated with YA survivor knowledge of physician recommendations for health monitoring.

### **Design/Method:**

Patients age  $\geq 16$  years seen in a multidisciplinary cancer survivor clinic were eligible. Participants completed the Patient-Reported Outcome Measurement Information System (PROMIS®) Short-form Physical Functioning, Fatigue, Depression, and Anxiety measures along with self-reported PCP visit behavior and history of medical diagnoses. Participant knowledge of their need for medical testing was assessed by comparing respondents' self-report to their physicians' report for the following: lab-work, urinalysis, echocardiogram, and thyroid ultrasound. Each participant received a surveillance knowledge score (range 0-4 with 0=none correct and 4=all correct).

### **Results:**

Participants (n=97) were 53.6% male, 87.6% Caucasian with average age at diagnosis of 11.6 years (range 0.02-25.7) and 20.6 years (range 7.2-35.9) at survey completion. The majority

(43.3%) were diagnosed with acute lymphoblastic leukemia with average treatment intensity score of 2.77 (SD=0.72). The majority reported regular attendance at PCP clinic visits (74.2%), satisfaction with their PCP (90.7%), and a visit to their PCP within the last year (75.2%). On average, patient-reported PROMIS scores fell within the average range of the reference population. When asked to report on their knowledge of recommended surveillance testing, a majority (58.8%) correctly reported lab-work frequency, while a minority reported accurate knowledge about urinalysis (40.2%), echocardiogram (23.7%), and thyroid ultrasound (42.3%) recommendations, with an overall knowledge score of 1.65 (ie, 1.65 correct out of 4, SD=1.25). Results of regression analyses suggested that demographic, disease, or psychosocial variables were not predictive of participant total surveillance knowledge scores.

**Conclusion:**

Despite attendance at a multidisciplinary survivor clinic, yearly receipt of a treatment summary, and a majority having visited a PCP recently, only a minority were able to correctly recall follow-up surveillance testing and overall knowledge scores were low. None of the demographic, disease, or psychosocial variables studied were predictive of participant knowledge in this study. Future research to improve YA knowledge and communication to their PCP is needed.

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Poster # 806

**FOCAL NODULAR HYPERPLASIA IN SURVIVORS OF CHILDHOOD CANCER**

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**Background:**

Focal nodular hyperplasia (FNH) is a rare liver lesion, accounting for 2% of pediatric liver tumors. Clinically relevant cases of FNH in the US have a reported prevalence of 0.03%. Prior studies have suggested an increased prevalence of FNH in survivors of childhood cancer, but analyses are generally limited by small numbers of patients and short follow-up.

**Objectives:**

The objective of this study is to describe the demographic and diagnostic variables among a large number of cases of FNH identified in a cohort of childhood cancer survivors treated at a tertiary cancer center.

**Design/Method:**

We performed a retrospective review of childhood cancer survivors at Memorial Sloan Kettering Cancer Center (MSK) with documented FNH on routine surveillance magnetic resonance imaging (MRI). Eligible survivors were: (1) aged  $\leq 21$  years at the time of primary childhood cancer diagnosis; (2) diagnosed with childhood cancer between 1990-2017; (3) survived  $\geq 12$  months from completion of therapy; and (4) seen in the MSK Long Term Follow Up Program at least once.

**Results:**

We identified FNH in 112 childhood cancer survivors (51.8% male, median age at primary diagnosis: 4.9 years [range: 0.1-21.1]; median follow-up from cancer diagnosis: 11.1 years [range, 4.0-27.8]). The most common primary cancer diagnoses were: neuroblastoma (n=55), sarcoma (n=24), leukemia (n=14), and lymphoma (n=7); 76.2% (n=16) of the leukemia/lymphoma patients had undergone allogeneic bone marrow transplant. Radiographic detection of FNH occurred at a median of 6.7 years (range: 0.8, 22.8) after the primary cancer diagnosis. Twenty-two patients (19.6%) had at least one hepatic comorbidity, including hemosiderosis/hemochromatosis (n=11), hepatic steatosis (n=5), transaminitis (n=2), hepatic fungal infection (n=1), perihepatic abscess (n=1), hepatic hamartoma (n=1), and hepatitis C (n=1). Twenty-nine females (53.7%) were on estrogen therapy. After initial identification of FNH, patients received up to 12 follow-up surveillance MRIs (median: 2) at a median interval of 6 months (range, 1-113). Twelve biopsies of suspicious lesions were performed in 10 patients; all showed benign findings. No patient went on to develop a malignancy of the liver.

**Conclusion:**

This report suggests that FNH may be more common in childhood cancer survivors than in the general population. Based on our institutional experience, the lesions appear to be benign and do not progress to malignancy. Further investigation is needed to identify treatment-related risk factors and optimal frequency of surveillance imaging.

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Poster # 807

**THE EFFECT OF PRIMING ON PATIENT-REPORTED OUTCOMES IN SURVIVORS OF PEDIATRIC CANCER**

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**Background:**

A diagnosis of pediatric cancer now carries an overall survival rate of over 80%, which has led to a growing population of survivors. The importance of using Patient Reported Outcomes (PROs) as a measure of late effects is therefore paramount to determine the burden of disease and its therapy for this population. Current PRO data for survivors of pediatric cancer is conflicted, with some studies suggesting significant late effects while others suggest survivors are similar to unaffected peers. The reason for the reported discrepancies is unknown. One hypothesis is that the research materials used to investigate late effects, including PROs, may be susceptible to priming. This study aims to determine the possible impact of priming on PROs from pediatric cancer survivors.

**Objectives:**

We aim to investigate if adolescents and young adult (AYA) patients will report more distress after receiving PROMIS® short form measures with a primed introduction focusing on late effects of cancer and its treatment than AYA patients who receive the same measures with a

neutral introduction.

**Design/Method:**

We conducted a randomized trial comparing introductions to PROMIS® short form questionnaires in AYA returning for annual follow up at Children’s Hospital of Pittsburgh’s survivorship clinic. Inclusion criteria included attending survivorship clinic and age 14.0 years or older. Participants were randomized into either “primed” or “neutral” survey introduction before completing six PROMIS® short forms assessing fatigue, pain, anxiety, depression, social interactions, and upper extremity functioning. Survey outcomes were converted from raw scores to T scores. Statistical analysis with Mann-Whitney U tests compared primed vs. neutral scores.

**Results:**

Participants' scores across all measures were comparable to PROMIS® norms, suggesting a lack of increased morbidity in survivors. Rates of dysfunction, using T-score cutoffs defined by PROMIS®, were similar among participants regardless of introduction. Survivors showed a statistically significant response to the primed introduction in domains social functioning and upper extremity functioning. Over 92% of recruited participants participated in the survey, demonstrating acceptability and feasibility in a long-term follow-up clinic.

**Conclusion:**

PROMIS® scores suggested minimal evidence for increased morbidity in pediatric cancer survivors in the six domains assessed by this work. We report a small but significant impact of priming on social functioning and upper extremity functioning. Priming did not have an impact on the other four domains assessed. More research is needed to determine if priming helps explain why studies of late effects using PROs in survivors of pediatric cancer are inconsistent.

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Poster # 808

**INCIDENT FOCAL NODULAR HYPERPLASIA (FNH) AND ASSOCIATED RISK FACTORS IN PEDIATRIC CANCER SURVIVORS**

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**Background:**

Focal Nodular Hyperplasia (FNH) is an epithelial tumor of the liver that has been reported in survivors of pediatric cancer and may be confused with other liver lesions. While thought to be benign, little is known about the natural history or factors associated with development of FNH in survivors of pediatric cancer.

**Objectives:**

To determine the prevalence of incident FNH in survivors of pediatric cancer who undergo abdominal imaging and associated risk factors.

**Design/Method:**

A single-center, retrospective, longitudinal study was conducted of patients diagnosed with cancer before the age of 21 years between January 1, 2007, and December 31, 2016, who underwent abdominal imaging at least six months after therapy completion. Patients treated with surgery alone or who received liver transplant were excluded. Patients were categorized as having FNH, a non-FNH liver lesion, or no incident liver lesion based on radiologic imaging report and pathology, when available. ANOVA and Fisher's exact tests were used to determine associations.

**Results:**

Of the 520 eligible patients, 21 (4.0%) developed an incident liver lesion during the study (median follow-up since therapy completion: 4.1 years; range: 0.5-12.6). Of the 21 patients with incident liver lesions, 14 (66.7%) had FNH, 4 (19.0%) had recurrent disease, 2 (9.5%) had vascular lesions, and 1 (4.8%) had an area of focal fat. Compared with patients with other non-FNH liver lesions or without liver lesions, FNH was associated with female sex (FNH 71.4%, non-FNH 14.3%, no lesion 41.5%,  $p=0.02$ ), younger age at diagnosis (median age FNH 2.2 years, non-FNH 3.4 years, no lesion 5.9 years,  $p=0.05$ ), primary diagnosis of neuroblastoma (FNH 50.0%, non-FNH 0.0%, no lesion 13.4%,  $p=0.007$ ), receipt of melphalan (FNH 42.9%, non-FNH 0.0%, no lesion 10.2%,  $p=0.004$ ), and history of autologous stem cell transplant (FNH 57.1%, non-FNH 0.0%, no lesion 7.4%,  $p=0.003$ ). No patients who developed FNH had history of allogeneic stem cell transplant, hepatitis, sinusoidal obstruction syndrome, or right ventricular dysfunction. Three patients (21.4%) who developed FNH were treated with hormone replacement therapy compared to no patients with a non-FNH lesion and 6.8% of patients without a liver lesion ( $p=0.06$ ).

**Conclusion:**

Patients with neuroblastoma and those who undergo autologous stem cell transplant are at increased risk for FNH. We plan to perform a nested case-control study to further evaluate risk factors for FNH in this population. Additionally, we plan to further characterize the liver lesions to evaluate characteristics of FNH that may guide future surveillance recommendations.

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Poster # 809

**CANCER SURVIVORSHIP: INTEGRATION OF EHR AND CANCER REGISTRY DATA TO IMPROVE LONG-TERM FOLLOW-UP CARE**

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**Background:**

Marked improvements in pediatric oncology care and survival shifted the focus toward the reduction of acute and long-term toxicities for childhood cancer survivors (CCS). Clinical guidelines exist to offer a framework for disease surveillance of late effects from cancer treatment, yet lack of follow-up is a significant barrier to early detection. The advent of the electronic health record (EHR) sparks unique approaches to construct, maintain, and leverage



CCS cohorts for health care delivery and as a platform for survivorship research. Ascertainment of chemotherapy exposures aids in risk stratification, assessment of adherence to guideline recommendations, and identification of patients lost to follow-up.

**Objectives:**

The primary purpose of this study is to utilize a novel approach to identify all eligible patients for a CCS cohort through integration of EHR and cancer registry data. Data mining of treatment exposure data in the EHR facilitates stratification of patients into risk cohorts, understanding of predictors of late effects, and identification of patients lost to follow-up.

**Design/Method:**

Using pediatric oncology patient data over a one-year period provided common ICD9/10 codes of patients from which to construct the cohort starting from our institutional implementation of Epic. To assure inclusion of all eligible patients, we are currently integrating data from the pediatric state-mandated cancer registry. Explanatory variables included age, race/ethnicity, language preference, and cumulative anthracycline dose. Primary outcomes included date of last clinic visit and echocardiogram.

**Results:**

Between July 1, 2013 and November 30, 2019, there were 871 pediatric oncology patients evaluated at our institution with ongoing analysis to identify the specific CCS cohort. Of these patients, 29.6% (n=258) were considered lost to follow-up (>1000 days since last visit). Patients lost were an average of 4.5 years older compared to patients not lost (p<0.001); however, there was no significant difference in preferred language (p=0.056), race/ethnicity (p=0.77) or type of tumor (p=0.14). Two-hundred-and-forty-six patients had documented anthracycline exposure and 60 patients had a cumulative anthracycline dose of >250mg/m<sup>2</sup>, of whom 83% (n=53) were adherent to guidelines (echocardiogram within last 2 years).

**Conclusion:**

Integration of EHR and cancer registry data represents a feasible, timely, and novel approach to construct a CCS cohort and re-engage patients lost to follow-up. This can facilitate adherence to guidelines as evidenced by echocardiogram screening of patients with high cumulative anthracycline exposure. Future applications include analysis of exposures and complications during therapy on late effects outcomes.

Funding: NIH “Transfusion Medicine and Hematology” (5T32 HL007057-44) training grant effective 07/01/2019

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Poster # 810

**BARRIERS TO ADHERENCE IN CHILDHOOD CANCER SURVIVORS**

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**Background:**

Childhood Cancer Survivors (CCS) are at high risk for chronic illness and premature death due to late complications associated with cancer treatment. Adherence to screening recommendations is relatively poor in this high-risk population. Identifying specific barriers to adherence can lead to interventions to address them.

**Objectives:**

The aims of this study are to (i) Characterize barriers to adherence to general medical care and specific screening procedures among adult CCS in long-term follow-up care; (ii) Identify sociodemographic and medical correlates of barriers to adherence; and (iii) Examine whether barriers to adherence relate to quality of life domains.

**Design/Method:**

Adult CCS from the Survivors Facing Forward program, a lifelong follow-up program for CCS at Cohen Children's Medical Center, were anonymously surveyed using the Barriers to Care Questionnaire (BCQ) for general medical care and for specific screening tests, and the Quality of Life Scale–Cancer Survivor (QOL-CS). Demographic data was also collected. The survey was distributed through REDCap®.

**Results:**

150 CCS started the survey, and 84 completed all 4 sections (BCQ, Specific Recommendations Barrier Survey, QOL-CS and demographics). Of the 84 who completed the entire survey, the median age was 25y (IQR:21-31), median age at completion of therapy was 13y (IQR:8-16) and the median time off-therapy was 14y (IQR10-19). 64% were female, 70% white, 7% black, and 9.5% Asian/Pacific Islanders. 8% identified as Hispanic. The median BCQ total score was 88.5 (IQR:78.4-95.7), with the lowest scores (greatest barriers) reported in the Skills and Pragmatism subscales (88.4 and 84.7 respectively). These sections include questions on the ease of navigating the health care system (Skills – facility in navigating referrals, communication between patient and physician...) and practical barriers (Pragmatism – cost, insurance, transportation...). There was no correlation between the BCQ scores and any demographic variable ( $p's > .05$ ). There was a statistically significant correlation between the BCQ Total score and the QOL-CS Total score ( $r_s = 0.47$ ,  $p < 0.0001$ ), as well as between the BCQ Total score and all QOL-CS subscales, except the spiritual well-being subscale.

**Conclusion:**

Barriers to screening for CCS are mostly health system related, including costs, access to insurance and practical barriers such as transportation. The significant association between the BCS and QOL-CS suggests that lower quality-of-life among CCS is associated with a perception of greater barriers to care. Adherence to screening recommendations among CCS can be improved by refining access to and usability of the health care system, and by addressing and improving the quality-of-life for CCS.

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Poster # 811

# VITAMIN D DEFICIENCY AND SUPPLEMENTATION IN PEDIATRIC CANCER SURVIVORS

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## **Background:**

Background: Vitamin D plays an important role in bone health. Pediatric cancer survivors have treatment-related skeletal complications, which can be exacerbated by vitamin D deficiency. Data on prevalence of vitamin D deficiency (VDD) and vitamin D insufficiency (VDI) in pediatric cancer survivors are scarce, and there is limited research assessing the effects of supplementation in this population.

## **Objectives:**

To identify baseline VDD and VDI in pediatric cancer survivors and determine whether supplementation increases vitamin D levels.

## **Design/Method:**

Pediatric cancer survivors (>2 years from end-of-therapy) [n=188] at Rady Children's Hospital-San Diego between 2012-2015 were included in the retrospective sample. VDD and VDI were determined by serum concentration of 25-hydroxy vitamin D. VDD and VDI were defined as  $\leq 20$  ng/mL and 21-29 ng/mL, respectively. The percentage that vitamin D levels increased between baseline vs. follow-up was calculated across the groups (non-supplemented, 1 supplement cycle and 2+ supplement cycles) using general linear modeling (unadjusted and adjusted[a] for age, sex and ethnicity). Treatment cycles each lasted a minimum of 8 weeks. Stratified analyses included sex (male vs. female), age (<10 years vs.  $\geq 10$  years), ethnicity (non-Hispanic vs. Hispanic), cancer type (solid vs. hematological) and insurance type (private vs. public).

## **Results:**

55.9% of the patients were Hispanic, and the mean age was  $11.9 \pm 5.3$ . Of the participants, 23.4% were VDD, 39.4% were VDI and 37.2% were vitamin D sufficient. Vitamin D levels increased by  $38\% \pm 74\%$  after 1 cycle of vitamin D supplementation ( $p=0.04$ ,  $p_a=0.1$ ) and  $35\% \pm 57\%$  after 2+ cycles of vitamin D supplementation ( $p=0.06$ ,  $p_a=0.14$ ). Following 1 cycle of vitamin D supplementation, vitamin D levels increased in boys (percent change  $49\% \pm 89\%$ ,  $p=0.02$ ,  $p_a=0.04$ ). Following 2+ cycles of vitamin D supplementation, vitamin D levels increased in older children (percent change  $39\% \pm 48\%$ ,  $p=0.04$ ,  $p_a=0.09$ ). Hispanics did not have a significant percent change ( $39\% \pm 76\%$ ,  $p=0.47$ ,  $p_a=0.44$ ) after 1 cycle of vitamin D supplementation, whereas non-Hispanics had a positive percent change ( $36\% \pm 75\%$ ,  $p=0.05$ ,  $p_a=0.04$ ).

## **Conclusion:**

VDD and VDI were prevalent in 63% of pediatric cancer survivors, which suggests that screening is indicated in this population. Supplementation was effective at improving vitamin D

levels in these patients. Certain sub-groups had a significant response to supplementation, which included boys, non-Hispanics, and older children. Further research is indicated to evaluate the differential response to supplementation and impact on bone health in cancer survivors.

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Poster # 812

## **HEPATIC NODULES IN CHILDREN TREATED FOR MEDULLOBLASTOMA: A SINGLE-CENTER EXPERIENCE**

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### **Background:**

Benign nodular hepatic lesions, including Focal Nodular Hyperplasia [FNH], have been reported in children following treatment for solid malignant tumors. Pathogenesis likely relates to non-specific chemotherapy-related vascular injury. High-dose chemotherapy/hematopoietic stem cell rescue [HDC-SCR] increased FNH risk. Medulloblastoma [MB], treated with surgery, craniospinal irradiation [CSI] and multiagent chemotherapy, or radiation-sparing HDC-SCR if young, is the most common pediatric central nervous system malignancy. However, reports of cancer therapy-related FNH and other benign liver abnormalities are exceedingly rare in this population.

### **Objectives:**

To describe incidence and management of liver nodules diagnosed in children treated for MB at this institution.

### **Design/Method:**

Review of patient medical records, radiographic imaging, pathology, and published literature.

### **Results:**

Between January 2006-January 2019, 81 children <18 years of age completed MB treatment and were subsequently followed with serial MRI through death [n=31] and current survival [n=50]. One child developed progressive bone and liver MB during therapy. Three children developed post-treatment hepatic nodules, with radiographic features of FNH detected by serial magnetic resonance imaging [MRI]. Each remains alive with stable number and size of hepatic nodules, normal hepatic function, and without MB recurrence.

Case 1: 20-year-old male treated at age 9 for standard-risk MB with gross total resection (GTR), CSI, and chemotherapy [ACNS0331] developed presumed FNH nodules diagnosed by surveillance MRI at age 10, 19 months after therapy completion. Biopsy, performed for increased nodule number and size, showed native liver with bile ductular proliferation with cholangitis.

Case 2: 9-year old male treated at age 4 for standard-risk MB with GTR, CSI, and chemotherapy

[ACNS0331] developed presumed FNH nodules diagnosed by surveillance MRI at age 9, 42 months after therapy completion. Hepatology elected to follow with serial imaging.

Case 3: 5-year old female treated at age 17 months for CNS-disseminated high-risk MB with near-total resection and HDC-SCR, developed presumed FNH nodules diagnosed by surveillance MRI at age 4, 30 months after therapy completion. Biopsy, performed for increased nodule size, showed native liver with siderosis. However, there was concern for sampling error.

**Conclusion:**

This report enriches existing literature regarding development of benign hepatic nodules following cancer treatment, focusing on MB patients. With increasing radiation-sparing HDC-SCR and improved survival, prevalence of hepatic nodules diagnosed by surveillance imaging may increase. Given the typically benign and non-aggressive nature of post-treatment hepatic nodules, conservative co-management with hepatology is warranted, reserving biopsy for situations where lesion number and size increases or concerns for MB metastases exist.

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Poster # 813

**RETROSPECTIVE PATIENT-LEVEL STUDY OF EARLY DEATH FROM CHILDHOOD CANCER IN COLORADO**

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**Background:**

Despite improvements in childhood cancer outcomes, 7.5% of pediatric cancer deaths occur in the first month post diagnosis, and this group of patients generally do not survive long enough to benefit from treatment advances. The risk factors for early death (ED), or death within 30 days of diagnosis, are understudied. Previous population-based analyses have identified that ED disproportionately affects Black and Hispanic children and those living in poverty. The patient-level characteristics remain poorly understood.

**Objectives:**

Determine which potential ED risk factors are assessable and not assessable through medical chart review. Characterize the risk factors for ED at childrens hospital, and determine \*\* Colorado how many potential ED risk factors are assessable through medical chart review, and characterize the ED population at Children's Hospital Colorado (CHCO). \*\*\*

**Design/Method:**

This was a retrospective case-control study of 89 oncology patients diagnosed from 1995-2016 and treated at Children's Hospital Colorado. Early death was defined as death within 1 month of diagnosis (n=45), with controls surviving >31 days chosen randomly from the same cohort (n=44). We initially identified 57 patients, of which 12 were excluded. Exclusion criteria was as follows: having no electronic chart records outside of their name and DOB, having a history of another oncologic diagnosis, or having post-transplant lymphoproliferative disorder. Electronic

medical records for each patient were manually reviewed for sociodemographic, clinical, and diagnostic course information. Crude and adjusted odds ratios and corresponding 95% confidence intervals were estimated for the association between early death and potential risk factors.

**Results:**

Factors associated with early death in univariate analyses included younger age, non-white race, hispanic ethnicity, primary language other than English, public or no insurance status, urban residence, hematologic malignancy, and advanced tumor stage and grade. ED patients had a longer period from first symptoms to first care; Otherwise, diagnostic timing between the two groups was not significant different but trended towards longer period. In multivariable analysis, black race and hispanic ethnicity were no longer risk factors for ED. Early death was more likely among patients with hematologic malignancies but less likely for those with central nervous system malignancies.

**Conclusion:**

At our institution, children who are of minority race and ethnicity, live in rural areas, and whose primary language is not English are at an elevated risk of dying within the first 30 days of cancer.. Chart review alone is not adequate to assess barriers to care and further prospective work is required to understand this issue.

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Poster # 814

**RIGHT ON SCHEDULE: IMPROVING CLINIC APPOINTMENTS SCHEDULED PRIOR TO DISCHARGE FROM THE HOSPITAL**

**Mahvish Rahim, Jordyn Griffin, Kerry Hege, Emily Mueller, Kristine Kauffman, Stacey Corman, Kari Anderson, Kelly Elliot, Stayce Woodburn, Meghan Drayton-Jackson**

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**Background:**

Children with hematologic and oncologic conditions have high healthcare needs that often require both inpatient and outpatient management. There is potential for lapse in care when patients transition between these settings. Inpatient discharge without a follow-up appointment scheduled can result in delayed care, loss to follow up, or unplanned hospital readmissions.

**Objectives:**

The aim of this quality improvement project is to increase the rate of scheduled follow up appointments at the time of inpatient discharge for all pediatric Hematology-Oncology patients.

**Design/Method:**

A baseline of the current state was established through a chart review of discharges from January 2019 to April 2019. This determined the percentage of patients who had a scheduled follow-up appointment on their discharge instructions. A Multidisciplinary team collaborated and developed several Plan-Do-Study-Act (PDSA) cycles to standardize and improve the process of

1) scheduling follow up appointments for scheduled admission, 2) communication to schedulers, 3) discussion of discharge planning on inpatient rounds, 4) initiating discharge planning earlier during a hospitalization.

**Results:**

QI Macros was used for statistical analysis via statistical process control charts and indicated that several PDSA cycles of interventions had a statistically significant impact in increasing the percentage of patients with a follow up appointment scheduled at the time of inpatient discharge from a baseline of 65% to over 80%.

**Conclusion:**

Improving our rates of scheduled outpatient follow up at the time of discharge improves the likelihood of timely follow up care. Further, this aides in work flow for our scheduling administrators by reducing additional phone calls to parents after hospital discharge to arrange follow up. Future efforts include continuing to improving the process of how clinic appointments are requested by providers and assessing both provider and patient satisfaction.

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Poster # 815

**IMPROVING THE CRITICAL LABORATORY VALUE NOTIFICATION SYSTEM FOR HEMATOLOGY/ONCOLOGY INPATIENTS**

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**Background:**

Appropriate handling of laboratory test result values that are deemed ‘critical’ is a component of both Joint Commission accreditation standards and Clinical Laboratory Improvement Amendments (CLIA) regulations and impacts patient safety. Hematology/oncology inpatients are a population that can generate a large volume of such critical results, some of which require action in an urgent manner. However, contacting a responsible provider who is able to provide timely acknowledgement of the value can be complicated by multiple barriers, reducing the proportion of results that are handled optimally.

**Objectives:**

The goal of this quality improvement project was to improve the percentage of critical laboratory value notifications for hematology/oncology inpatients that were acknowledged by a licensed individual provider (LIP) in a timely fashion after being generated. Our smart aim was, by six months after project initiation, to have 75% of such notifications acknowledged by a LIP within 30 minutes of their generation.

**Design/Method:**

A multidisciplinary team was formed that analyzed the key drivers and potential interventions

for critical laboratory value notifications. It was determined that multiple drivers could be addressed simultaneously with the use of a single intervention: laboratory and call center personnel sent screenshots of critical values directly to the LIPs caring for hematology/oncology inpatients through a HIPAA-compliant phone messaging system, and the LIPs sent acknowledgement of receipt of the value through the same mechanism. Run charts were used to track the proportion of critical values for hematology/oncology inpatients acknowledged in a timely manner by a LIP, and the percentage of such values acknowledged in a timely fashion for inpatients that were not followed by hematology/oncology, and therefore not receiving this intervention, was tracked as a balancing metric.

**Results:**

The proportion of critical value notifications for hematology/oncology inpatients that were acknowledged by a LIP within 30 minutes of generation increased by approximately 70% (from 1-5% to 70-80%) in the month the new system was first utilized, and demonstrated a sustained response in following months, while the proportion for patients on other services did not show a substantial change, staying at approximately 50-60%.

**Conclusion:**

Use of a phone-based messaging system for both notification and provider acknowledgement significantly improved timely, closed-loop communication of critical laboratory values for hematology/oncology inpatients.

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Poster # 816

**ASSESSMENT OF AWARENESS AND ATTITUDE AMONG TRAINEES REGARDING ONCOFERTILITY**

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**Background:**

Oncofertility is an umbrella term that includes care from both cancer and fertility health-care providers. Education and oncofertility exposure for trainees in adult and pediatric oncology and radiation oncology is critical to the future treatment of oncology patients.

**Objectives:**

This study aimed to determine the current knowledge, practice and need for an established oncofertility curriculum during their training period

**Design/Method:**

This study involved distribution of an online survey via email communication to pediatric and adult oncology fellows and radiation oncology residents through their program directors and program coordinators in the United States obtained through ACGME website. All responses were compiled in a REDCap database. Data was described using medians and ranges for continuous variables; counts and percentages for categorical variables.



**Results:**

A total of 210 survey responses were received and analyzed. Out of those received, 92(44%) were from pediatric oncology, 68 (33%) were adult oncology, 47(22%) from radiation oncology and 2(1%) from joint adult/peds hematology oncology programs. With regard to knowledge about risk of fertility with chemotherapy and radiation, 135 (64%) identified the risk with alkylating agents as high and 155 (75%) with abdominal pelvic radiation. However the majority of respondents were unsure about dose of radiation for LD50 in ovaries (53%) and azoospermia (53%). Majority of respondents identified the right Fertility Preservation (FP) techniques for respective ages. Regarding oncofertility training, 135 (66%) of them had witnessed or carried out a FP conversation with patients, 102 (48%) felt that they were not comfortable with discussing FP options. A majority of the trainees 130 (61%) had access to a fertility center in their institute, however 98 (47%) they had to rely on outside consultations. 108 (53%) were unsure if there was funding for FP for their patients. With respect to barriers to fertility preservation, the biggest limiting factor was a patient being too ill 180 (89%).

**Conclusion:**

This study shows that majority of the trainees had some familiarity with FP, however there is a considerable minority that did not know risk of infertility with alkylating agents, radiation and age appropriate FP techniques. Access for patients to FP, funding continues to be an issue. This study is limited by a low response rate and the respondents may not represent the totality of trainees nevertheless trainees in pediatric and adult oncology and radiation oncology may benefit from standardized curriculum as half of them still continue to feel uncomfortable discussing this aspect of care with their patients.

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Poster # 817

**ASSESSING MORAL DISTRESS IN TRAINEES ON A PEDIATRIC HEMATOLOGY-ONCOLOGY ROTATION**

**Kendra Johnston, Suzanne Holm, Victor Aquino, Tanya Watt**

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**Background:**

Moral distress occurs when people believe they know the right thing to do but feel unable to pursue that course of action due to organizational and other constraints<sup>1</sup>. After several trainees verbally expressed feeling morally distressed during their inpatient hematology-oncology rotation, we developed this quality improvement project to assess contributors to and attempt to mitigate moral distress.

**Objectives:**

1. Identify themes causing moral distress.
2. Create a moral space to discuss moral distress.
3. Develop interventions to mitigate moral distress.

**Design/Method:**

At the end of their hematology-oncology rotation, trainees were given a validated survey measuring components of moral distress, defined by Ann Hamric, by multiplying the frequency of a distressing situation by the intensity of distress<sup>2</sup>. Each possible source yields a score of 0-16. A fellow, psychologist, and trainees met for one hour to discuss moral distress and items identified in their surveys as causing high distress. Trainees were encouraged to reflect on their experiences openly after assuring confidentiality. Changes to the process were implemented over time based on initial results, as determined by scores on the measure and themes identified in sessions with trainees.

**Results:**

A total of 26 residents have completed the survey. The most common, higher scoring themes were related to poor communication, documentation requirements, volume of patients, and lack of continuity. A hematology-oncology specific theme was the inability to discuss the prognosis with the patient/family. Themes identified in discussion included feeling inadequate due to lack of involvement with patients' significant events, such as new diagnosis discussions, and caring for actively dying children. Based on initial results, trainees were given a checklist at the start of the rotation to ensure participation in important discussions, and an additional survey was added assessing whether trainees found these sessions useful. Preliminary information indicates that the implemented checklist is helping residents feel emboldened to communicate more openly to obtain training experiences. Six trainees have completed the post-intervention survey and each endorsed usefulness of the meeting.

**Conclusion:**

We identified that many hematology-oncology residents experience components of moral distress, and that residents who have participated in sessions focused on discussing these experiences find having this time to reflect useful. Additionally, this process has informed targeted interventions to mitigate moral distress during this rotation. Future directions include assessing whether residents have more moral distress on this rotation as compared to other rotations during their training, and how to best address any differences found.

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Poster # 818

**BURNOUT IN PEDIATRIC ONCOLOGY PROVIDERS**

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**Background:**

Although cure rates have increased for many common childhood cancers, pediatric oncology providers will nonetheless witness parents outliving their child. Coping with progressive disease, relapse and the death of a child with cancer are emotional experiences that contribute to provider burnout. Provider burnout negatively impacts the quality, safety and the cost of health care. Burned out physicians have twice the odds of making a medical error. A paucity of data exists regarding the prevalence of burnout among pediatric oncology providers. Much of the data

comes from multidisciplinary studies with other specialists, or studies of pediatric oncology nurses.

**Objectives:**

Our objective was to measure burnout among a network of pediatric oncology providers. Working together with the American Society of Clinical Oncology Quality Training Program and the American Medical Association we evaluated provider burnout of pediatric oncology physicians and advance practice providers using the validated Mini-Z 2.0 Survey with the questions drawn mainly from the Physician Worklife Study, MEMO study, and Healthy Workplace study. The Mini Z was developed by Dr. Mark Linzer and team at Hennepin County Medical Center, Minneapolis, MN.

**Design/Method:**

We deployed an online survey (Mini-Z 2.0) between 7/30/19 to 9/5/19 to 47 pediatric oncology providers in the St. Jude Affiliate Program (SJ AP). The Mini-Z assesses system drivers related to burnout and includes single-item measures for satisfaction and burnout. The Mini-Z 2.0 scoring consists of an overall score (range: 10-50) and two subscales (ranges 5-25); higher scores indicate a more joyful workplace. We then compared to results to the proprietary AMA national benchmark study of 9523 physicians and advance practice providers.

**Results:**

The response rate was 44.6%. Physicians accounted for most respondents (71.4%). Overall the SJ AP scored higher on the Mini-Z than the national benchmark (31.8 vs 30.6) and scored closer to the Joy Target (score=40). Specifically, in the domain of supportive work environment SJ AP scored higher than the national benchmark (18.1 vs 17.3). Satisfaction levels among SJ AP providers (85.7%) exceeded the national benchmark (73.3%), and correspondingly the SJ AP providers had lower levels of burnout (42.9% vs 50.5%) compared with the national benchmark. The major stressor identified was the electronic medical record, which was described as frustrating and time consuming.

**Conclusion:**

We assumed burnout rates in our network of providers would be like the national benchmarks, however the SJ AP providers had less burnout and higher job satisfaction.

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Poster # 819

**FOPHO: IMPROVING FELLOW EDUCATION USING A LEARNER-CENTERED, LEARNER-DRIVEN APPROACH**

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**Background:**

Due to demanding clinical responsibilities and the time constraint of work hour limitations,

Pediatric Hematology-Oncology (PHO) fellows may find it challenging to learn the fundamentals of PHO through hands-on experience alone. PLAN: In a survey of 17 fellows from a large PHO fellowship program, all fellows felt they would benefit from initiation of a formalized, longitudinal educational curriculum. The most commonly identified topics for further teaching were diagnostic work-up (5/17) and management (7/17). Fellows identified liver tumors, germ cell tumors, cancer predisposition syndromes, and genomics as areas of greatest weakness with leukemia and anemia as areas of greatest strength. While most fellows were neutral as to whether or not they would pass boards, the majority felt they did not know what to study for boards.

Combining the principles of Knowles' adult learning theory, Kolb's experiential learning cycle, and constructivist learning theory, we created a learner-driven, learner-centered lecture series, Foundations of Pediatric Hematology-Oncology (FoPHO).

**Objectives:**

1) To significantly increase clinical knowledge in fundamental PHO topics 2) To increase attendance at a core teaching conference to >75% of the first-year fellows and >50% of upper level fellows.

**Design/Method:**

DO: After identifying gaps in education and barriers to attendance, we implemented bi-monthly lectures to provide practical clinical knowledge for independent practice. Sessions were scheduled to optimize fellow attendance and faculty excused fellows to attend. Fellows selected speakers based on observed teaching skills and clinical expertise. Topics were given priority based on relevance to clinical service. Faculty speakers were given a recommended format for the lecture and asked to provide a summary handout.

**Results:**

STUDY: In pre- and post-session surveys, all fellows reported an increase in subject knowledge with an average reported knowledge improvement of 78% per session. Attendance goals were met in 63% and 100% of the sessions among first-year and upper level fellows, respectively.

**Conclusion:**

A learner-driven and learner-centered curriculum is effective at increasing core clinical knowledge for fellows. According to Knowles, adult learners should be involved in the planning and execution of their education and information should be relevant and applicable. The steering committee for FoPHO is comprised of 5 upper level fellows. Per the Kolb learning cycle, these sessions provide abstract conceptualization (e.g., overview of disease, explanation of treatments) and foster reflective observation (e.g., case discussions). ACT: Offering these lectures throughout the year and to all years of fellows will allow learners to apply knowledge by building on past experiences (i.e., constructivism).

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Poster # 820

**BURNOUT IN FIRST YEAR PEDIATRIC HEME/ONC FELLOWS IS ASSOCIATED WITH SUBOPTIMAL PATIENT CARE**

**Michael Terao, Deena Levine, Purva Bulsara, Zhaohua Lu, Jennifer Kesselheim, Justin Baker**

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**Background:**

Burnout is a syndrome of emotional exhaustion, depersonalization, and low personal accomplishment. A previous study reported that 46% of first year pediatric hematology/oncology fellows have a high level of burnout, and burnout was associated with decreased patient centeredness (Moerdler, ASPHO Abstracts, 2019). We examined burnout and suboptimal patient care in first year pediatric hematology/oncology fellows.

**Objectives:**

To describe the prevalence of burnout and suboptimal patient care in first year pediatric hematology/oncology fellows.

**Design/Method:**

A cross-sectional online survey was sent to first year pediatric hematology/oncology fellows in July 2019. We defined burnout as scoring high in emotional exhaustion ( $> 26$ ), high in depersonalization ( $>9$ ), and/or low in personal accomplishment ( $<34$ ) on the Maslach Burnout Inventory using previously established cutoffs (Maslach Burnout Inventory Manual, 3rd Edition, 1996). Fellows self-reported suboptimal patient care practices/attitudes (Shanafelt, Ann. Intern. Med., 2002).

**Results:**

We sent 53 surveys and received 25 responses for a 47% response rate from fellows representing 19 institutions in 17 states. Burnout was found in 8 of 25 fellows (32%). Suboptimal patient care was reported several times a year or monthly by 12 of 25 fellows (48%). The two most common suboptimal patient care practices/attitudes reported several times a year or monthly were "I did not fully discuss treatment options or answer a patient's questions" or "I paid little attention to the social or personal impact of an illness on a patient" (reported by 11 of 25 fellows, 44%). A multivariable linear regression of emotional exhaustion, depersonalization, and personal accomplishment with stepwise selection showed that only depersonalization remained in the model, with increased depersonalization associated with increased suboptimal patient care practices/attitudes ( $p = 0.0002$ , adjusted  $R^2 = 0.45$ )

**Conclusion:**

After 1 month of fellowship, approximately one-third of fellows were burned out and approximately half reported suboptimal patient care. We believe this burnout represents recent exposure to pediatric residency rather than due to fellowship. We are concerned that trainees entering fellowship already burned out will be at higher risk for worsening burnout over time. We will measure burnout and suboptimal patient care practices/attitudes after several months of fellowship to determine how these metrics change in first year fellows who are already burned out. We found a significant association between depersonalization and suboptimal patient care practices/attitudes. Interventions to improve patient care and depersonalization should target

improving interpersonal communication with patients, and improving awareness of the social/personal impact of illness on the patient.

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Poster # 821

## **USING A REGIONAL PROJECT ECHO TO ENGAGE PEDIATRIC HEMATOLOGISTS/ONCOLOGISTS IN EDUCATION ABOUT SCD**

**Lisa Shook, Christina Farrell, Charles Quinn, Lori Crosby**

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### **Background:**

Approximately 15,000 individuals in the Midwest live with sickle cell disease (SCD). It is a lifelong, disorder with complications and comorbidities difficult to manage, especially for providers with self-reported limited knowledge and comfort in evidence-based management of SCD. Project ECHO is a telementoring model, designed initially to educate primary care providers (PCPs) about chronic illnesses, and create virtual communities of learners by bringing together healthcare providers using videoconferencing, didactic presentations and case-based learning.

### **Objectives:**

To engage pediatric hematologists/oncologists in provider education about SCD.

### **Design/Method:**

Sickle Treatment and Outcomes Research in the Midwest (STORM) is a HRSA-funded eight-state regional provider network that aims to increase provider knowledge about evidence-based management of SCD. Using the Project ECHO model, STORM TeleECHO was launched in March 2016 as an innovative, regional virtual approach to provider education in the Midwest.

### **Results:**

Since STORM TeleECHO's launch in 2016, 41 sessions have been held with over 73 unique registered attendees and 32% (n=23) self-identified as pediatric hematology providers. The majority are physicians (78%) with 26% treating 51-100 sickle cell patients in their practice. Other pediatric hematology attendees include physician assistants, nurse practitioners and registered nurses. Years of experience treating SCD ranges vastly (17% 5 years or less; 30% 6-10 years; 17% 11-15 years; 4% 16-20 years; and 30% 20+ years). Pediatric hematologists from 3 countries and 10 states have participated in a session; 24 didactic lectures and 29 case presentations have been presented by pediatric hematologists.

After attending at least one TeleECHO session, 100% of pediatric hematologists reported their overall experience was valuable and they would participate in the future, as well as recommend the program to colleagues. 92% reported learning best practice guidelines for SCD; and 92% reported feeling "very confident" identifying candidates for hydroxyurea. Furthermore, 83% reported feeling "very confident" prescribing hydroxyurea; and providing care for SCD patients. Pediatric hematologists have claimed 152 CME credits and 117 MOC (Part II) credits (since

2017) from the American Board of Pediatrics.

**Conclusion:**

STORM TeleECHO is an innovative strategy to virtually connect providers to educate about the evidence-based management of SCD. Pediatric hematologists have been instrumental as teaching faculty for STORM TeleECHO: presenting didactic lectures and case-based scenarios, and providing case recommendations. Moreover, pediatric hematologists reported increasing their own knowledge by participating in STORM TeleECHO. The wide range of years of experience and the number of SCD patients followed by pediatric hematologists has contributed to successful experiential learning and mentoring among participants of STORM TeleECHO.

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Poster # 822

**DEVELOPMENT AND TESTING OF AN ASYNCHRONOUS HEMOPHILIA LEARNING MODULE**

**Tiffany Lucas**

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**Background:**

Hemophilia is a chronic disease; and over the pediatric lifespan of a patient, there are different management and treatment decisions required based on various disease and patient-specific milestones. Educating trainees about this disease in the pediatric population requires many hours of patient contact so that exposure to those various milestones can be ensured. Alternatively, an interactive asynchronous online module could facilitate exposure to the most common milestones in a patient with severe hemophilia within a limited amount of time.

**Objectives:**

This pilot project aims to produce and test an online module with new content as to its educational efficacy.

**Design/Method:**

IRB approval was obtained in January 2018 and development of the module was conducted from summer 2018 thru winter 2019 in conjunction with University of California San Francisco's Office of Technology Enhanced Education using the Qualtrics platform. The module was developed based on World Hemophilia Foundation guidelines for diagnosis and treatment of hemophilia and updated to include basic information on use of emicizumab after U.S. Food and Drug Administration and European Medicines Agency approval. Data was collected via the Qualtrics platform on length of time required to complete the module, pre-test knowledge assessment, and embedded testing within the module as well as post-use comfort and confidence scales with qualitative comments.

**Results:**

The module was successfully developed and administered to 9 institutional fellows. It was also offered to young faculty and available to advance care practitioner and medical student trainees

rotating thru the division. Estimated length of use of the modules was 45 minutes, providing an exposure to a full pediatric hemophilia lifespan within this limited amount of time.

**Conclusion:**

This pilot project demonstrated the feasibility of development of a module on an online platform, and has been shown to be easy to use, time-limited, and increases the accuracy of medical management decisions. It can be used as a shared curricular element with various pediatric hematology/oncology programs and hemophilia treatment centers for training regarding the basics of diagnosis, treatment, and complications of pediatric hemophilia care.

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Poster # 823

**RELATIONSHIP-CENTERED COMMUNICATION TRAINING TO IMPROVE PATIENT EXPERIENCE AND PROVIDER BURNOUT**

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**Background:**

Effective communication is a crucial aspect of high-quality healthcare. While more than half of U.S. physicians have been reported to experience at least one symptom of burnout, studies have shown that providers with elevated emotional intelligence and communication skills have less burnout and higher patient satisfaction scores. Pediatric hematology/oncology (PHO) providers have challenging discussions with patients/families, but most receive little formal training in communication. One approach to communication skills training is relationship-centered communication (RCC), which focuses on empathy, reflective listening, and patient/family understanding.

**Objectives:**

We aimed to evaluate the impact of RCC skills training on patient experience and provider burnout for PHO providers (physicians and advanced practice providers) at a quaternary care pediatric hospital in collaboration with the Academy of Communication in Healthcare (ACH).

**Design/Method:**

Hospital-wide, 5.5 hour RCC skills courses taught by ACH-trained providers were held for over 1000 providers from all disciplines (46 PHO providers) from July 1, 2016 to July 1, 2019. Patient experience was measured using five provider questions from Press Ganey email surveys (PGS), and provider burnout was measured by the Maslach Burnout Inventory (MBI). Both surveys were collected pre- and post-course.

**Results:**

Of the 46 PHO providers who took the course, 15 had both pre- and post-course PGS. A total of 98 pre-course and 262 post-course PGS were collected for analysis. Mean scores from one PGS question regarding “care provider’s concern for questions/worries” showed significant



improvement (pre: 90.6±19.8 v post: 95±13.2, p=0.03). Mean scores for the other PGS questions also improved post-course but did not reach statistical significance. Fifteen MBI surveys were collected for analysis. No significant difference was seen between pre- and post-course mean scores for the three MBI subscales. However, mean scores for one MBI question regarding treating patients as “impersonal objects” demonstrated a significant reduction three months post-course (pre: 1.7±1.3 v post: 1.3±0.6, p=0.05).

**Conclusion:**

This study demonstrates improvement in specific aspects of both patient/family experience and provider burnout after RCC skills training. Our results suggest that learning RCC skills may improve patient experience and be a mechanism to reduce provider burnout. A large, multi-institutional study is needed for further validation.

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Poster # 824

**IMPROVEMENT IN PERCEPTIONS OF SAFETY CULTURE IN PEDIATRIC ONCOLOGY STAFF AFTER TEAMWORK TRAINING**

**Kathryn Laurie, Helen Leszczynska, Thomas Murphy, Mira Blecherman**

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**Background:**

Issues of patient safety in hospitals have been an increasingly recognized issue over the past two decades since the publication of the Institute of Medicine’s review in 1999, though designing effective measurements and means of improvement has been challenging. The majority of hospital deaths occur as a consequence of medical errors, which are in large part thought to be due to a failure of effective communication. The use of an evidence-based teamwork system has been shown to improve communication and thus could have a positive impact on patient safety. Pediatric oncology patients are particularly vulnerable to adverse events from medical errors, due to prolonged hospital stays, limited ability to communicate, decreased physiologic reserve, and use of toxic medications. There is a need to assess safety attitudes within the pediatric oncology community in order to determine where and how provider communication can be improved.

**Objectives:**

This study aimed to measure safety attitudes in the Pediatric Oncology staff before and serially after a multidisciplinary teamwork and communication training initiative with a goal to improve patient outcomes.

**Design/Method:**

This study was conducted in four phases, including intervention development, training intervention, sustainment interventions, and data collection and analysis. A commercially available teamwork and communication skills program (MedTeams; Dynamics Research Corporation) was used to train a select group of Pediatric Oncology staff members. This steering group then conducted mandatory training for Pediatric Oncology staff members. A modified

Agency for Healthcare Research and Quality Survey on Patient Safety Culture was administered to participants before training, then three months later with a plan to administer an additional twelve month post-training survey in March 2020.

**Results:**

In total, 154 (92%) of 168 Pediatric Oncology staff employed at our single institution participated in the training, including technicians, nurses, advance practice nurses, residents, and attending physicians. Three months post-training, 150 staff completed surveys. The percent of respondents who agreed with the statement: “In this unit we discuss ways to prevent errors from happening again” increased from 79% to 92% (p=0.19). The percent of respondents who disagreed with the statement: “Things fall between the cracks when transferring patients from one unit to another” increased from 40% to 49% (p=0.18).

**Conclusion:**

Compulsory training in teamwork skills has a positive impact on Pediatric Oncology staff perceptions of communication and the safety of patient hand-offs. Further study is needed to correlate staff safety attitudes with more objective measures of patient quality and safety.

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Poster # 825

**IMPLEMENTING A COMMUNITY BASED PEDIATRIC PALLIATIVE CARE EDUCATION MODEL WITH A NATIONAL CURRICULUM**

**Hatel Moonat, Loan Nguyen, Faith Kinnear-Crozier**

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**Background:**

Despite the growing need for palliative care services, formal standardized training of health care providers on this topic is lacking. The Education in Palliative and End-of-Life Care (EPEC) Project is a national, evidence based curriculum designed to increase provider knowledge in core palliative care topics utilizing a train-the-trainer (TTT) model to disseminate its content (EPEC®-Pediatrics is designed for pediatric providers).

**Objectives:**

1. Assess baseline learning needs of staff on pediatric palliative care (PPC) at two Texas Children’s Hospital community campuses.
2. Develop and implement a sustainable education training model using EPEC®-Pediatrics and its TTT philosophy to enhance primary PPC delivery at the community campuses.

**Design/Method:**

Baseline needs assessment- Formal anonymous electronic survey sent to providers, social workers, child life, chaplain, and pharmacy.

Knowledge improvement- Two to four providers (from each campus) who routinely provide direct PPC to patients were identified. These individuals completed the EPEC®-Pediatrics

curriculum (18 online self-study modules and in-person TTT session) to become an EPEC®-Pediatrics Trainer.

Knowledge dissemination and transfer- EPEC®-Pediatrics Trainers selected ten core PPC topics to teach end learners (hospital staff from various service lines) at the campuses over 18 months. We will use pre- and post-knowledge assessments and written surveys to measure the effectiveness of the training.

**Results:**

Baseline surveys performed at West campus in 2017 (71% response rate) and The Woodlands campus in 2018 (40% response rate) identified areas of improvement including: 1) information accessibility to help identify and utilize PPC experts to assist with end-of-life care; 2) understand differences between palliative and hospice care; 3) comfort with end-of-life discussions with patients and families; 4) proficiency to implement inpatient or outpatient "do not resuscitate;" and 5) effective symptom management for an actively dying patient, postmortem care, and debriefing support.

Five providers have enrolled in this pilot, representing oncology (N=2), pediatric hospital medicine (N=1), and pediatric and neonatal intensive care (N=2). All have completed the EPEC®-Pediatrics online modules; 4 out of 5 providers have completed the in-person TTT conference to become an EPEC®-Pediatrics Trainer. This study is currently in the implementation phase of knowledge dissemination/transfer at time of this submission.

**Conclusion:**

Needs assessments from two Texas Children’s Hospital community campuses highlight common barriers to delivering PPC in the community setting. Utilizing a national PPC curriculum with a TTT philosophy could allow for an effective approach to educating health care providers on this topic, particularly where resources are limited.

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Poster # 827

**A 30-DAY TWITTER PROFILE OF #SICKLECELL DURING TWO NEW DRUG APPROVALS AND A MAJOR CONFERENCE**

**Ahmar Zaidi, Alexander Glaros, Michael Callaghan**

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**Background:**

Use of social media to disseminate medical information continues to increase. With increased accessibility, it has become important for providers to maintain a presence on these platforms in order to ensure accessibility of accurate information. Understanding what types of messages move the needle in the social media environment is key to improving this form of communication. We hypothesized that with the FDA approval of two new medications for sickle cell disease in 2019, Oxbryta (voxelotor) and Adakveo (crizanlizumab), twitter mentions of these drugs would increase, and tweets would be seen predominantly in areas of the country with high

prevalence of sickle cell disease. We aimed to identify the patterns of Twitter use during this pivotal time in sickle cell disease and delineate the type of conversations occurring, where engagement was stemming from, and how the conversation was being influenced.

**Objectives:**

To identify Twitter trends associated with the release of two new sickle cell drugs and ASH 2019.

**Design/Method:**

We used Symplur to identify patterns in #SickleCell from November 14, 2019 to December 14, 2019. The approval of Adakveo was on November 15, 2019 and the approval of Oxbryta was on November 25, 2019. The Annual American Society of Hematology Meeting was from December 7-10, 2019. We analyzed tweet activity, locations, and sentiment of tweets through the Symplur interface.

**Results:**

There were 8,281 tweets and 22,824,699 impressions from 3,119 users. There were clear increases in tweets on the day of approval for Adakveo and Oxbryta, with a higher peak for Oxbryta. There was a spike in the number of tweets surrounding the ASH Annual Meeting. The Geolocation map shows that the most engagement came from users in the USA, Nigeria, Saudi Arabia, Canada, India, Tanzania, France and Kenya (in order). In the USA, activity was increased in states with a high prevalence of sickle cell. 20% of the users were physicians, 8% advocacy groups and 41% were people with sickle cell disease. Amongst the tweets from these groups, positive comments were 75%, 79%, and 61% from the physicians, advocacy groups, and people with sickle cell respectively.

**Conclusion:**

People with sickle cell disease and physicians engage frequently through twitter. Around drug launches and congresses engagement increases suggesting Twitter is an important source for new information in sickle cell disease. Symplur can be used to gauge the reaction of different stakeholder group to news events in sickle cell disease.

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Poster # 828

**IMPROVING DISCHARGE EDUCATION FOR PATIENTS AND CAREGIVERS THROUGH THE USE OF A MULTI-TEAM MODEL**

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**Background:**

For safe discharge planning, consensus recommendations from a Children's Oncology Group expert panel support a patient/family centered approach, in conjunction with a team-based support network. Multiple studies have examined patient and provider satisfaction, varying methods to relay the wealth of information from provider to patient, and parental insight into

ways to reduce errors. However, there is no data that specifically address parental comprehension of critical discharge instructions.

**Objectives:**

We hypothesized that a multidisciplinary team-based discharge process would improve parental comprehension and retention of critical instructions for newly diagnosed children with cancer. Our research aimed to include pediatricians, pediatric oncologists, nurses, pharmacists, and social workers, in conjunction with take home material, to provide consistent anticipatory guidance to also ensure parental comfort and satisfaction with the process.

**Design/Method:**

This was a year-long quality improvement initiative consisting of four plan-do-study-act cycles at an academic tertiary care children’s hospital with a designated pediatric hematology/oncology floor. Our interventions included the following multidisciplinary components: residents providing comprehensive education, nursing reviewing thermometer/fever guidelines and line care, social work providing on-call information, pharmacy reviewing medications, and the attending confirming parental comprehension. English and Spanish written instructions were created to aid in discharge teaching. A checklist, designated order set, and nursing-specific education tab in the electronic medical record served as reminders for discharge teaching. We developed an eleven-question parental survey to gauge comprehension of key discharge instructions, collected at the first post-hospitalization clinic visit.

**Results:**

In our pre-intervention data set (n=7), all families had a deficiency of knowledge in at least one key area. After initiating the intervention (n=26), correct identification of 1) temperature criteria increased from 57% to 78%, 2) return precautions increased from 36% to 79%, 3) 24/7 on-call number increased from 43% to 100%, 4) Bactrim prophylaxis increased from 38% to 96%, and 5) first-line anti-emetic recall increased from 71% to 92% and second-line recall increased from 14% to 85%. Our overall retention rate of key discharge teaching has improved from 50% to 90%.

**Conclusion:**

Initiation of our comprehensive cancer-specific program to ensure consistency of provider-delivered education and improve parental knowledge of home-care instructions at first hospital discharge has been highly successful. The project will continue for a sustainability period and we expect that all components will be embraced as standard of care within our institution. We believe that this model is generalizable to and can be easily adopted by the broad pediatric oncology community.

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Poster # 829

**A FAMILY-CENTERED TEACH-BACK PROGRAM TO REDUCE THE EXTERNAL  
CENTRAL LINE AMBULATORY CLABSI RATE**

**Chris Wong, Marie Desrochers, Margaret Brill-Conway, Riley Mahan, Kelly Eng, Amy  
Billett**

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**Background:**

Central line associated blood stream infections (CLABSI) occur frequently in the pediatric oncology (PO) population increasing morbidity, mortality, and costs. Families in the home provide much external central line (CL) care but often have limited opportunities to develop best practice line care skills, key to infection prevention.

**Objectives:**

To achieve a 25% decrease in the external Ambulatory CLABSI Rate after implementing a family-centered teach-back (TB) program.

**Design/Method:**

A family-centered return-demonstration TB program of CL skills was implemented including multiple initial hands-on learning sessions in the clinic or hospital, followed by on-going sessions in the clinic. TBs were performed with an expert nurse coach during routine visits and incorporated co-developed CL care cognitive aids. Plan, do, study, act cycles were used to test changes starting April 2016 after identifying key drivers through a pilot. Key changes: culture change-new expectation of TB participation until independent; embedding TBs into routine care with a dedicated nurse champion; checklist development to standardize content, approach, performance, and proficiency evaluation and consistent documentation in the health record. Statistical process control charts (SPC) tracked changes over time.

**Results:**

More than 90% of patients had at least one family member or self, participate in the program and reached independence with flushing the CL. Since January 2015, the external CL ambulatory CLABSI rate had consistently remained unchanged, calculated at 1.06/1000 CL days. As of February 2019, the monthly rate was below the SPC center line for seven consecutive months, meeting criteria to recalculate the center line, with a decrease in the rate to 0.6/1000 CL days (44% rate decrease).

**Conclusion:**

Ensuring families' independence with external CL care in the home is a safety priority which can be achieved through a teach-back program embedded into routine care and can lead to a decrease in the ambulatory CLABSI rate.

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Poster # 830

**EPIDEMIOLOGY OF RESPIRATORY VIRUSES: A COMPARATIVE STUDY BETWEEN CHILDREN WITH AND WITHOUT CANCER**

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**Background:**

Respiratory viral infections (RVIs) affect children year-round, with seasonal-specific patterns. Pediatric oncology patients are uniquely vulnerable to infection due to chronic immunosuppression, but it is not known whether they are predisposed to different seasonal patterns of RVIs than healthy children. There is also limited data on the impact of RVIs on cancer patients and their treatment.

**Objectives:**

Compare seasonal distribution of RVIs affecting pediatric cancer patients to non-cancer patients. Describe the clinical impact of RVIs on pediatric cancer patients.

**Design/Method:**

Retrospective study utilizing institutional databases of children ages 1-18 with cancer presenting to clinic and emergency department (ED) and those without cancer presenting to ED with respiratory symptoms and a positive nasal viral polymerase chain reaction (PCR) at NYU Winthrop Hospital from 2014-2019. One in ten non-cancer patients were randomly selected from the database. Fisher's exact test and Wilcoxon rank-sum test were used as deemed appropriate for bivariate comparisons. Multiple logistic regression models were developed for age-adjusted analyses of the outcomes.

**Results:**

Seventy pediatric cancer patients (211 RVI episodes) and 220 pediatric non-cancer patients (235 RVI episodes) were included in the study. Eighty percent of oncology patients had hematologic malignancies. Human rhino/enterovirus was the most common infection in both groups in the spring, summer, and fall. In the winter, on unadjusted variables, Coronavirus was more commonly detected in cancer patients than non-cancer patients ( $p=0.015$ ). Conversely, Respiratory Syncytial Virus (RSV) was more commonly detected in non-cancer patients than cancer patients ( $p=0.023$ ). On multivariable analysis, when adjusted for age, cancer patients had three times greater odds of having Coronavirus compared to non-cancer patients with odds ratio (95% Confidence Interval) of 3.03(1.2-7.7),  $p=0.019$ , but the difference in RSV did not persist (OR= 0.53(0.26-1.09),  $p=0.083$ ).

In the pediatric cancer population, intravenous antibiotics were administered in 46% of RVIs. Neutropenia was present in 32.7% of RVIs and chemotherapy was held for count suppression in 19% for an average of 6.9 days. Hospitalization rate was 17.5% with 13.5% of admissions requiring intensive care. Average length of stay was 4.6 days. IVIG was administered in 5.7% of episodes.

**Conclusion:**

We compared the epidemiology of RVIs in pediatric cancer patients to the general pediatric population by season. We found no difference in incidence of RVIs except for significantly greater detection of Coronavirus in cancer patients in the winter. Furthermore, RVIs cause significant morbidity and disruption of treatment in children with cancer.

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## USE OF AN AFFINITY-ENHANCED CD22-DIRECTED CAR TO TARGET ANTIGEN-LOW ALL SUBMISSION

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### **Background:**

Immunotherapy has emerged as an effective treatment modality for patients with relapsed and/or refractory ALL. While CD19-directed therapies have demonstrated impressive response rates, a substantial number of patients will relapse after these therapies, many of which are due to loss of the CD19 antigen. CD22-directed CAR T cells have demonstrated the ability to induce remissions in patients who have relapsed after CD19-directed therapy, however, the durability of such remissions is short due to a high rate of relapse with leukemia expressing levels of CD22 that are below the threshold required for CAR T cell activation. Thus, changes to the structure of the CAR which allow for the targeting of CD22-low leukemias may improve the overall efficacy of this treatment by decreasing antigen-low relapses.

### **Methods:**

In these studies, we investigated the impact of CD22 density on CAR T cell activation using leukemia cells expressing variable amounts of CD22. We interrogated the impact of antigen-density on CD22-directed CAR T cells expressing either the standard-affinity CAR or a novel high-affinity CAR on in vitro activation, signal transduction and in vivo efficacy in a xenogeneic mouse model.

### **Results:**

In both the standard- and high-affinity CD22 CAR, we noted a significant decrease in the expression of activation markers, cytotoxic degranulation and cytokine production in response to CD22-low leukemia cells. For each of these measures of T cell activation, we observed a dose-dependent increase in response to increasing levels of CD22 antigen. These findings correlated to diminished T cell signaling in response to CD22-low target cells, particularly through the ERK pathway. Furthermore, while all CD22-directed CAR T cells demonstrated in vivo efficacy against leukemia expressing wild-type levels of CD22, the high-affinity CD22 CAR demonstrated superior protection in mice inoculated with CD22-low leukemia. Interestingly, despite the differences in vivo, the high-affinity CD22 CAR T cells did not show improved in vitro T cell activation when compared to the standard-affinity CARs, however the high-affinity CARs did demonstrate enhanced signaling through the ERK pathway in response to both wild-type and low levels of CD22.

### **Conclusions:**

These results demonstrate the importance of antigen density on the efficacy of CD22-directed CAR T cell therapy and demonstrate the potential benefit of enhancing the affinity of the CAR to overcome antigen-low relapses after CD22 CAR T cell therapy.

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## TIMING OF INDUCTION TREATMENT FOR REACTIVATION OF CYTOMEGALOVIRUS IMPACTS OVERALL SURVIVAL IN PEDIATRIC ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT

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### **Background:**

Despite significant advances in treatment and prophylaxis, reactivation of cytomegalovirus (CMV) remains a major complication following allogeneic hematopoietic cell transplant (allo-HCT). Methods to decrease risk of CMV reactivation and long-term sequelae of CMV disease include controlling for risk factors and administering appropriate antiviral treatments. Although they have been shown to be effective, these treatments carry considerable adverse effects that may limit their early or extended use.

Objective: To assess optimal timing to initiate induction treatment in the pediatric allo-HCT population

### **Methods:**

We performed a retrospective analysis of pediatric patients who received conventional or ex-vivo T-cell depleted (TCD) allo-HCT from January 2010 – June 2018 at Memorial Sloan Kettering Cancer Center. CMV reactivation was defined as  $\geq 1$  CMV PCR  $>500$  copies in whole blood or  $>137$  copies in plasma within 180 days post-transplant. Induction treatment was typically initiated for CMV PCR  $\geq 1000$  copies in whole blood,  $\geq 300$  in plasma, or rising viremia from baseline. Hospital databases and medical records were utilized to identify patients and collect data. Time-dependent Cox and multi-state models of competing risks were performed. This study was approved by Institutional Review Board.

**Results:** Our study consisted of 227 patients (54 days - 27 years old) who underwent allo-HCT for malignant (N=143) and non-malignant (N=84) diseases. TCD represented 76% of all allografts. CMV donor (D) and recipient (R) serostatus were: D+/R+ N=90, D+/R- N=29, D-/R+ N=38, D-/R- N=70. Cumulative incidence of CMV reactivation was 24.8% within 180 days post-allo-HCT and 15 patients (27%) developed CMV disease. Median time to CMV reactivation was 24 days (IQR 14-33). Of the 56 patients who reactivated, 41 (73%) patients received induction treatment. Six patients were excluded from this analysis due to previous CMV viremia and induction treatment prior to allo-HCT. Median time from CMV reactivation to induction treatment was 6 days (IQR 1-15). CMV serostatus of D+/R+ was predictor for reactivation when compared to D-/R+ (HR=2.1, [95% CI 1.1 - 4, P<0.001]). Overall survival (OS) varied significantly based on timing of induction in both conventional and TCD transplants (p=0.04). There was no association found with timing of induction treatment and risk of developing CMV disease.

### **Conclusions:**

A short interval between CMV reactivation and initiation of induction treatment was significantly associated with improved OS in pediatric allo-HCT. Further evaluation into effect of CMV prophylaxis and timing of induction treatment on additional CMV outcomes will optimize treatment options and improve clinical outcomes.

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## **RISK FACTORS AFFECTING HOSPITAL READMISSION WITHIN THE FIRST 100 DAYS FOLLOWING HOSPITAL DISCHARGE AFTER HEMATOPOIETIC CELL TRANSPLANTATION (HCT) IN THE PEDIATRIC POPULATION.**

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### **Background:**

Pediatric patients undergoing allogeneic hematopoietic cell transplantation (alloHCT) remain at high risk for complications months after transplantation. Many are readmitted for management of complications, but data is limited on factors that affect readmission post-HCT.

### **Objective:**

To identify factors that increase risk of readmission.

### **Design/Method:**

Patients who survived initial alloHCT hospitalization were analyzed for the primary endpoint readmission within 100 days post-discharge. Variables were compared between patients who were readmitted and those not readmitted after discharge. Univariable analysis identified factors associated with increased risk of readmission and were confirmed with multivariable analysis.

### **Results:**

171 patients underwent initial alloHCT from 2008-2018, at a median age of 9.1 years (range 3mo-20y). 134 patients were readmitted within 100 days following alloHCT discharge. The most common indications for readmission were fever (49%) or infection without fever (22%). The only variable found to increase odds of readmission was having a Broviac central line at discharge (OR 4.76, 95% CI 1.79-14.3,  $p=0.002$ ) compared to port-a-cath, PICC, or no central line. Age, conditioning intensity, graft versus host disease (GVHD) prophylaxis, graft and donor source, performance status, veno-occlusive disease, acute GVHD, and disease indication were not associated with increased odds of readmission. The demographics of patients readmitted early (0-30d) differed from patients readmitted late (31-100d) after discharge. Of 84 children readmitted early, more received peripheral blood stem cell grafts (40%), myeloablative conditioning (71%), had ALL (20%), and had a documented infection during transplant hospitalization (64%), particularly bacterial. Of those not readmitted early, 50 were readmitted late and more received bone marrow grafts (76%), had AML (20%), and had a Broviac at discharge (96%).

### **Conclusion:**

We highlight that a majority of children are readmitted following alloHCT hospitalization, most commonly for fever or infection. A significant risk factor for readmission was the presence of a

Broviac at discharge. This is a potentially modifiable risk factor and suggests that alternative central lines, such as a port-a-cath, may decrease readmission rates. This data can further prospective studies to reduce readmission rates.

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## **RISK FACTORS ASSOCIATED WITH LENGTH OF STAY AND COST OF PEDIATRIC AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (AUTOHCT)**

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### **Background:**

Risk factors associated with length of inpatient stay (LOS) and cost in adults undergoing AutoHCT have been studied extensively. Unfortunately, there is a paucity of studies designed to identify causes of increased LOS and cost in children undergoing AutoHCT.

Objective: This study seeks to identify modifiable factors that can decrease LOS and/or cost, which could potentially result in decreased healthcare utilization and improvements in patient care.

### **Design/Method:**

We examined 100 consecutive AutoHCTs performed for malignant disease (2007-2019). In order to assess risk factors associated with LOS/cost, we evaluated demographic, socio-economic, and pre- and post-transplant variables. AutoHCT cost (n=87) for inpatient hospitalization was provided by Pediatric Health Information System database.

### **Results:**

Median Age: 4.39 years (0.7178-22.0466, IQR:2.78;11.21), 61% male, 53% Non-Hispanic, 69% White, and 39% with normal nutritional status. History of preceding *C. difficile* was found in 18% of patients. Median CD34 cell dose infused was 6.14x10<sup>6</sup>/kg. Median time to neutrophil and platelet engraftment was 11 and 20 days, respectively. The Incidence of grade 3-4 mucositis, post-transplant bacteremia, and post-transplant *C. difficile* was 55%, 19%, and 25%, respectively. 29% of patients had fever >5 days. Median LOS was 27 days (23-33). Median total cost for in-patient stay per transplant up to Day+ 100 was \$241,378.06 (\$103,510-\$2,425,884, IQR:\$159,750;259,406).

On multivariate logistic regression analysis, increased LOS was associated with younger age (OR=0.8077, 95%CI:0.674-0.969, p=0.0211) and fever >5 days (OR=7.138, 95%CI:1.809-28.164, p=0.005). Grade 3-4 mucositis trended towards longer LOS; however, this was not statistically significant (OR=4.073, 95%CI:0.926-17.921, p=0.0632). Non-Hispanic ethnicity (OR=0.146, 95%CI:0.0344-0.616, p=0.002) and absence of post-transplant *C. difficile* (OR=0.120, 95%CI:0.0171-0.849, p=0.0337) were associated with shorter LOS. Hispanic vs. Non-Hispanic patients median LOS was 30 days (17-191) vs 26 days (15-49), and LOS with and without *C. difficile* infection was 30 days (20-81) vs. 26 days (15-191), respectively.

On multivariate analysis, decreased cost of the first 100 days post-transplant was associated with transplant performed after 2014 (P=0.0043) and lack of post-transplant bacteremia (p=0.0452). Increased cost was associated with fever > 5 days (p= 0.0452).

**Conclusion:** Surprisingly, median CD34 cell dose, neutrophil/platelet engraftments were not associated with LOS. Hispanic and younger patients had an increased LOS, which will be further investigated. Post-transplant C. difficile infection resulted in increased LOS, potentially indicating a need for better treatment strategies and more prompt prophylaxis in at risk patients. It is encouraging that AutoHCT cost in recent era has decreased, which could be related to improved supportive care.

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## OPTIMIZING VANCOMYCIN DOSING IN THE PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT POPULATION

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### **Background:**

Vancomycin is commonly used for the empiric and targeted treatment of gram positive infections in patients receiving hematopoietic stem cell transplant (HSCT) and immune effector therapy. Achieving a timely therapeutic level, to adequately treat infections while avoiding sub therapeutic levels as well as toxicity, is critical. This remains a challenge in pediatrics as there is limited data regarding optimal dosing and also due to smaller volume of distribution, shorter half-life and differences in renal clearance based on age. Despite these known differences, patients are frequently started on a standard dose of 15mgs/kg regardless of age so delaying the therapeutic benefit of Vancomycin.

Objective: To achieve a therapeutic Vancomycin trough level within 48 hours of administration of the first dose.

### **Methods:**

Using the Plan Do Study Act (PDSA) cycle, patients receiving hematopoietic cellular therapy and immune effector therapy receiving Vancomycin were retrospectively reviewed over a 12 month period. The time taken to achieve a therapeutic Vancomycin trough defined as 10-20mcg/mL was recorded along with their age, renal function, comorbidities, concurrent use of nephrotoxic medications and previous Vancomycin doses if applicable. Based on the results, a standardized order set was created with the recommendations for initial Vancomycin dose per kg for age as follows: 80mgs/kg/day for patients < 6 years, 60mgs/kg/day for those aged 6-11 years and 45mgs/kg/day for patients ≥ 12 years. To measure the impact of this intervention, it was compared to the time taken to achieve a therapeutic Vancomycin dose for patients for whom this intervention was not yet implemented and therefore not utilized.

### **Results:**

58 patients were reviewed over a 12 month period. 19 patients received Vancomycin based on the above recommendations and the average number of doses to achieve a therapeutic level was

5 and the average number of days was 1.13. In the nonintervention group, 28 patients (71.7%) achieved a therapeutic level after an average of 7.6 doses and 2.18 days. 11 patients (28.2%) failed to achieve a therapeutic level prior to drug discontinuation. No supratherapeutic level was obtained in either group.

**Conclusion:**

Gram positive bacterial infection remains a major cause of morbidity post HSCT. Optimization of Vancomycin dosing is crucial to attaining the desired Vancomycin trough and dosing should be tailored according to age, renal function and other comorbidities. Providing appropriate dosing recommendations through standardized orders can be an effective strategy in optimizing Vancomycin dosing and achieving a therapeutic level within 48 hours of initiation.

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**RETROSPECTIVE REVIEW OF UNIVERSAL NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY IN ARIZONA SINCE 2018**

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**Background:**

Severe combined immunodeficiency (SCID) is a primary T lymphocyte deficiency disorder with variable degrees of B lymphocyte and natural killer cell deficiencies which leads to increased risk of life threatening bacterial, viral and fungal infections. Early diagnosis and treatment with definitive therapies including allogeneic hematopoietic cell transplant, gene therapy or enzyme replacement provide cures for this patient population.

Newborn screening (NBS) for SCID started in Wisconsin in 2008 and was adopted in all 50 states, including the District of Columbia, over the next 10 years with Arizona approving statewide screening in 2017. Prior to NBS, the true incidence of SCID in the U.S. was unknown(1), but now the presumed incidence is approximately 1 in 58,000 live births(2), with higher frequencies seen in Hispanic (1 in 37,000)(3) and Abathascan native (1 in 3,500 live births)(4) populations. Additionally, SCID NBS aids to diagnose T cell lymphopenia related disorders (TCLRD) seen in 1 in 14,000 live births.(5)

Arizona's population is unique as there are higher percentages of American Indian/Alaskan Native (5.3%) and Hispanic/Latino (31.6%) populations compared to the general population of the U.S. (1.3% and 18.3%, respectively)(6). With nationwide screening for SCID, individual states can evaluate data to help determine the overall incidence of SCID and TCLRD in the U.S.

**Objective:**

Identify the incidence of SCID and TCLRD in Arizona. In addition, describe the underlying genetic etiologies of SCID patients in Arizona and their definitive treatment choice.

Design/Method: Using the Arizona State Department of Health Services Newborn Screening Department's raw data and Phoenix Children's Hospital electronic medical record, we performed a retrospective chart review of positive newborn screens in the state of Arizona from January 1, 2018 through December 31, 2019.

**Results:** In the first 2 years of NBS for SCID in Arizona, there were 159,726 live births in Arizona, 34 positive NBS, and 7 confirmed diagnoses of SCID. We are finalizing the data on the incidence rates for SCID and TCLRD in Arizona, the false positive NBS rate and concluding the data collection of the genetic etiology of the seven SCID patients and their clinical courses.

**Conclusion:** Arizona has a unique population compared to the general U.S. and, to date, our incidence of SCID is approximately 1 in 23,000 live births which is higher than the presumed national incidence.

References:

- (1) Puck, Acad Sci, 2011.
- (2) Van der Bur, Front Pediatr, 2019.
- (3) Kwan, J Allergy Clin Immunol, 2013.
- (4) Kwan, JAMA, 2014.
- (5) Ding, J Pediatr, 2016.
- (6) United States Census Bureau, 2020.

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## **OUTCOMES AFTER ALLOGENEIC TRANSPLANT IN PATIENTS WITH HEMOPHAGOCYtic LYMPHOHISTIOCYTOSIS**

**Erin Goode, Holly Miller, Dana Salzberg, Courtney Campbell, Kristen Beebe, Jennifer Stahlecker, Roberta H Adams, Alexander Ngwube**

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### **Background:**

Hemophagocytic lymphohistiocytosis (HLH) is a severe systemic inflammatory syndrome characterized by excessive inflammation, which can be fatal if unsuccessfully controlled. Using myeloablative conditioning, hematopoietic stem cell transplant (HSCT) is curative. Myeloablative therapy is associated with high early mortality in this patient population. Recent reports indicate that reduced intensity conditioning regimens are associated with decreased early mortality but frequently associated with loss of graft/loss of chimerism post-transplant necessitating DLI or second HSCT. This supports the need to identify new conditioning strategies that would be more successful with fewer side effects. Gungor et al reported that a busulfan based reduced intensity-conditioning regimen was safe and efficacious in patients with chronic granulomatous disease<sup>1</sup>. This conditioning strategy was adopted in HLH transplants at Phoenix Children's Hospital.

### **Objective:**

The goal of this study is to report our experience using reduced intensity conditioning (RIC) regimens; initially alemtuzumab/fludarabine/melphalan based and then, recently, busulfan/fludarabine based regimen.

**Design/Method:** Retrospective chart review of patients with HLH that underwent HSCT from 2009 to present at Phoenix Children's Hospital. Demographic data, chimerism, survival outcomes, and adverse events were assessed during that time.

**Results:** Thirteen patients received HSCT for HLH from 2009 to 2019 at Phoenix Children's Hospital. From 2009 to 2016, patients received alemtuzumab, fludarabine, melphalan +/- thiotepa conditioning regimen (Cohort 1). Graft loss and variable chimerism data, as well as increased adverse events, were noticed with this regimen. In 2006, because of the high incidence of mixed chimerism, conditioning regimens were switched to busulfan, fludarabine, alemtuzumab and thiotepa (Cohort 2). These patients have showed improved outcomes, although with variable chimerism data. Data collection and analysis is still ongoing.

**Conclusion:** Reduced intensive conditioning regimens are safe, but mixed chimerism continues to remain a concern. These results demonstrate a need for future approaches that maintain low early mortality with improved sustained engraftment.

Reference:

1. Gungor, The Lancet, 2014

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## **SEVERE COLD AGGLUTININ AUTO-IMMUNE HEMOLYTIC ANEMIA POST UMBILICAL CORD BLOOD TRANSPLANT FOR B-THALASSEMIA**

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### **Background:**

Autoimmune hemolytic anemia following hematopoietic stem cell transplantation (HSCT) occurs in estimated 3 -6% of post-HSCT patients. Cold agglutinin autoimmune hemolytic anemia (cAIHA) is a fraction of that small percentage. This rare complication presents with severe anemia. Treatment of post-transplant cAIHA is challenging and there is no established therapy. Disease manifestations are severe and often refractory to treatment.

### **Objective:**

To review the clinical course of a pediatric patient with beta thalassemia major status post UCB transplant who presented with severe cAIHA.

### **Design/Method:**

We reviewed the medical records to characterize the presentation, time course and response to therapy for this patient.

### **Results:**

Our patient is a 2-year-old male with transfusion dependent beta thalassemia major. He underwent 6/6 UCB transplant following preparative regimen with campath, fludarabine, melphalan and thiotepa. He received cellcept and cyclosporine for GVHD prophylaxis. His HSCT course was complicated by hyperacute GVHD on D+8 requiring topical and systemic steroid therapy, and C. difficile infection. He engrafted D+24, was discharged from the hospital D+36, and returned home D+97. He presented to his local hospital D+139 with fever and anemia. Laboratory evaluation showed hemoglobin (hgb) 4.7g/dl. His AIHA was direct coombs

positive for complement CD3, but negative for IgG, consistent with cAIHA. Infectious work-up positive for Parainfluenza and C. Difficile, but negative for Mycoplasma. Course was complicated by hepatitis, acute kidney injury and hypertension. Therapy was started with high dose solumedrol and IVIG. He received numerous blood transfusions. He failed to respond to initial therapy, and weekly rituximab was initiated. Clinical improvement (transfusion independence) was achieved following the second dose. He received 4 doses and had a rising hgb level. At time of discharge, patient continued to have a positive direct coombs with hemolysis requiring oral lasix for elevated potassium. He remained hospitalized for 21 days and remained local for 15 days past discharge.

**Conclusion:**

cAIHA is a rare, life-threatening complication for patients undergoing HSCT. Our patient had multiple known risk factors for this complication including campath and non-malignant indication for HSCT. Although he did not respond to high dose steroid therapy, the treatment did slow the hemolytic process. He has had resolution of this episode, however limited case reports suggest repeated episodes may occur. Should he develop a subsequent episode we would consider daratumamab or complement inhibitors.

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**DNMT3A MUTATIONS IN PEDIATRIC ACUTE MYELOID LEUKEMIA MAY BE ASSOCIATED WITH ADVERSE OUTCOME AND POTENTIALLY IMPACT RISK STRATIFICATION**

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**Background:**

Acute myeloid leukemia (AML) accounts for 20% of pediatric acute leukemias. Its 5 year survival ranges widely from 22-90% based on subtype and cytogenetics. The DNA methyltransferase 3A (DNMT3A) mutations, most frequently at arginine 882 (DNMT3A<sub>mut</sub>) is observed in 14-34% of adult AML patients and is associated with inferior outcomes and anthracycline resistance. This mutation has been reported in 0-1.4% of pediatric AML patients, however its prognostic implications remain unclear. Here we present 2 pediatric AML patients with DNMT3A mutations, who were initially treated as intermediate risk AML but later associated with inferior outcome.

**Objective:**

Describe the outcome of pediatric AML patients with DNMT3A mutations. Methods: We retrospectively reviewed the clinical course of 2 pediatric AML patients with DNMT3A mutations.

**Results:**

Patient 1: 17 year old male presented with AML M2, normal cytogenetics and DNMT3A R882 missense mutation (exon 23). He achieved minimal residual disease (MRD) negative complete remission (CR) after induction I (Cytarabine, Daunorubicin, and Etoposide (ADE)). He remained



in remission throughout Induction II (ADE), Intensification I (Cytarabine, Etoposide) and Intensification II (Cytarabine, Mitoxantrone) but later had leukemia relapse post Intensification III (Cytarabine and Erwinia). He received 2 cycles of Clofarabine and Cytarabine and achieved morphologic remission (but MRD positive) before consolidation with hematopoietic stem cell transplant (HSCT) from a matched unrelated donor. He failed to sustain clinical remission thereafter and died of leukemia progression 6 months post-transplant. Patient 2: 12 year old male with AML M5, normal cytogenetics and DNMT3A (non R882) frameshift mutation (exon 20). He achieved CR after induction I (ADE), however, his disease relapsed after Induction II (ADE). He then received 2 cycles of high dose cytarabine and etoposide as intensification I and II and achieved MRD negative CR after intensification I but again relapsed at the end of intensification II. He then attained MRD negative CR with Fludarabine, cytarabine and filgrastim before proceeding to HSCT from a matched unrelated donor. He is now 3 months post-transplant and is alive and remains in molecular remission.

**Conclusion:**

DNMT3A mutations, although rare in pediatric AML, may be associated with poor prognosis and impact risk stratification. Further research is needed to determine the clinical significance of DNMT3A mutations in pediatric AML and the role of upfront BMT.

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**IMMUNE PHENOTYPE IS HIGHLY VARIABLE LEADING UP TO DINUTUXIMAB THERAPY FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION AND AT RELAPSE IN PATIENTS WITH HIGH-RISK NEUROBLASTOMA**

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**Background:**

Despite the addition of autologous stem cell transplantation (ASCT) and dinutuximab immunotherapy, cure rates remain poor in patients with high-risk neuroblastoma (HR-NBL). We previously found that following ASCT, patients with HR-NBL had limited immune reconstitution with low numbers of cytotoxic NK cells at the time of dinutuximab initiation<sup>1</sup>. Thus, treatment with dinutuximab following ASCT may not be the most appropriate time for this targeted therapy. Evaluation of disease-response and longitudinal analysis of the immune system in patients who receive dinutuximab post-transplant compared to those who receive it following relapse may provide information on the most appropriate time for immunotherapy.

**Objectives:**

To longitudinally analyze immune cell phenotypes of patients with HR-NBL during induction chemotherapy, ASCT, time of relapse, and dinutuximab therapy and correlate these findings with disease-specific outcomes.

**Methods:**

Blood samples from patients with HR-NBL were collected at the end of induction chemotherapy, following ASCT, at the time of relapse, and during immunotherapy. Mononuclear cells were

isolated using density gradient centrifugation and immediately cryopreserved. T-, B-, and NK cell subtypes were analyzed with respect to differentiation, activation, and exhaustion using a single 21 color multiparameter flow cytometry panel. Immune phenotype was analyzed during different phases of treatment and correlated with responses.

### **Results:**

A total of 67 samples from 17 individual patients at various stages of treatment have been collected. Spectral analysis of our antibody panel was validated on fresh samples from normal controls. Processing, staining, and analysis was then compared between fresh samples and those that were cryopreserved and processed immediately following thawing or rested for 18 hours in media at 37°C. Rested samples universally led to immune subset determination (e.g. cytokine releasing and cytotoxic NK cells, B lymphocytes, Tregs, CD4+ and CD8+ T-cell subsets (Tnaïve, TCM, TEM, and TEMRA) that best reflected those measured in matched fresh samples. Using this method, immune reconstitution remains abnormal in patients at the time of dinutuximab therapy both following transplant and at relapse. Preliminarily, patients with high numbers of CD4+ cells or high percentages of cytokine-releasing NK cells prior dinutuximab therapy appear to have worse or better long-term disease control respectively.

### **Conclusion:**

Detailed and accurate peripheral immune cell subset analysis can be measured using small amounts of blood taken repetitively in patients during treatment for HR-NBL. Ongoing analyses may lead to an ability to predict patient responses to immunotherapy in these patients.

### **Reference:**

1 Nassin, Biology of Blood and Marrow Transplantation, 2018

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## **NEUROCOGNITIVE OUTCOMES IN CHILDREN, ADOLESCENTS & YOUNG ADULTS WITH HIGH-RISK SICKLE CELL DISEASE (SCD) FOLLOWING FAMILIAL HAPLOIDENTICAL (FHI) STEM CELL TRANSPLANTATION: A PROSPECTIVE STUDY FROM PRE HSCT PERIOD TO 2 YEARS POST HSCT (IND 14359)**

**Suzanne Braniecki, Susan K. Parsons, Shalini Shenoy, Qiuhu Shi, Theodore B. Moore, Julie-An Talano, Allyson Flower, Anne Panarella, Sandra Fabricatore, Erin Morris, Jordan Milner, Robert C. McKinstry, Mitchell S. Cairo**

*New York Medical College, Valhalla, New York, United States*

### **Background:**

The cognitive and neurological impairments associated with SCD are due to cerebral vascular injury including attention, memory, processing speed, executive functioning, and lower general intellectual functioning (DeBaun et al, Blood, 2012). Processing speed in particular is a vulnerable domain and is independently decreased in SCD patients unrelated to overt or silent infarctions (Stotesbury et al, Neurology, 2018).

Patients with SCD have demonstrated stable to improved CNS functioning following matched sibling BMT (Walters et al, 2010, Biol BMT; Bhatia et al, BMT, 2014).

**Objectives:**

We aimed to determine changes in neuroimaging and neurocognitive sequelae in individuals with high-risk SCD prior to and following myeloimmunoablative conditioning (MIAC) and FHI AlloSCT utilizing CD34 enrichment and T cell addback.

**Methods:**

Haploidentical stem cell transplant (HISCT) with MIAC with CD34 enrichment was performed as previously described by Cairo et al (JAMA Peds, 2019). Participants had a baseline, 1 year and 2 year MRI that were reviewed by blinded central neuroimaging and completed neurocognitive screener (DIVERGT, Krull, et al) and an abbreviated, standardized neurocognitive test battery (IQ, memory, attention, language, motor, processing speed) over three time points (baseline, Day +365 and Day +730). Neurocognitive domain scores were calculated for each area of functioning at each timepoint.

**Results:**

Nineteen SCD patients were enrolled and received HISCT (12 males, 7 females, mean age, 13.5 years, range 3-21). At baseline, seven patients had evidence of an overt stroke and four patients had evidence of a silent infarct. At 1 and 2 years post-transplant, there were no new overt and/or silent infarcts, and no new cerebral vasculopathy. Intellectual functioning, memory, language and attention/executive function remained stable to improved at year one and two, respectively. Similarly, processing speed was significantly improved at 2 years versus baseline ( $p < 0.03$ ). There were significant age related differences between younger ( $< 13$ yr) and older children ( $> 13$ yr) for language functioning and visual spatial skills; older children demonstrated a greater improvement in language functioning, but worsening visual spatial skills over time ( $p < 0.046$ ,  $p < .006$ , respectively). While not significant, younger children tended to have higher scores overall for intelligence and processing speed.

**Conclusions:**

HISCT utilizing CD34 enrichment and MNC addback in patients with high risk SCD results in stable to improved neurocognitive functioning, with significant improvement on processing speed. Age-related differences were found as well in language and visual spatial functioning. Thus, HISCT has the potential to ameliorate SCD neurocognitive progression and potentially significantly improve functioning (supported by R01FD004090).

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**USE OF AZACITIDINE AND PROPHYLACTIC DONOR LYMPHOCYTE INFUSIONS AFTER HEMATOPOIETIC STEM CELL TRANSPLANT FOR PEDIATRIC ACUTE MYELOID LEUKEMIA: A RETROSPECTIVE REVIEW**

**Emily Huschart, Holly Miller, Dana Salzberg, Courtney Campbell, Kristen Beebe, Jennifer Stahlecker, Kyrie Magee, Roberta H. Adams, Alexander Ngwube**

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**Background:**

Outcomes for pediatric patients who undergo hematopoietic stem cell transplant (HSCT) for acute myeloid leukemia (AML) remain extremely poor. Thirty to eighty percent of patients relapse with majority relapsing in the first 12 months after transplant. Many post-transplant strategies have been proposed as maintenance therapy. However, there remains no clear standard of care in this area. Azacitidine is safe and potentially effective when given after transplant. Studies have shown pre-emptive Donor Lymphocyte Infusion (DLI) may also improve overall survival. We hypothesize that the combination of azacitidine and prophylactic DLI may be a safe and effective strategy to decrease AML relapse after HSCT.

**Objective:**

To report our experience using azacitidine followed by prophylactic DLI as maintenance therapy following HSCT for patients with AML at Phoenix Children’s Hospital.

Design/Method: Retrospective chart review of patients with high risk AML that underwent HSCT and were treated with post HSCT maintenance therapy. All patients were conditioned with a myeloablative regimen of busulfan, cyclophosphamide, and melphalan. We started treating all patients with high risk AML with azacitidine and DLI maintenance therapy after HSCT. Azacitidine is started on Day +60 at 36 mg/m<sup>2</sup> intravenously for 5 days. This is repeated every 28 days for 6 cycles. Prophylactic DLI is started after Day +120; patient must be off immunosuppressant for 1 month. Patients who develop grade III or IV GVHD are not eligible for DLI. Escalating cell doses of prophylactic DLI are given every 6 weeks for 3 doses. The starting dose is dependent on donor source.

**Results:**

Ten patients have been treated on this protocol with a median age at transplant of 13 years (range 2-18 years). Nine patients (90%) were MRD negative at time of transplant. Five patients have completed maintenance therapy. Three patients (30%) required azacitidine dose reductions due to cytopenias. Three patients (30%) developed grade I skin GVHD. One patient (10%) developed grade III liver GVHD that resolved but now has chronic GVHD of the lungs. One patient developed grade IV gut GVHD prior to Day 100 and was not eligible for prophylactic DLI. Nine patients (90%) remain in remission with median length of follow up of 9 months (range 3-22 months). One patient relapsed at Day +90 and was MRD positive (0.09%) at time of transplant.

**Conclusion:**

Post HSCT maintenance therapy with azacitidine and prophylactic DLI in pediatric setting is feasible and safely tolerated. The clinical benefits still need to be assessed.

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**THE SAFETY AND EFFICACY OF TARGETED VIRUS SPECIFIC CYTOTOXIC T-LYMPHOCYTES (VST) MANUFACTURED BY THE IFN- $\gamma$  CYTOKINE CAPTURE SYSTEM (CCS) FOR THE TREATMENT OF REFRACTORY ADENOVIRUS (ADV), CYTOMEGALOVIRUS (CMV), EPSTEIN BARR VIRUS (EBV) AND BK VIRUS (BKV) IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS (CAYA) AFTER ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLO-HSCT), SOLID ORGAN TRANSPLANTATION (SOT), OR WITH PRIMARY IMMUNODEFICIENCY (PID) (IND# 17449).**

Allyson Flower, Janet Ayello, Lauren Harrison, Erin Morris, Meghan Sturhahn, Elena Maryamchik, Yongping Wang, Lynn O'Donnell, Rolla Abu-Arja, Dean Lee, Julie Talano, Bryon D. Johnson, Mitchell S. Cairo, Nancy Bunin

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### **Background:**

Viral infection remains a major cause of morbidity and mortality after allo-HSCT (Bollard/Heslop Blood 2016). Anti-viral agents for treatment of viral infection in immunocompromised patients are limited in efficacy and associated with toxicity (Gerdemann BBMT 2004; Sili Cytother 2012). Use of VST for immunocompromised patients with viral infections can provide therapeutic benefit and improve OS (Bollard/Heslop Blood 2016; Sutrave Cytother 2017). Methods of VST production include ex-vivo expansion and direct selection (Gottlieb Cytother 2017). Ex-vivo expansion requires prolonged manufacturing time, is associated with exhaustion, and provides a limited donor pool. Direct selection results in rapid production and allows for expanded HLA matching. A multicenter consortium (VIRCTLIC) was created to investigate safety and efficacy of VST manufactured by the IFN- $\gamma$  CCS process automated on the CliniMACS<sup>®</sup> Prodigy device (Miltenyi Biotec) for immunocompromised patients with viral infection.

### **Objective:**

To determine safety and efficacy of VST for immunocompromised CAYA patients with viral infection.

### **Design/Methods:**

CAYA patients after allo-HSCT, SOT or with PID with refractory ADV, CMV, EBV or BKV infections despite 2 weeks of appropriate anti-viral therapy, and/or resistance to anti-viral agents and/or intolerance to anti-viral agents were eligible. Donors were screened with viral specific antigen (PepTivator<sup>®</sup>) to predict successful VST manufacturing. Eligible donor PBMC were collected with non-mobilized apheresis. VST were isolated using the CliniMACS<sup>®</sup> Prodigy following stimulation of PBMC with specific viral MACS PepTivator<sup>®</sup> pools, generously provided by Miltenyi Biotec. Production of CD4<sup>+</sup> and CD8<sup>+</sup> VST was performed as previously described (Feuchtinger Blood 2010). Target cell dose was 0.5x10<sup>4</sup> CD3<sup>+</sup>/kg for HLA mismatched related donors and 2.5x10<sup>4</sup> CD3<sup>+</sup>/kg for matched related donors. Based on response and safety, VST were given every 2 weeks, for a maximum of 5 infusions.

### **Results:**

Eight patients were treated for ADV (5), BKV (1), CMV (1), and EBV (1), 6 males, aged 1.5-38 years. Median number of VST infusions was 2.5 (1-5). Mean $\pm$ SEM CD3<sup>+</sup> cell dose was 0.49 $\pm$ 0.01x10<sup>4</sup>. There were 6 CR (PCR negative), 1 PR (PCR $\geq$ 1 log decrease), and 1 not yet evaluable (ORR 100%, CRR 85.7%). Median time to maximal response was 46 days (range 7-111). No patient developed aGVHD, cGVHD, infusion reaction or CRS associated with VST.

### **Conclusion:**

Preliminary results of this pilot study demonstrate that VST are safe, well tolerated and efficacious in CAYA with refractory viral infections after alloHSCT, SOT or with PID.

Manufacturing utilizing the CliniMACS® Prodigy device is rapid, reproducible and effective. Accrual is ongoing.

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## **A CASE OF CVID WITH MULTIFOCAL CNS COMPLICATIONS SUCCESSFULLY TREATED WITH ALLOGENEIC HSCT**

**Matthew Kudek, Rachel Phelan, Julie Talano**

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### **Background:**

Common variable immunodeficiency (CVID) is an immunologic disorder defined by hypogammaglobulinemia of multiple isotypes. Patients with mild phenotypes have normal life expectancies and disease is usually controlled with replacement immunoglobulin and immunomodulatory therapy. There is a subset of patients with very severe phenotypes and manifestations including granuloma formation, organomegaly, autoimmunity, malignancy, and decreased life expectancy. Patients suffering from severe complications have been successfully treated with hematopoietic stem cell transplant (HSCT). There is a paucity of reports on the use of this approach for individuals with CVID-related central nervous system (CNS) complications.

### **Objective:**

To describe successful treatment of a patient with severe neurologic disease secondary to CVID by allogeneic HSCT.

### **Design/Methods:** Case Report

### **Results:**

A 24-year old male with CVID diagnosed at age five was referred to our institution for transplant evaluation. Complications of his CVID have included a high-grade B cell lymphoma treated with chemotherapy, and infiltrative pulmonary and CNS granulomas. The patient's first CNS lesion was discovered following an acute onset of neurologic impairment. A biopsy of the lesion later confirmed an inflammatory process, negative for malignancy and infection. As his CNS disease progressed to a multifocal process, the patient also developed a seizure disorder. Over the patient's 19-year disease history, his CVID could not be adequately managed with corticosteroids, rituximab, azathioprine, 6-mercaptopurine, or sirolimus. For 18 months leading up to transplant, he required monthly abatacept and methylprednisolone 1000 mg IV qweek for CNS disease control. In November 2019, following conditioning with busulfan, fludarabine, and ATG, the patient received an allogeneic transplant from a 10/10 HLA matched unrelated donor with GVHD prophylaxis consisting of CSA and short course methotrexate. Complications of transplant included grade 1 skin acute GVHD managed with topical corticosteroids, and a febrile illness with a concurrent rise in serum galactomannan consistent with aspergillus and treated with voriconazole. The patient is currently day +70 post-BMT, with 100% donor chimerism. He has remained seizure free for the duration of his post-transplant course. MRI head completed day +60 shows improving CNS inflammatory lesions.

### **Conclusion:**

We describe a patient with highly morbid CVID successfully treated by a reduced toxicity matched unrelated allogeneic HSCT. Given the paucity of literature describing the use of HSCT for CVID with severe CNS comorbidity, our report of this effective treatment option is important to increase awareness of treatment alternatives for future patient care.

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## **ABNORMAL BLOOD PRESSURES IS PREVALENT IN CHILDREN WITH SICKLE CELL DISEASE THAT PRESENT FOR HEMATOPOIETIC STEM CELL TRANSPLANT**

**Alexander Ngwube, Holly Miller, Dana Salzberg, Kristen Beebe, Jennifer Stahlecker, Roberta Adams, Dorothy Douglas**

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### **Background:**

Hypertension is an established risk factor for post hematopoietic stem cell transplantation (HSCT) neurological complications such as posterior reversible encephalopathy syndrome in patients with sickle cell disease (SCD). SCD is a genetic disorder associated with anemia with the major manifestation of vaso-occlusive crises. While this disease causes vascular injuries leading to end organ damage, little is known about blood pressure (BP) levels or prevalence of hypertension in children with SCD coming to HSCT.

### **Objectives:**

To determine the prevalence of pre-transplant hypertension using 24 hour ambulatory blood pressure evaluation in patients with SCD.

### **Methods:**

We performed a retrospective chart review of SCD patients that presented for a pre-HSCT work up at Phoenix Children's Hospital. All patients underwent 24-hour ambulatory blood pressure monitoring (ABPM). Clinical information regarding indications for HSCT and SCD-related complications were obtained. Baseline characteristics obtained included age, gender, weight, height, body mass index (BMI) percentile, BMI-Z score and clinic BP. Also obtained was pre HSCT Tc-99 evaluation of glomerular filtration rate reports and pre HSCT urine albumin to creatinine ratio results.

### **Results:**

Twenty three patients were evaluated. Median age was 10 years (range 4–19), body mass index (BMI) 16.85 kg/m<sup>2</sup> (range 14.8–35.5), and 50% were male. Participants' BP profiles were categorized based on the combination of office and 24-hour BP readings as follows: (1) normotensive: normal office and ambulatory BP; (2) white coat HTN: elevated office BP and normal ambulatory BP; (3) ambulatory HTN: elevation of both office and ambulatory BP; and (4) masked HTN: normal office BP and elevated ambulatory BP. Dipping status was defined as the percentage drop in the mean BP from wake to sleep periods. Abnormal dipping was defined as a decline of <10%. Four participants (17.4%) met criteria for hypertension based on ABPM. Of the four hypertensive participants, only one had clinic hypertension with ambulatory hypertension; and three had masked hypertension detected on ABPM. Youngest child with

ABPM confirmed hypertension was five years of age. Another 12 participants (52.2%) had some abnormal ABPM parameters (abnormal dipping).

**Conclusions:**

Findings from our study indicate that BP abnormalities is prevalent in SCD children that present for HSCT. More attention should be given to monitoring and management of BP in children with SCD that present for HSCT. Early identification of hypertension in SCD children can confer benefit because hypertension is an important modifiable risk factor for neurological complication such as PRES.

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**FOOD INSECURITY: THE MD ANDERSON CHILDREN’S CANCER HOSPITAL’S EXPERIENCE WITH A GLOBAL HEALTH CRISIS**

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**Background:**

Food insecurity, or inadequate access to food for an active, healthy life at all times, is a global public health problem which affects one in five US households with children. Household food insecurity is a known risk factor for poor health and hospitalization in children. Moreover, malnutrition is common in patients with advanced cancer and has been shown to be associated with poor treatment-related outcomes including toxicity and response. By identifying sociodemographic characteristics associated with food insecurity and potential barriers to food access, care teams may be able to improve food security in pediatric patient households with the potential to improve overall health, hospitalizations, and even treatment outcomes.

**Objective:**

Assess the current status of food insecurity for pediatric patient families at MD Anderson (MDA) Children’s Cancer Hospital, identify sociodemographic characteristics of caregivers and potential barriers to food access, and identify sociodemographic characteristics and food security-related practice considerations of MDA pediatric healthcare providers.

**Design/Method:**

Anonymous surveys were distributed to caregivers of pediatric patients and providers at the MDA Children’s Cancer Hospital, as part of a quality improvement project. Caregiver surveys utilized validated measures of food insecurity, assessed sociodemographic characteristics and topics related to potential food access barriers. Provider surveys were distributed to physicians and advanced practice providers to assess background demographic characteristics and food security-related practice considerations.

**Results:**

Of 32 completed caregiver surveys, 40.6% of households screened positively for food insecurity. Of those, 30.8% were Non-Hispanic White, 38.5% Hispanic, and 30.8% African American. 23.1% had a household income <\$29,999, 53.8% between \$30,000-59,000, and 15.4% between



60,000-89,999. 38.5% were single, 23.1% married, and 30.8% divorced/separated. Education level included 23.1% elementary/some high school, 38.5% high school/GED, 15.4% some college, and 23.1% college graduates. 61.5% reported strong agreement that they would lose income during their child's hospital stay. 51 providers were surveyed with 38 respondents. 57.9% of providers reported being knowledgeable about food security to some extent (strongly agree, agree, somewhat agree). No providers reported referring patients to community agencies involved in improving food access.

**Conclusion:**

These results suggest that food insecurity may be of significant concern for caregivers of pediatric cancer patients at MDA. Given the potential negative impact of food insecurity on health and treatment outcomes, interventions may be needed to improve patient food security status. Next steps involve implementation of Plan-Do-Study-Act (PDSA) methodology to assess interventions aimed at reducing food insecurity and improving food access in this population.

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**EFFECT OF PRE-TRANSPLANT BODY MASS INDEX IN CHILDREN UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION**

**Brian N. Dang, Satiro De Oliveira, Ashley Gray, Holly Wilhalme, LaVette S. Bowles, James Chang, Theodore B. Moore**

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**Background:**

Obesity is an increasing problem in the United States, with one in five adolescents being obese, and a leading cause of morbidity and mortality. However, the relationship between weight status and hematopoietic stem cell transplants (HSCT) outcomes is inconsistent in the literature, with some studies showing no difference in overall survival between obese and normal weight patients, while others showing improved outcomes with increasing BMI. The effects of obesity on HSCT is especially unclear and understudied in the pediatric population.

**Objective:**

To characterize the effects of a child's pre-transplant BMI on hematopoietic stem cell transplantation outcomes in a single institution.

**Design/Methods:**

We conducted a retrospective analysis of HSCT patients treated between 2005 and 2018 at the Mattel Children's Hospital at University of California, Los Angeles. Patients were evaluated at baseline (time of transplant) for body mass index (BMI), which was converted to a weight category of underweight (UW), normal, overweight (OW), and obese (OB) using the BMI-for-age percentile growth charts. Post-transplant follow-up data included acute graft vs. host disease (GvHD) within the first 100 days, chronic GvHD after 100 days and use of steroids, and overall survival.

**Results:**

In total, we identified 297 cases of HSCT between 2005 and 2018. Our results show a

trend of lower survival probability for individuals in the OB and OW categories compared with those who were normal or UW. OB individuals also showed a trend towards earlier mortality compared with normal/UW individuals that approached significance ( $p < 0.1690$ ). The rates of mild acute GvHD (grade 0-2) were 83.3%, 83.5%, 84.4%, and 74.4% for individuals in the UW, normal, OW, and OB weight categories respectively. The rates of severe acute GvHD (grade 3-4) were 16.7%, 16.5%, 15.6%, and 25.6% for individuals in the UW, normal, OW, and OB weight categories respectively. The rates of limited chronic GvHD were 83.3%, 92.2%, 88.1%, and 94.4%, while the rates for moderate-severe chronic GVHD were 16.7%, 7.8%, 11.9%, and 5.6% for individuals in the UW, normal, OW, and OB weight categories respectively.

### **Conclusion:**

Our results suggests that a high pre-transplant BMI may have a negative effect on overall survival. In addition, obese children appear to be at higher risk for severe acute GvHD. As a result, the weight status of individuals should be considered and addressed in the pre-transplant setting to optimize outcomes.

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## **SUCCESSFUL THIRD HAPLOIDENTICAL STEM CELL TRANSPLANT AFTER GRAFT FAILURE OF TWO PRIOR MATCHED UNRELATED DONOR TRANSPLANTS IN SICKLE CELL DISEASE**

**Daniel Prior, Lev Gorfinkel, Judy Carbonella, Jeff Agli, Carolyn Demsky, Linda Eford, Aron Flagg, Farzana Pashankar, Niketa Shah**

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### **Background:**

Allogeneic stem cell transplantation (SCT) is the only curative option for sickle cell disease (SCD). SCT from Human Leukocyte antigen (HLA) matched sibling donors (MSD) is curative in >90% of cases but is limited by donor availability (<20%). Unrelated donors are an alternative, but fully HLA-matched unrelated donors (MUD) are infrequent due to the rarity of similar HLA haplotypes in the registry. Unrelated donor and haploidentical transplants have increased the risk of graft versus host disease (GVHD) and graft failure compared to MSD SCT. There are reports of successful repeat SCT after graft failure in patients with SCD. However, to our knowledge, there are no reported cases of successful third SCT after two graft failures.

### **Objective:**

To evaluate factors contributing to the success of a third haploidentical peripheral blood SCT (PBSCT) after two graft failures from MUD SCT.

### **Methods and Results:**

A 13-year-old girl with severe SCD underwent reduced intensity MUD SCT. Fludarabine, melphalan, thiotepa, and distal alemtuzumab were used for conditioning. Tacrolimus, methotrexate, and abatacept were used for GVHD prophylaxis. She engrafted on D+10 but had graft failure on D+28 due to Cytomegalovirus viremia and Herpes Simplex Virus 1 infection. She recovered her autologous bone marrow, with her innate SCD afterward. Ten months later,

she underwent a second MUD SCT with myeloablative conditioning, using busulfan, cyclophosphamide, and antithymocyte globulin. Tacrolimus and methotrexate were used for GVHD prophylaxis and letermovir for CMV prophylaxis. She engrafted on D+17, had graft failure on D+32 after sudden-onset cytokine release syndrome, and remained aplastic afterward. Notably, she had no HLA antibodies to either prior donor. Finally, she underwent an emergency rescue haploidentical PBSCT from her mother on D+60 post second SCT. She received ATG, fludarabine, cyclophosphamide, and total body irradiation (TBI) 400 cGY for conditioning, and post-transplant cyclophosphamide, mycophenolate, and tacrolimus/sirolimus for GVHD prophylaxis. She engrafted on D+16 and had 100% donor cells on her D+30 and D+60 evaluations.

**Conclusions:** Factors associated with her first graft failure include reduced intensity conditioning, viral infection, and inherent cellular immunity. Her second graft failure, following myeloablative conditioning, was likely mediated mainly by cellular-level rejection. The success of her third graft was likely due to immunosuppressive effects of TBI and the megadose PBSCT. This case shows that third SCT can be effectively performed without major acute toxicities in SCD. More research is needed to understand the mechanisms for graft failure in SCD, and for developing conditioning regimens that minimize toxicity without compromising engraftment.

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**DETERMINING THE SAFETY AND EFFICACY OF PROPHYLACTIC DEFIBROTIDE ADMINISTRATION IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH SICKLE CELL DISEASE FOLLOWING MYELOIMMUNOABLATIVE CONDITIONING (MAC) AND HAPLOIDENTICAL STEM CELL TRANSPLANTATION UTILIZING CD34+ SELECTION AND T-CELL (CD3) ADDBACK (IND127812)**

**Jordan Milner, Justine Hung, Janet Ayello, Qiuhu Shi, Julie Talano, Theodore Moore, Deborah Friedman, Alan Dozor, Liana Klejmont, Harshini Mahanti, Erin Morris, Sandra Fabricatore, Elizabeth Mintzer, Allyson Flower, Kenneth R. Cooke, Mitchell S. Cairo**

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**Background:**

Sickle cell disease (SCD) is a hemoglobinopathy and vasculopathy resulting in vaso-occlusive crises, chronic end-organ damage, shortened life span and the only curative therapy is allogeneic stem cell transplant (Talano/Cairo, EJH, 2015). Approximately 16 percent have an HLA matched unaffected sibling (Bhatia/Cairo, BMT, 2014). We demonstrated the safety and efficacy of familial haploidentical transplants (FHI) in this population with 100% engraftment and 90% 1 year EFS (Cairo et al, JAMA Peds, 2019). The incidence of sinusoidal obstructive syndrome (SOS) in SCD AlloSCT recipients is approximately 32% (McPherson, BMT, 2011). Defibrotide primarily targets endothelium and reduces endothelial cell injury (Falanga et al, Leukemia, 2003 and Scallia et al, Clin Pharm, 1996). Corbacioglu et al, (Lancet 2012) demonstrated the safety and efficacy of prophylactic defibrotide for SOS in high risk pediatric AlloSCT recipients.

**Objective:**

To determine the safety and efficacy of defibrotide prophylaxis for SOS in children, adolescents and young adults (CAYA) with high-risk SCD following MAC and FHI AlloSCT, utilizing CD34+ selection with CD3 addback.

**Design/Methods:**

Patients with SCD aged 2 to 35 years with high risk SCD (stroke,  $\geq 2$  acute chest syndrome in past 2 years,  $\geq 3$  pain crises in last 2 years, abnormal TCD study,  $\geq 1$  silent infarct lesion on MRI) were enrolled after being consented, (NCT02675959). Patients were in two cohorts (2 to 17.99 years and 18 to 34.99 years of age) for age based analysis and treatment. All patients received a MAC regimen prior to receipt of an FHI with CD34+ selection and CD3 addback peripheral blood stem cell transplantation (PBSCT), as we have demonstrated (Cairo et al, ASH, 2018). Defibrotide was given day -10 during conditioning through day +21 following transplant.

**Results:**

We have enrolled eight patients with high risk SCD, five in cohort 1 (median age 9.9 years) and three in cohort 2 (median age of 24 years) with a gender ratio (M/F) of 4/4. Patients had either maternal (n=7) or sibling (n=1) donor. Patients had early neutrophil engraftment (median day +11 (day +7 to day +14)). All tolerated  $109 \pm 11.2$  doses of defibrotide. There were no severe adverse nor bleeding events probably or directly related to defibrotide. No patient developed SOS.

**Conclusion:**

The preliminary data suggests defibrotide is safe and well tolerated in CAYA patients with high-risk SCD following MAC and FHI AlloSCT, utilizing CD34+ selection with CD3 addback. This study was funded by a grant from Jazz Pharmaceuticals. Supported by FDA R01FD004090.

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**EFFECTIVELY TARGETING OSTEOSARCOMA, NEUROBLASTOMA AND GLIOBLASTOMA WITH EXPANDED NATURAL KILLER CELLS COMBINED WITH N-803 (ALT-803, IL-15 SUPERAGONIST) AND TIM-3 BLOCKADE**

**Yaya Chu, Jeremy Rosenblum, Dean A. Lee, Jeffrey T. Safrit, Mitchell S. Cairo**

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**Background:**

Children with recurrent and/or metastatic osteosarcoma (OS), neuroblastoma (NB) and glioblastoma (GBM) have a dismal even-free survival (EFS) (<25%). Most of these tumor cells highly express GD2 antigen on the surface. Dinutuximab is an anti-GD2 monoclonal antibody that has significantly increased EFS in children with GD2+ neuroblastoma. NK cells have shown significant alloreactive anti-leukemic effects following haploidentical stem cell transplantation. However, the adoptive transfer of NK cells showed poor clinical response in patients with solid tumors. The NK resistance, on NK side, is mainly due to the small numbers of active NK cells, the short lifespan of NK cells, poor persistence and trafficking, and lack of specific tumor targeting. Our group has successfully expanded peripheral blood Natural Killer cells (exPBNK) with irradiated feeder cells. IL-15 is a critical factor that supports the development, proliferation, survival and trafficking of NK. N-803 (ALT-803) is a superagonist of an IL-15 variant bound to

an IL-15R $\alpha$ +Su-Fc fusion with enhanced biological activity. Tim-3 is an immune checkpoint protein. It was found expressed on active NK cells besides T cells and its expression in cancer patients NK cells correlated with disease stage and prognosis.

**Objective:**

To determine if the combination of N-803 and TIM-3 blockage significantly enhances exPBNK cell cytotoxicity against OS, GBM and NB.

**Method:**

PBMCs were expanded with lethally irradiated K562-mbIL21-41BBL cells. CD56+CD3-exPBNK cells were isolated using Miltenyi NK cell isolation kit. N-803 was generously provided by Altor BioScience. ExPBNK were cultured with 3.5ng/ml ALT-803 and 10 or 20ug/ml anti-TIM-3 antibody. NK proliferation, NK receptors expression and cytotoxicity were examined as we previously described (Chu/Cairo et al, Oncoimmunology, 2017).

**Results:**

N-803 increased NK activating receptor's expression: NKG2D, NKp30, NKp44, and NKp46. N-803 significantly enhanced exPBNK in vitro cytotoxicity against OS, NB and GBM (p<0.001) compared to IgG control. Furthermore we found that Tim-3 levels were significantly enhanced on expanded NK cells when exPBNK cells were incubated with OS cells, indicating Tim-3 may be involved in exPBNK exhaustion when exPBNK cells are in contact with tumor cells. When combined with anti-Tim-3 blocking antibody, N-803 significantly enhanced exPBNK mediated antibody-dependent cellular cytotoxicity (ADCC) (p<0.001) and IFN- $\gamma$  (p<0.001) and perforin (p<0.001) release from exPBNK against OS, NB and GBM compared to exPBNK, N-803+exPBNK, or anti-Tim-3+exPBNK.

**Conclusions:**

The combination of N-803 and anti-Tim3 blockage significantly enhanced exPBNK in-vitro cytotoxicity against OS, NB and GBM cells. In-vivo effects of the combination are under investigation.

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**SOLUBLE IL-2 HAS A DOSE-DEPENDENT EFFECT ON NATURAL KILLER CELL EXPANSION ON A MEMBRANE-BOUND IL-21 EXPRESSING FEEDER CELL PLATFORM**

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**Background:**

Ex vivo expansion of NK cells for adoptive immunotherapy frequently relies upon soluble interleukin 2 (IL-2) to drive, at least in part, fold expansion and activation. A wide range of IL-2 dosing has been utilized with doses as low as 50 IU and as high as 6000 IU, mimicking T cell expansion protocols.

**Objectives:**

We sought to determine the effect varying IL-2 dose has on the fold expansion, phenotype, and cytotoxicity of NK cells expanded on a membrane-bound IL-21 (mbIL21) feeder cell.

**Method:**

Primary peripheral NK cells were enriched from anonymized human donor discarded leukopaks utilizing RosetteSep™ Human NK Cell Enrichment Cocktail and gradient centrifugation. These NK cells were then expanded in serum free media by 14-day co-culture with a genetically-modified mbIL21 feeder cell and varying IL-2 dose per experimental condition - 50 IU/mL, 100 IU/mL, 1000 IU/mL, and 6000 IU/mL. Fold expansion was calculated for each condition at the end of 14 days. Cytotoxicity was measured by calcein-release assay following co-culture with a K562 target cell at several effector:target ratios. The phenotype of cells cultured in 50 IU/mL and 6000 IU/mL were then assessed by mass cytometry (CyTOF) with a 40-marker panel.

**Results:**

The mean fold expansion (n=8) in 50 IU is 3265 after 14-day expansion, while it is 1947 in 100 IU (p=0.0229), 397.9 in 1000 IU (p=0.0115), and 417.9 in 6000 IU (p=0.011). The mean % lysis (n=6) at an effector to target ratio of 5:1 is 86.37% for cells grown in by NK cells grown in 50 IU, 88.67% for cells grown in 100 IU, 67.04% for cells grown in 1000 IU, and 59.54% for cells grown in 6000 IU; however, there is not a statistical difference between 50 IU/mL and 1000 IU/mL or 6000 IU/mL (p=0.0555 and p=0.052, respectively). Phenotypically (n=3), there is an increase in the median metal intensity (MMI) for CD69 and CD56, but a decreased in MMI for NKG2D, NKG2A, and CD94 with an increase in IL-2 dose from 50 IU/mL to 6000 IU/mL.

**Conclusion:**

IL-2 has a significant, dose dependent effect on NK cell fold expansion with increasing dose above 50 IU/mL having a suppressive effect that seems to correspond with a change in phenotype.

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**GVHD FOLLOWING TISAGENLEUCCEL FOR RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT**

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**Background:**

Outcomes of relapsed acute lymphoblastic leukemia (ALL) are poor and the toxicity of relapse therapy remains high. Treatment for relapsed ALL includes intensive chemotherapy followed by allogeneic hematopoietic cell transplant (HCT) which can have significant morbidity and mortality. Graft-versus-host-disease (GVHD) is one of the most common causes of mortality following HCT. Novel therapies, such as chimeric antigen receptor T cells (autologous T cells that have been engineered to target specific tumor antigens), offer a targeted approach to treating relapsed ALL which may improve efficacy and minimize toxicity.

In 2017, the FDA approved tisagenlecleucel for relapsed and refractory ALL based on promising early clinical trials' results. There are many life-threatening complications of CART therapy but the majority of patients have tolerated this therapy well. Notably, no GVHD has been reported in the literature in patients receiving tisagenlecleucel for relapsed ALL after HCT.

**Objective:**

To describe a case of GVHD following tisagenlecleucel for relapsed ALL following allogeneic HCT.

**Design/Methods:**

A 22-year-old female diagnosed with Ph-like B ALL had persistent disease after induction therapy according to CALGB 10403. She then received blinatumomab and achieved minimal residual disease (MRD) negativity. This was followed by a myeloablative conditioning (Palifermin/Fludarabine/total body irradiation) and a haploidentical peripheral blood stem cell transplant. GVHD prophylaxis included post-HCT cyclophosphamide in combination with tacrolimus and mofetil mycophenolate. She had no acute or chronic GVHD. She relapsed 5 months following HCT with Ph-like B ALL. She achieved MRD negativity after 3 cycles of inotuzomab and underwent T cell collection at which time her chimerisms were 100% donor. She received lymphodepleting chemotherapy and tisagenlecleucel infusion. A follow up bone marrow evaluation day +60 post CART showed MRD negativity, ongoing B cell aplasia, and 100% donor chimerisms.

**Results:**

About 4 months after tisagenlecleucel infusion, she presented with an asymptomatic, maculopapular rash and ocular discharge and irritation after sun exposure. The rash involved the periorbital area, neck, axilla, trunk and arms and was biopsy proven grade 2 GVHD. She was treated with topical steroids. About 3 days later, she presented with worsening rash, dry mouth, dry eyes, fatigue, and crampy abdominal pain. These symptoms were attributed to worsening GVHD and budesonide was started. Symptoms improved and she tolerated a steroid wean. She remains symptom free with ongoing remission, B cell aplasia, and 100% donor chimerisms 12 months after tisagenlecleucel.

**Conclusion:**

This is the first report of GVHD following tisagenlecleucel for relapsed ALL after HCT in a patient without prior history of GVHD. This complication was successfully managed with oral budesonide with persistence of B cell aplasia and highlights the need to consider GVHD in differential diagnosis following tisagenlecleucel infusion.

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**IMPLEMENTING PROGRAMMATIC CHANGE OF PERI-TRANSPLANT NUTRITIONAL OUTCOMES THROUGH CREATION OF A NUTRITION TASK FORCE ADDRESSING DIET IN PEDIATRIC STEM CELL TRANSPLANT PATIENTS.**

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**Background:**

Improvements to supportive care therapy has been vital to improved outcomes of hematopoietic stem cell transplants (HSCT). Specifically, nutrition is affected by a complex network of challenges after a patient undergoes a stem cell transplant including but not limited to nausea, vomiting, changes in the mucosal barrier of the GI tract, and psychosocial factors. There is a lack of new evidence as the best way to approach these patient's dietary recommendations as it related to oral diet restrictions and initiation of supplemental nutrition through enteral and parental methods.

**Objectives:**

We created a nutrition task force to evaluate current research in overhauling our nutritional recommendations and implementing a standard dietary approach for all patients receiving a stem cell transplant which include: The main objectives of the task force were: 1) early nutrition consultation in the pre-BMT evaluation, 2) an updated transplant safe diet that was less restrictive than previous neutropenic diet recommendations and focused on safe food handling, and 3) placement of nasogastric tube with enteral feeds on day -1 for all patients prior to the onset of mucositis to optimize continued me.

**Design/Methods:**

Starting in July 2018 after several meetings of the multidisciplinary nutrition task force, a nutrition care bundle was rolled out with a new transplant safe diet and care was made to initiate standard NGT placement on day -1. Education was provided to appropriate medical, nursing, and dietary services groups that would be in contact with stem cell patients.

**Results:**

Successful implantation of the objectives were implemented on the hematology oncology care unit for patients on the bone marrow transplant service. Future directions will be aimed at We look forward to continued implementation and integration of the above changes and looking to compare clinical data pre- and post- implementation as it relates to nutritional status, GVHD, and infection rates.

**Conclusion:**

Nutritional support is considered an integral part of the supportive care of HSCT patients. Enteral nutrition has been the main tool for providing nutritional support to patients undergoing HSCT at our transplant center.

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**A SYSTEMATIC REVIEW OF STUDIES ON DEFIBROTIDE PROPHYLAXIS FOR VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS)**

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**Background:**

Defibrotide is approved to treat hepatic VOD/SOS with renal or pulmonary dysfunction after hematopoietic cell transplantation (HCT) in adult and pediatric patients in the US, and to treat severe hepatic VOD/SOS post-HCT in patients aged >1 month in the EU. Several studies have examined the utility of defibrotide for the prophylaxis of VOD/SOS.

**Objective:**

To estimate the overall incidence and risk of developing VOD/SOS after IV defibrotide prophylaxis using published literature.

**Design/Methods:**

PubMed/Embase were searched through July 8, 2019 for studies using defibrotide in prevention or prophylaxis of VOD/SOS, excluding phase 1 studies, case reports with <10 patients, and reviews. Pooled VOD/SOS incidence estimates with 95% confidence intervals (CI) were calculated using a random effects model after Freeman-Tukey Double Arcsine Transformation; the Mantel-Haenszel method and random-effects modeling (Stata Software) were used for overall incidence rates and risk ratios, respectively. For age analyses, only studies specifying adult and/or pediatric data were included. Safety results were not pooled due to differences in study reporting. Analyses were performed at NOVEL Health Strategies, Bethesda, MD, USA.

**Results:**

Overall, 349 records were identified; 22 studies had  $\geq 10$  patients, 14/22 studies reported IV defibrotide administration for VOD/SOS prophylaxis (6 adult studies, 5 pediatric studies, and 3 both/not specified), and 10/14 studies reported incidence of severe/very severe VOD/SOS (per the investigator).

Overall incidence of VOD/SOS was 5% (95% CI: 2%-8%) with IV defibrotide prophylaxis; in adult and pediatric patients, the incidence was 4% (95% CI: 1%-8%) and 8% (95% CI: 6%-11%), respectively. Overall incidence of severe/very severe VOD/SOS was 2% (95% CI: 0%-4%) in the 10 studies reporting disease severity. Among 6 studies with data on IV defibrotide prophylaxis and controls (eg, heparin or no prophylaxis), the risk ratio for VOD/SOS with defibrotide prophylaxis versus controls was 0.43 (95% CI: 0.20-0.96; P = 0.040).

Safety results in individual studies were generally consistent with the known defibrotide safety profile in the prophylactic setting.

**Conclusions:**

This analysis suggests a low incidence of VOD/SOS following prophylaxis with IV defibrotide, at 5%, regardless of age group (4% in adults and 8% in pediatric patients), and a lower relative risk for VOD/SOS with defibrotide prophylaxis versus controls in the overall population.

Limitations include the limited number of controlled, peer-reviewed studies, variations in VOD/SOS diagnostic/severity criteria, and defibrotide doses across studies. Results support further evaluation of defibrotide prophylaxis of VOD/SOS, in adult and pediatric patients; a phase 3 study (NCT02851407) is ongoing.

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**SUCCESSFUL USE OF MTOR INHIBITOR FOR STABILIZATION OF FALLING CHIMERISM POST UNRELATED BONE MARROW TRANSPLANT IN A PATIENT WITH A HISTORY OF SICKLE CELL DISEASE AND STROKE**

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**Background:**

The use of Reduced Intensity Chemotherapy (RIC) preparative regimens for patients with sickle cell disease (SCD) undergoing bone marrow transplant (BMT) is associated with decreased organ toxicity. However, RIC is also associated with an increased incidence of mixed chimerism and subsequent unstable engraftment. Donor myeloid chimerism under 25% is associated with disease recurrence. There is limited literature about the long-term stability of the graft and the management of patients near this threshold, especially in patients at high risk for recurrent stroke.

**Objectives:**

To describe a single case report of a patient with a history of SCD and stroke who experienced falling chimerism post-unrelated BMT stabilized with sirolimus.

**Design/Methods:**

A 10 year old male with hemoglobin SS received an 8/8 matched unrelated (sickle trait negative) donor BMT with a RIC preparative regimen of alemtuzumab, fludarabine, and melphalan on BMT CTN 0601. After initial mixed chimerism in the first year following BMT, the patient achieved full donor engraftment in the setting of acute graft versus host disease. After trending falling chimerisms, the patient presented five years post BMT with a myeloid chimerism of 21%, lymphoid chimerism of 57%, and Hemoglobin S fraction of 47.1%. At this time, sirolimus was initiated with therapeutic levels (5-15 ng/ml).

**Results:**

In the year following initiation of sirolimus, the patient's chimerism stabilized at 18-29% donor myeloid and 48-78% donor lymphoid engraftment. The patient received partial exchange transfusions twice for Hemoglobin S fraction over 50% for neuroprotection when the myeloid chimerism was below 20% donor, but he has not returned to scheduled chronic transfusions. He remains without disease recurrence with Hemoglobin S under 50% with myeloid chimerism over 20% donor for the last ten months with no transfusions during this time. Most recent MRI/MRA demonstrated stable cerebrovascular disease with no further infarctions.

**Conclusion:**

mTOR inhibitors with close monitoring may be useful in the stabilization of low levels of donor mixed chimerism in patients who received RIC BMT for cure of SCD as an alternative to second transplant or chronic transfusion therapy.

Reference: Abraham A, et al, *Biology of Blood and Marrow Transplant*, 2017

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**AN ADVANCE CARE PLANNING INTERVENTION IMPROVES UNDERSTANDING OF END OF LIFE PREFERENCES BETWEEN ADOLESCENT/YOUNG ADULT BONE MARROW TRANSPLANT PATIENTS AND THEIR SURROGATE DECISION-MAKERS**

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**Background:**

Advance care planning prepares patients and their families for future health care decisions. Adolescent and young adult bone marrow transplant patients often lack the opportunity to clarify or communicate their treatment goals, values, and end-of-life preferences with their surrogate decision-makers and healthcare providers.

**Objectives:** To examine the efficacy of family-centered advance care planning for adolescent and young adult bone marrow transplant patients in improving congruence about end-of-life treatment goals

**Methods:**

Intervention study at The University of Minnesota Masonic Children's Hospital in Minneapolis, Minnesota, USA. Inclusion criteria were age 14-26, English speaking, undergoing bone marrow transplant for any reason, had a designated surrogate > 18 years who was English speaking. Dyads underwent the Family-Centered (FACE) Advance Care Planning Intervention which included the Respecting Choices Next Steps interview with completion of the Statement of Treatment Preferences, which posed 4 scenarios and asked the patient to choose to continue treatment, discontinue treatment, or unsure. Main outcome measure was improvement of congruence on the Statement of Treatment Preferences among the participant/surrogate dyad.

**Results:**

Eleven patient/surrogate dyads completed the pre-and post-intervention Statement of Treatment Preferences. The mean age of the adolescents was 18 years; 7(63%) were male, 9(82%) were white, 9 (82%) of surrogates were mothers. After the intervention, the number of patients who chose to continue treatment in each scenario was 90% in the high treatment burden/low chance of survival, 18% high treatment burden/limited prolongation of life, 45% high survival/functional disability, and 45% high survival/cognitive disability. The intervention resulted in significantly increased congruence for 100% of the disease specific scenarios; high treatment burden/low chance of survival  $\hat{I}^{\circ}=1.17$ ,  $p=0.02$ , high treatment burden/ limited prolongation of life  $\hat{I}^{\circ}=0.51$ ,  $p=0.05$ , high survival/functional disability  $\hat{I}^{\circ}=0.65$ ,  $p=0.03$ , high survival/cognitive disability  $\hat{I}^{\circ}=0.64$ ,  $p=0.05$ .

**Conclusions:** Advance care planning enabled adolescent and young adult bone marrow transplant patients to clarify their goals and improve the understanding about end-of-life treatment preferences between patients and their surrogates. These maturing patients should be offered the opportunity to explore these discussions, consistent with respect for patient autonomy and the provision of quality palliative care.

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**AUTOIMMUNE CYTOPENIAS FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT IN PEDIATRIC PATIENTS: A CASE-CONTROL COHORT STUDY**

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**Background:**

Autoimmune cytopenia (AIC) is a rare, but serious complication of allogeneic hematopoietic cell transplantation (allo-HCT), and treatment can have severe consequences.

**Methods:**

We performed a retrospective case-control study of pediatric allo-HCT transplant recipients at Children's Hospital Colorado (June 2005-March 2019). The clinical and transplant-related characteristics, outcomes and late effects between AIC patients (n=20) and controls (n=40) matched by primary disease category and donor source were compared.

**Results:**

The incidence of AIC was 5.6% in allo-HCT recipients (n=354). Of these, 75% had non-malignant disease (n=15). Thirteen developed hemolytic anemia (65%), 5 had thrombocytopenia (25%), 1 had Evans syndrome (5%) and 1 had neutropenia (5%). Median time to AIC was 219 days (range 97-1205 days). There was no difference between cases and controls for gender, age, conditioning regimen, serotherapy, TBI use, GVHD prophylaxis, chronic GVHD, or time to neutrophil and platelet recovery. Compared to controls, more cases had ABO mismatch (50% vs. 40%, p=0.07), and more grade I-II acute GVHD (93.9% vs. 50%, p=0.06). Seventeen (85%), had full donor chimerism prior to AIC diagnosis. Cases were less likely to have achieved T cell reconstitution, CD4+ count >400/ uL, (30% vs 67.5%, p = 0.01) prior to diagnosis. Cases (40%) were less likely to have achieved B cell reconstitution, defined as CD19+ count >50 cells/uL compared to controls (60%, p=ns). Fifteen (75%) received steroids as part of initial AIC therapy and 17 (85%) received rituximab. Only 25% (n=5) responded to initial therapy and 13.3% (n=2) received steroids as single first-line therapy. Despite resolution of AIC, 70.6% (n=12) of patients were receiving IVIG for hypogammaglobulinemia at a median of 597.5 days from last rituximab dose. Iron overload was more prevalent in cases (n=8 vs n=1, p=0.0004, median of 2.3 years after HCT). Among AIC patients, 25% developed avascular necrosis of a large joint compared to 5% (n=2) of controls (5 vs. 2, p=0.04). Additionally, cataracts were observed in 15% of cases compared to 2.5% of controls (3 vs. 1, p=0.07), and there was no impact on bone mineral density. The overall survival (OS) of the AIC cohort was similar to the control group (85% vs 82.5%). No patients in the AIC cohort died from AIC-related complications.

**Conclusions:**

In this case-control study of pediatric HCT patients, the majority of AIC patients did not respond to first-line therapy and required multiple therapies to achieve a complete response. Late effects from AIC-directed therapies include prolonged hypogammaglobulinemia, iron overload and cataracts.