2022 ASPHO Conference Paper and Poster Index

Papers

Posters

Plenary Paper # 2001

EFFECTS OF THE CDC'S 2016 OPIOID GUIDELINES ON PEDIATRIC AND ADULT PATIENTS WITH SICKLE CELL DISEASE

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Background: New guidelines were instituted by the Centers for Disease Control and Prevention (CDC) in 2016 for the prescription of opioid analgesics. Despite acknowledgement that it was not intended to restrict opioid therapy to individuals with sickle cell disease (SCD), the patients stated that it decreased access to opioid analgesics. The CDC is seeking evaluations of the intended and unintended impact of the guideline on patient outcomes.

Objectives: To evaluate the effect of the *CDC Guidelines for Prescribing Opioids for Chronic Pain* on prescribing practices and health outcomes among pediatric and adult patients with SCD.

Design/Method: This retrospective cohort study employed an interrupted time series analysis using the IBM® MarketScan® Commercial Database (1/1/2011-12/31/2019). Individuals who were ≥1 year old, had ≥3 SCD diagnoses documented within 5 years, and no cancer diagnosis were included. Prescription opioid use outcomes (opioid prescription rate, mean total morphine milligram equivalents [MME] per patient, mean daily MME per opioid prescription, mean number of days supplied per opioid prescription) and health outcomes (rates of vaso-occlusive crisis [VOC]-related emergency department [ED] visits and hospitalizations) were measured on a monthly basis. Segmented regressions (breakpoint: March 2016) were conducted for all outcomes to compare their trends before and after the guideline release.

Results: Among 14 979 patients (1-65 years old, 56.9% female) included, 5 459 were pediatric patients (age<18; mean[SD] age=8.3[5.3]) and they experienced significant decreases in the total MME per patient (–7 MME/month, P=0.016) and the number of days' supplied per prescription (-0.03 days/month, P<0.001), but a significant increase in the VOC-related hospitalization rate (+0.10 hospitalizations/100person-month, p=0.022) after the guideline release vs. pre-guideline period. There was no significant change in the opioid prescription rate, daily MME per prescription, or the rate of VOC-related ED visits. Among 9 520 adult patients (age≥18; mean[SD] age=36.1[12.2]), there were significant decreases in the opioid prescription rate (-0.41 prescription/100person-month, p<0.001), total MME per patient (–221 MME/month, P=0.001), daily MME per prescription (–11 MME/month, P<0.001), and days' supplied per prescription (-0.05 days/month, P<0.001), but significant increases in the rates of VOC-related ED visits (+0.07 visits/100person-month, p=0.045) and hospitalizations (+0.20 hospitalizations/100person-month, p<0.001) in the post-guideline vs. pre-guideline period.

Conclusion: The CDC guideline release timing corresponded with decreases in opioid prescribing practices and unfavorable health outcomes among patients with SCD. The guideline may have an unintended negative impact on this population, with greater impact in adults compared to pediatric patients.

This study was funded by the American Association of Colleges of Pharmacy.

Plenary Paper # 2002

BETIBEGLOGENE AUTOTEMCEL IN PEDIATRIC PTS WITH TRANSFUSION-DEPENDENT β-THALASSEMIA IN PHASE 3 TRIALS

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Background: Phase 3 studies evaluating betibeglogene autotemcel (beti-cel) gene therapy in patients with transfusion-dependent β-thalassemia (TDT), HGB-207 (non-β^0/β^0 genotypes; NCT02906202) and HGB-212 (β^0/β^0, $\beta^0/\beta^{+IVS-I-110}$, $\beta^{+IVS-I-110}/\beta^{+IVS-I-110}$ genotypes; NCT03207009), demonstrated positive outcomes in adults.

Objectives: We describe interim efficacy and safety of beti-cel in pediatric patients treated in HGB-207 and HGB-212.

Design/Method: Autologous CD34+ cells were transduced ex vivo with BB305 lentiviral vector to produce beti-cel. Patients underwent pharmacokinetic-adjusted busulfan-based myeloablation followed by beti-cel infusion. Transfusion independence (TI; weighted average hemoglobin [Hb] ≥9 g/dL without red blood cell transfusions for ≥12 months) was the primary endpoint. Data are presented as median (min–max).

Results: As of 9 March 2021, 27 pediatric patients were treated and followed for 25.5 (4.1–41.5) months: 16 patients <12 years (HGB-207: n=8; HGB-212: n=8) and 11 patients ≥12–<18 years at assent (HGB-207: n=6; HGB-212: n=5). The youngest patients were 4 years of age (n=3). Neutrophil and platelet engraftment occurred at Day 26 (16–39) and 50 (20–94), respectively. TI was achieved in 10/12 evaluable patients <12 years and 10/10 evaluable patients ≥12–<18 years. The duration of ongoing TI was 23.2 (12.5–37.9) months in pediatric patients (n=20), with TI rates (90.9% [20/22]) similar to adults (85.7% [12/14]).

Weighted average Hb during TI in patients <12 years and ≥12–<18 years was 10.0 (9.7–11.5) g/dL (n=10) and 11.7 (9.6–13.2) g/dL (n=10), respectively. At last visit, beti-cel-derived adult Hb (HbA^{T87Q}) was 8.6 (6.0–10.2) g/dL (n=10) and 9.4 (4.4–11.8) g/dL (n=10), respectively. In adults, the weighted average Hb during TI was 12.6 (9.3–13.7) g/dL and HbA^{T87Q} at last visit was 9.6 (7.9–12.7) g/dL (n=12). Markers of ineffective erythropoiesis and iron overload improved in pediatric patients who achieved TI.

Non-hematologic ≥Grade 3 adverse events (AEs) in ≥3 patients <18 years were stomatitis (n=15), febrile neutropenia (n=15), epistaxis (n=6), decreased appetite (n=5), increased alanine aminotransferase (n=3), hypoxia (n=3), pharyngeal inflammation (n=3) and pyrexia (n=3). Veno-

occlusive liver disease occurred in 3 patients <18 years (Grade 4 [n=2], Grade 2 [n=1]); events resolved with defibrotide. Drug-product related AEs were reported in 4 patients (thrombocytopenia and tachycardia [n=1 each]; abdominal pain [n=2]). No replication-competent lentivirus, clonal predominance or insertional oncogenesis was reported.

Conclusion: Pediatric patients with diverse TDT genotypes achieved TI rates comparable to adults. The safety profile of the treatment regimen was reflective of busulfan myeloablation. beti-cel is a potentially curative gene therapy for pediatric patients with TDT through the ability to achieve TI with near-normal to normal Hb levels.

Sponsored by bluebird bio.

Paper # 2003/Young Investigator Award Recipient

BLOCKING THE BCL10-MALT1 INTERACTION IN DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL) is characterized by oncogenic gain-of-function mutations that cause inappropriate activation of the three protein CARMA1-BCL10-MALT1 (CBM) signaling complex, which then drives lymphomagenesis. MALT1, the effector protein of this complex, possesses protease and scaffolding activities, both of which contribute to activation of the pro-survival NF-κB transcription factor. Existing MALT1 inhibitors target only MALT1 protease function and recent studies demonstrate that MALT1 protease inhibitors have efficacy in blocking MALT1-dependent lymphomagenesis. The clinical utility of isolated MALT1 protease inhibitors is thought to be limited by the inflammation that results from inhibiting only MALT1 protease function without inhibiting MALT1 scaffolding function.

Objectives: Here we seek to identify a pharmacologic approach to simultaneously block both MALT1 protease and scaffolding activities. We aimed to define the precise site of interaction between MALT1 and BCL10 and then evaluate whether a small molecule that blocks this interaction is able to inhibit both constitutive MALT1 protease and scaffolding activities in ABC-DLBCL lymphomagenesis.

Design/Method: Site directed mutagenesis and co-immunoprecipitation were used to identify a site of interaction between MALT1 and BCL10. An in silico drug-docking screen was used to identify M1i-124 as a compound predicted to disrupt this interaction. We tested the ability of M1i-124 to block the BCL10-MALT1 interaction using an ELISA assay. *In vitro* studies and *in vivo* xenograft experiments were performed to test the effect of M1i-124 on MALT1 oncogenic function in ABC-DLBCL tumor cells.

Results: Using mutagenesis and co-immunoprecipitation, we identified a region of MALT1 located between immunoglobulin-like domains 1 and 2 (Ig1-2) that is required for interaction with BCL10. Using an in silico drug screen targeting this MALT1 interface, we identified M1i-124 as a potential inhibitor of the BCL10-MALT1 interaction. We show that M1i-124 inhibits the binding of BCL10 and MALT1 in an ELISA assay. We find that M1i-124 inhibits both MALT1 protease and MALT1 scaffolding functions in ABC-DLBCL cells as well as tumor growth in an ABC-DLBCL xenograft mouse model.

Conclusion: A small molecule that is predicted to bind to the interface between MALT1 Ig1-2 domains is effective in inhibiting MALT1 protease and scaffolding functions in ABC-DLBCL cells and inhibiting ABC-DLBCL lymphomagenesis in a xenograft mouse model. These results demonstrate that targeting the BCL10-MALT1 interaction is a valid strategy for inhibiting MALT1-dependent lymphomagenesis. This approach to targeting the MALT1 oncoprotein may have a therapeutic advantage over MALT1 protease inhibitors as it may avoid inflammation associated with selective MALT1 protease inhibition.

Paper # 2004/Young Investigator Award Recipient

PTEFB-DEPENDENT TRANSCRIPTION REORGANIZATION UNDERPINS THE GLIOMA ADAPTIVE RESPONSE TO RADIOTHERAPY

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Background: Dynamic regulation of gene expression is fundamental for cellular adaptation to exogenous stressors. The functional endpoint of epigenetic signaling is the productive transcriptional elongation by RNA polymerase II (Pol II) at the appropriate genomic loci. PTEFb-mediated promoter proximal pause-release of Pol II is a conserved regulatory mechanism for synchronous transcriptional induction best described in response to heat shock, but this pro-survival role has not been examined in the applied context of cancer therapy.

Objectives: To characterize the scope and kinetics of transcriptional mechanisms underpinning the adaptive response to ionizing radiation (IR) in order to define specific regulators or cofactors amenable to therapeutic disruption.

Design/Method: In order to examine the dynamics of chromatin reorganization following radiotherapy, we performed a combination of ChIP-, ATAC-, and RNA-seq in model systems of diffuse intrinsic pontine glioma (DIPG) and other pediatric high-grade gliomas (pHGG) following IR exposure. We interrogated IR-induced gene expression in the presence or absence of PTEFb blockade, including both mechanistic and functional consequences of concurrent inhibition or genetic depletion. We utilized culture models with live cell imaging to assess the therapeutic synergy of PTEFb inhibition with IR, as well as the therapeutic index of this intervention relative to normal controls. Finally, we employed orthotopic models of pHGG treated with conformal

radiotherapy and CNS-penetrant PTEFb inhibitors in order to assess tolerability and anti-tumor effect *in vivo*.

Results: Rapid genome-wide redistribution of active chromatin features and PTEFb facilitates Pol II pause-release to drive nascent transcriptional induction within hours of exposure to therapeutic ionizing radiation. Concurrent inhibition of PTEFb imparts a transcription elongation defect, abrogating canonical adaptive programs such as DNA damage repair and cell cycle regulation. This combination demonstrates a potent, synergistic therapeutic potential agnostic of glioma subtype, leading to a marked induction of tumor cell apoptosis and prolongation of xenograft survival.

Conclusion: These studies reveal a central role for PTEFb underpinning the early adaptive response to radiotherapy, opening new avenues for combinatorial treatment in these lethal malignancies. In conjunction with our collaborators, this data will collectively form the basis for a phase 1, first-in-children trial of PTEFb inhibition in pediatric gliomas.

Paper # 2005

DEFINING THERAPEUTIC VULNERABILITIES OF PERSISTER CELLS IN HIGH-RISK NEUROBLASTOMA

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Background: High-risk neuroblastoma is a pediatric cancer arising from the developing sympathetic nervous system with a 50% relapse rate that is typically fatal. At least two subpopulations of neuroblastoma cells were previously described that can transdifferentiate, adrenergic and mesenchymal, the latter being more resistant to chemotherapy. Nevertheless, mechanisms of therapy resistance remain largely unknown.

Objectives: Identify and characterize the malignant cellls that are responsible for relapsed high-risk neuroblastoma.

Design/Method: We used single nucleus RNA and ATAC sequencing to identify and characterize the cells that survive chemotherapy, termed here “persister cells”, from a cohort of 20 matched diagnostic and post-induction chemotherapy high-risk neuroblastoma patients and two patient derived xenograft (PDX) models from diagnostic tumors. Confirmatory functional studies using flow cytometry, small molecule inhibition and Western Blot were performed in eight representative cell lines derived from neuroblastomas at diagnosis and treated with standard-of-care chemotherapy. An RNA-seq dataset of 153 high-risk neuroblastoma patients was used to validate key pathways.

Results: Residual malignant cells in the post-chemotherapy tumor samples clustered into three

main groups separated by response to therapy. The most prevalent group of persister cells in responders (N=16) displayed low MYC(N) activity even in the presence of *MYCN* amplification. This group also demonstrated decreased expression of the adrenergic core regulatory circuit genes including *PHOX2B, ISL1, HAND2*, along with marked activation of TNF-alpha via NF-kB signaling. We validated decreased expression of *MYCN* (2-fold decrease, $p<0.0001$) and *PHOX2B* (3.1-fold decrease, $p<0.0001$) in PDXs following chemotherapy. MYCN protein levels were decreased and nuclear p65 levels were elevated in cell lines that survived chemotherapy. Downstream targets of NF-kB, including BCL-XL, were upregulated in persister cells in 12 of 16 responding tumors from high-risk patients. BCL-XL protein levels were elevated in cell lines following chemotherapy. Furthermore, combining chemotherapy with pharmacologic inhibition of I-kappa-kinase 2 (ML120B) resulted in increased killing of persister cells.

In addition, we classified 153 diagnostic high-risk neuroblastomas as predominantly adrenergic or mesenchymal using RNA-seq, showing that mesenchymal tumors were enriched with NF-kB pathway activation signatures. We then validated high nuclear p65 levels in 3 untreated mesenchymal cell lines. Finally, key genes of the mesenchymal signature (CD44, VIM) were upregulated in patient tumors following chemotherapy.

Conclusion: NF-kB signaling is increased in mesenchymal neuroblastoma subpopulations, induced by chemotherapy, and mediates *de novo* and acquired chemotherapy resistance in high-risk neuroblastoma. We postulate that concomitant silencing of this pathway and/or key downstream targets such as BCL-XL could eliminate persister cells and prevent disease relapse.

Paper # 2006

ARMED ONCOLYTIC ADENOVIRUS AS EXPERIMENTAL THERAPY FOR PEDIATRIC MALIGNANT GLIOMAS

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Background: Despite radiation and chemotherapy, Diffuse Intrinsic Pontine Glioma (DIPG) are the most lethal brain tumors in children. New treatment modalities are urgently needed. Our group has just finished a phase-I trial for naïve DIPG using Delta-24-RGD adenovirus (NCT03178032). The trial showed that the administration of oncolytic viruses is safe and resulted in prolonged OS, but failed to induce complete remission in a percentage of the children. GITR and OX-40 are potent T-cell activators. For that reason, we generated Delta-24-GREAT and Delta-24-RGDOX—encompassing GITRL and OX-40L, respectively— in the backbone of Delta-24-RGD. We hypothesized that the combination of T-cell activators and oncolytic viruses will result in a robust anti-tumor immune response.

Objectives: Characterize the anti-tumor effect of Delta-24-GREAT and Delta-24-RGDOX and determine the mechanisms of action.

Design/Method: We used murine (NP53, XFM, PKC) and human (TP54, TP84, DIPG IV) DIPG cell lines. Infectivity assay was determined using Ad-GFP-RGD adenoviral vector. We examined the in vitro expression of viral ligands, and the replication properties and cytotoxic activity of the armed viruses. DIPG cells were orthotopically implanted in the pons of mice. The armed oncolytic virus was injected intratumorally. Mice were followed for survival. Flow cytometry was used to examine the tumor microenvironment.

Results: Adenovirus infected more than 80% of the murine and human DIPG cells. Dose escalation experiments showed decreased viability with increasing doses of oncolytic viruses. The infection transduced efficiently GITRL and OX-40L in more than 80% of the treated cells. NP53-bearing mice showed increased survival and 30% of long-term survivors (P=0.003, median OS PBS 25.5 days vs 35.5 days for treated mice). In agreement with these data, the survival of XFM tumor-bearing mice was prolonged upon the infection with Delta-24-RGDOX (P=0.018, median OS PBS 9 days vs 12.5 treated mice). Finally, flow cytometric analyses of the treated tumors showed increased frequency and activation of T-cell populations. Challeging experiments showed the development of an anti-tumor immune memory.

Conclusion: Delta-24-GREAT and Delta-24-RGDOX infect, replicate in, and kill glioma cells. Infection is followed by the transduction of the T-cell activators GITRL and OX-40L. Furthermore, Delta-24-RGDOX treatment displayed a superior anti-DIPG activity than parental virus and it was mediated by enhanced antitumor immune response. Our data should propel the development of clinical study to test the safety and efficacy of oncolytic viruses armed with GITRL and OX40L in patients with DIPG.

Paper # 2007

NOVEL THERAPY FOR CYTARABINE-RESISTANT AML UTILIZING THE COMBINATION OF AZD5991 AND ONC213

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Background: Resistance to cytarabine (AraC)-based chemotherapy is the main cause of treatment failure in acute myeloid leukemia (AML). Thus, new effective therapies against AraC-resistant AML are needed. The anti-apoptotic Bcl-2 family protein Mcl-1 and oncoprotein c-Myc are overexpressed in AML, associated with AraC resistance, disease relapse, and poor prognosis. Therefore, targeting Mcl-1 and c-Myc in AraC-resistant AML is a rational therapeutic option. Moreover, recent studies have demonstrated that AraC-resistant AML cells rely on oxidative phosphorylation (OXPHOS). Thus, targeting OXPHOS may represent another rational approach to combat AraC-resistant AML cells. AZD5991 is a selective Mcl-1 inhibitor and has shown efficacy in AML. Our preliminary studies demonstrated that knockdown of Mcl-1 or inhibition of c-Myc significantly enhances the antileukemic activity of AZD5991 against AML. Thus, the combination of AZD5991 with a therapeutic agent that downregulates Mcl-1 and c-Myc should enhance the antileukemic activity of AZD5991. ONC213 is a novel imipridone which downregulates Mcl-1 and c-Myc.

Objectives: To determine the *in vitro* and *in vivo* antileukemic activity of combined ONC213 and AZD5991 in AML cells with either intrinsic or acquired resistance to AraC.

Design/Method: The proposed study focuses on *in vitro* antileukemic activity of this novel combination against AraC-resistant AML cells and the underlying molecular mechanisms of action. We use MTT assays to measure viable cells, Annexin V/Propidium iodide (PI) staining and flow cytometry analysis to measure cell apoptosis, western blotting to measure protein levels, and Seahorse influx analyzer to measure OXPHOS.

Results: We found that Mcl-1 and c-Myc proteins were upregulated or unchanged in AraC-resistant AML cell lines. These resistant cell lines had decreased or no deoxycytidine kinase (dCK). ONC213 suppressed Mcl-1 and c-Myc in these AraC-resistant cell lines and could modestly overcome AraC resistance only in the presence of dCK. In contrast, ONC213 significantly and synergistically enhanced AZD5991-induced apoptosis in these cells. Knockdown of Mcl-1 significantly enhanced AZD5991-induced apoptosis which was further enhanced by c-Myc inhibition.

Conclusion: ONC213 synergistically enhances AZD5991-induced apoptosis in AraC-resistant AML cells mediated by suppression of both Mcl-1 and c-Myc. Studies are underway to determine the role of OXPHOS in the synergistic antileukemic activity of ONC213 and AZD5991 against AraC-resistant AML cells and *in vivo* efficacy of this promising combination therapy. The results of this study will form a solid foundation for the clinical evaluation of this promising combination therapy to combat AraC-resistant AML in children, which may also be applicable to AML in adults.

Paper # 2008

ENRICHMENT OF HIGH-RISK INNATE IMMUNE CELLS IN HISPANIC AND BLACK CHILDREN WITH B-ALL

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Background: Black and Hispanic children with B-acute lymphoblastic leukemia (B-ALL) experience worse outcomes compared to their non-Hispanic white (NHW) counterparts. Immune-based therapies have improved the outcomes of children with B-ALL, however, impact of racial/ethnic background on immune microenvironment is less studied.

Objectives: Characterize the immune microenvironment in the bone marrow (BM) of pediatric patients with B-ALL at diagnosis and evaluate differences in immune landscape based on race/ethnicity.

Design/Method: BM from 61 children with newly diagnosed B-ALL(Hispanic=21, Black=17, NHW=23) was obtained via the Aflac Biorepository. High-dimensional analysis was performed

utilizing single cell mass cytometry with 61 markers to characterize T, NK and myeloid cells. Data was analyzed using Cytobank and high-dimensional visualization platforms such as ViSNE. Clinical data including self-reported race/ethnicity and NCI-risk classification were obtained for all samples.

Results: Multi-dimensional analysis was carried out for each cell population to dissect race/ethnicity-associated differences. ViSNE clustering of NK cells identified 3 different NK populations, including a distinct population of mature CD57+ NK cells with $Tbet^{hi}$, $HLADR^{hi}$, $granzymeB^{hi}$, CD27- phenotype. The distribution of NK subsets was highly impacted by race/ethnicity. Hispanic (H) patients had higher proportions of CD57+ mature NK cells when compared with other cohorts, (40 ± 4% vs 33 ± 2%; p=0.03) with pronounced differences apparent within standard risk (SR) patients. H-SR had higher proportion of CD57+ NK cells compared to other SR patients (mean H-SR 43.4 ± 5.87% vs 26.3 ± 2.87% p= 0.0049). ViSNE clustering of myeloid cells identified 5 clusters based on patterns of cell surface markers, including a distinct $CD11c+CD16+DR^{hi}$ inflammatory/non-classical myeloid population. Further analysis showed that NHW-SR patients have significantly lower proportions of CD16+DR+ myeloid cells compared to Hispanic, Black and NHW-HR patients (mean NHW-SR 3.67 ± 2.56% vs Others 10.8 ± 7.87% p= 0.0394). Notably, a phenotypically similar population has recently been implicated in leukemic progression in preclinical models (Witkowski et al, Cancer Cell 2020). In contrast to innate cells, T cell clusters were broadly comparable between different racial/ethnic cohorts.

Conclusion: These studies provide detailed single-cell proteomic analysis and highlight the impact of racial/ethnic background on immune microenvironment in pediatric B-ALL. Our data identify differences in innate immunity with enrichment of high-risk immune-populations in Hispanic and Black children and depletion of inflammatory myeloid populations in NHW-SR children with B-ALL. These variations may contribute to the observed differences in outcomes and may impact the application of immune therapies in racial/ethnic subsets.

Paper # 2009

MTHFR POLYMORPHISMS ARE ASSOCIATED WITH DECREASED METHOTREXATE TOLERANCE IN PEDIATRIC ALL

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Background: Methotrexate (MTX) forms a critical component in the treatment of pediatric acute lymphoblastic leukemia (ALL). MTX, through its action on the folate metabolic pathway, interferes with DNA and protein synthesis, thereby exerting it's antileukemic effects. MTHFR is an enzyme that serves as the rate limiting step within this pathway and there is evidence that certain MTHFR single nucleotide polymorphisms alter physiologic responses to MTX, including drug toxicity.

Objectives: To assess the effect of MTHFR genotype on tolerance to MTX.

Design/Method: We performed a retrospective analysis of pediatric patients treated at our institution from January 2012 to March 2021 to assess correlation between different MTHFR genotypes and MTX induced toxicities. We examined tolerance to MTX, specifically maximum tolerated oral MTX doses during maintenance, maximum tolerated Capizzi MTX (C-MTX), and MTX clearance times during high dose MTX (HDMTX). We also examined the frequency MTX-associated toxicities.

Results: Within our study population, 47 out of 242 patients were tested for MTHFR SNPs, with 33/47 demonstrating the commonly studied polymorphisms, C677T and A1298C. Of these, 9 were heterozygous for the C677T polymorphism, 9 were homozygous for the C677T polymorphism, 6 were heterozygous for the A1298C polymorphism, none were homozygous for the A1298C polymorphism, and 9 were heterozygous for both the C677T and A1298C polymorphisms. Patients with MTHFR genotypes including homozygous C677T and compound heterozygous C677T/A1298C demonstrated significantly decreased tolerance to oral MTX as demonstrated by decreased maximum tolerated MTX dosing relative to control (11.9 ± 9.5 vs. 19.9 ± 7.5 mg/m^2, $p < 0.05$ and 11.4 ± 6.1 vs. 19.9 ± 7.5 mg/m^2, $p < 0.01$, respectively). In contrast to this observation, only patients with the homozygous C677T genotype showed significantly decreased tolerance to C-MTX (174 ± 89 vs. 285 ± 90 mg/m^2, $p<0.05$). There were no genotypes associated with lengthening or shortening of clearance times in response to HDMTX. Clinically significant MTHFR genotypes were likely to be detected in the presence of myelosuppression (OR= 5.4, 95% CI 1.3-17.5, $p< 0.02$), but no other known MTX adverse effects demonstrated predictive ability. Lastly, no genotypes were associated with increased risk of developing MTX leukoencephalopathy or thrombosis.

Conclusion: MTHFR genotypes including homozygous C677T and compound heterozygous C677T/A1298C are associated with decreased tolerance to MTX and increased myelosuppression. Further exploration is needed to determine if reduced dosing of MTX is warranted to minimize toxicity.

Paper # 2010

REAL-WORLD OUTCOMES FOR PEDIATRIC PATIENTS AGED <3 YEARS WITH R/R ALL TREATED WITH TISAGENLECLEUCEL

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Background: Real-world outcomes with tisagenlecleucel in children and young adults with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL) are similar to those observed in clinical trials (John, Blood, 2021; Pasquini, Blood Adv, 2020). Although patients <3 years of age were excluded from clinical trials, successful leukapheresis and manufacturing have been demonstrated in this age group (Willert, Blood, 2021). Real-world clinical outcomes for these patients are reported here.

Objectives: Report clinical outcomes from the CIBMTR registry for patients <3 years at time of request for tisagenlecleucel.

Design/Method: Patients received tisagenlecleucel in the USA after August 30, 2017. Efficacy and safety were assessed at each reporting center in patients with ≥3 months' follow-up. Efficacy outcomes included complete response (CR), duration of response (DOR), event-free survival (EFS) and relapse-free survival (RFS). Adverse events of interest included cytokine release syndrome (CRS), neurotoxicity and infections.

Results: As of September 8, 2021, 47 patients were infused, with median age 20.4 months (median age at diagnosis: 6.7 months; 51.1% female; median weight: 10.3 kg). Indication was primary refractory disease in 17% of patients; relapsed in 57.4%. Pre-infusion, disease status was morphologic CR in 25.5% (19.1% MRD-negative). 34.0% of patients had ≥5% bone marrow blasts; 78.7%, *KMT2A*-rearrangement; no patients had Down syndrome. Prior treatment included alloSCT (19.1%), blinatumomab (12.8%) and inotuzumab (6.4%). Most patients (78.7%) were transplant-naïve.
Median age at leukapheresis was 18 months (range, 3–35; N=44, 3 patients with missing data); median, 1 day of leukapheresis. There was one manufacturing failure, which was successful upon repeat. Median dose, $2.4x10^6$/kg CAR+ T-cells; viability 89.8%. Median time from apheresis to infusion: 46 days (diagnosis to infusion: 251).

In the efficacy set (N=38; median follow-up: 23.8 months), 76.3% of patients had CR within 100 days. Three-month DOR and RFS were 79.9% (median not reached for either); EFS, 65.2% (median 9.7 months).

In the safety set (N=41; median follow-up: 23.1 months), 63.4% experienced CRS within 100 days (Grade ≥3: 7.3%; median time to onset: 6.5 days; median duration: 6 days) and 12.2% neurotoxicity (7.3%; 9 days; 8 days). Three patients experienced seizures. All neurotoxicity resolved. Clinically significant infections within 100 days were reported in 39.0%. Two deaths were reported within 30 days, both due to progressive disease.

Conclusion: Registry data reveal high rates of durable response and a favorable safety profile in patients <3 years with R/R ALL treated with tisagenlecleucel. Data stratified by age and body weight will be presented.

Funding: Novartis.

Paper # 2011

SCD25 AND FERRITIN LEVELS BEST DISTINGUISH CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome that is caused by underlying genetic defects or occurs secondary to triggers which lead to a distinct constellation of features. Current diagnostic criteria are based on enrollment criteria established for the HLH-2004 clinical study despite their unknown sensitivity or specificity. Both delayed diagnosis and misdiagnosis can be detrimental to patient outcomes.

Objectives: Validate the discriminatory power of the HLH-2004 parameters using a large cohort of curated controls and patients with confirmed HLH.

Design/Method: We gathered a cohort of control patients with HLH features and compared it to a cohort of patients with confirmed HLH (fulfilling ≥5 HLH-2004 diagnostic criteria or a known genetic defect). Controls included patients younger than 21 years without diagnosis of HLH or leukemia, and in whom a CBC, ferritin, and one additional HLH-related parameter was obtained within a narrow time window at Cincinnati Children's Hospital from 2010-2020. Peak/nadir values from a range of clinical and laboratory parameters obtained within 14 days of presentation were assessed. Patients presenting with fever were defined as intermediate pretest probability controls. Patients who had soluble CD25 (sCD25, sILR2a) levels examined were defined as high pretest probability controls. Peak values were compared to peak baseline values in patients treated for HLH.Receiver-operating curves were used to identify the most useful diagnostic parameters. Cutoff points were derived from the highest Youden-index point. Results were validated using patients with known genetic defects, the gold standard for diagnosis.

Results: We identified 18,204 potential controls, 907 intermediate pretest probability controls, and 321 high pretest probability controls. Hemoglobin, platelet count, absolute neutrophil count, sCD25, ferritin, triglycerides, and fibrinogen showed significant discriminatory ability (area under the curve (AUC) ≥0.7) between the HLH cohort and both control groups. The individual parameters with the greatest discriminatory power were sCD25 (AUC of 0.89) and ferritin (AUC of 0.95 when compared to intermediate pretest probability controls and 0.94 when compared to high pretest probability controls). Discriminatory ability further improved with a combined elevation of sCD25 and ferritin (AUC 0.96). Optimized thresholds of sCD25 and ferritin were higher than HLH-2004 cutoffs in each analysis. Moreover, when comparing controls to genetically diagnosed patients, sCD25 had the highest discriminatory power with an AUC of 0.96 and with ferritin, a combined AUC of 0.98.

Conclusion: Of the current HLH-2004 criteria, sCD25 and ferritin are the strongest individual diagnostic markers. Diagnostic power further improves with combined elevation and higher, optimized threshold values.

Paper # 2012

THE IMPACT OF TIME-TO-ANTIBIOTIC DELIVERY IN PEDIATRIC CANCER PATIENTS WITH FEBRILE NEUTROPENIA

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Background: Time-to-antibiotic (TTA) is defined as the time between patient presentation to a medical center with febrile neutropenia (FN) and any intravenous antibiotic administration. A TTA benchmark of <60 minutes is a metric set by U.S. News and World report, and compliance directly impacts pediatric oncology program rankings. Seeking to meet this metric has the potential for inferior care including inappropriate choice of antibiotics for severely neutropenic patients and use of painful intramuscular injections.

Objectives: To assess whether shorter TTA leads to fewer adverse outcomes in pediatric cancer patients with FN.

Design/Method: Pediatric cancer patients diagnosed 2006-2013 at a single institution were identified, and episodes of severe FN were abstracted. Inclusion criteria for FN episodes included fever (≥38.0°C), central line presence, not already on intravenous antibiotics, and an absolute neutrophil count (ANC) <500 cells/µl. TTA was evaluated both as a continuous variable and nominally (over/under 60 minutes). Continuous variables were compared using Wilcoxon Rank Sum test, and nominal variables were compared using Pearson's Chi square/Fisher's exact test. Primary outcomes included intensive care unit (ICU) admission, vasopressor support, death, length of hospital stay, need for bolus intravenous fluids (by 6 or 24 hours), or new oxygen requirement.

Results: Of 706 FN episodes, 4 (0.6%) required immediate ICU admission at presentation with a median TTA of 18 minutes (range 11-25 minutes). The remaining 702 episodes had a median TTA of 68.5 minutes (interquartile range [IQR] 46-106, range 4-793), and 39.7% were given antibiotics in <60 minutes. ICU care was required ≤6 hours in 0.6%, ≤24 hours in 2.1%, and ≤7 days in 3.3%. Continuous and nominal TTA were not associated with ICU admission at any time, and ICU patients had shorter TTA at all time points. Vasopressor support within 7 days occurred in 2.4%. TTA was shorter in the vasopressor group (61 vs. 69 minutes), and vasopressor support was not associated with TTA. Mortality during the FN episode occurred in 0.6%. TTA was shorter for those who died (median 51.5 vs. 69 minutes), and mortality was not associated with TTA. Length of stay, bolus intravenous fluid administration, and new oxygen requirement within 7 days were also not associated with TTA. Blood stream infections occurred in 17%, and when assessing all outcomes in this population, there were no associations with TTA.

Conclusion: We did not observe that shorter TTA, particularly at the 60-minute timepoint, improves clinical outcomes. Alternative metrics are instead needed to better define quality of care.

Paper # 2013

THE COST-EFFECTIVENESS OF HYDROXYUREA FOR SICKLE CELL DISEASE AMONG CHILDREN IN SUB-SAHARAN AFRICA

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Background: Globally, the burden of sickle cell disease (SCD) disease is concentrated (75%) in Sub-Saharan, Africa (SSA). Mortality rates (50% to 90%) are high among children with SCD in SSA, due to limited resources. Reductions in complications associated with disease are well

established with hydroxyurea (HU) use among children with SCD in SSA despite limited adoption of HU.

Objectives: To conduct a cost-effectiveness analysis (CEA) of HU treatment compared to standard of care (SOC) for children with SCD in SSA. The perspective of the analysis was the Angola Ministry of Health.

Design/Method: We developed a Markov model with microsimulation utilizing real-world data (RWD) obtained from the published literature. Heath state monthly transitions consisted of: SCD symptom free; vaso-occlusive; acute chest syndrome (ACS)/ pneumonia; blood transfusion; hospitalization; and a death state (final). Health utilities and costs were in quality-adjusted life years (QALYs) and United States Dollars (USD), respectively. Hypothetical patients had a starting date at birth and were followed for 10 years using a cycle time of one month. The willingness-to-pay threshold (WTP) was set at $20,000 USD. Outputs included, incremental cost-effectiveness ratio (ICER) of HU compared to SOC. A one-way sensitivity analysis was performed to assess uncertainty.

Results: HU was found to decrease costs -$3,628 and increase QALYs, 1.8 per patient compared to SOC from a total of 1 million simulated patients. This translated to an ICER of -$2,016/ QALY. Mean monthly times within the symptom free health state increased by 71% for HU compared to control, resulting in a reduction among deleterious health states: vaso-occlusive (-87%)*;* ACS/ pneumonia (-90%); transfusions (-94%); and hospitalizations (-95%). HU was expected to decrease costs and increase QALYs in 95% of simulated patients. A one-way sensitivity analysis varying costs of HU treatment by low, high, and neutral, all increased effectiveness by 1.8 QALYs and maintained the cost-effectiveness-ICERs (-$3,185/QALY; -$789/ QALY; and $86/ QALY), respectively.

Conclusion: HU was a cost-effective treatment, expected to reduce costs and increase QALYs, for SCD in Angola, Africa. HU treatment is a noninvasive modality that can improve survival and reduce complications associated with disease. Despite limited resources, investment in HU may have a substantial cost-effective impact on the mortality among newborns and children with SCD. Results from our analysis may help inform policymakers on resource allocation to reduce the burden of SCD.

Paper # 2014

EARLY HYDROXYUREA USE MAY BE NEUROPROTECTIVE IN CHILDREN WITH SICKLE CELL ANEMIA

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Background: Sickle cell anemia (SCA)-related neurocognitive dysfunction begins early and affects executive functioning and attention. Evidence suggests hydroxyurea may be neuroprotective, but is limited to children who began therapy well after the onset of cognitive decline. In 2014, Cincinnati Children's (CCHMC) began treating children as young as six months;

these children offer a unique population to evaluate the effects of the early introduction of hydroxyurea on neurocognition.

Objectives: To compare the neurocognitive status of children with SCA who initiated hydroxyurea before five years to an unaffected, matched cohort and to historically treated patients to assess whether hydroxyurea may be neuroprotective.

Design/Method: We completed a cross-sectional analysis of the neurocognitive status of our SCA population. Children >3 yo with SCA were enrolled in two cohorts: 1) children with SCA (HbSS or HbS-beta^{0}thalassemia) who began hydroxyurea <5 yo and 2) children with SCA who did not qualify for the first cohort (on hydroxyurea or chronic transfusions (CTT)). Unaffected controls (patients' siblings or from CCHMC primary care clinic) were matched to each child in the first cohort by age, race, and sex. All participants completed the NIH Toolbox: Cognition Battery, a shortened neuropsychological evaluation (mean 100, SD 15).

Results: We enrolled 30 patients into the first cohort with 31 matched controls (early hydroxyurea: mean age 7.2 +/- 3.1 years, 50% female). The traditionally-treated SCA cohort included 20 patients (mean age 15 +/- 5.1 years, 70% female). There were no differences in age, sex, patient or maternal education, and Area Deprivation Index (socioeconomic status) between the early hydroxyurea and control cohorts. The early hydroxyurea patients and controls scored no differently on the composite cognition (86 +/- 13 versus 87 +/- 14, $p = 0.6$); conversely, the early hydroxyurea patients scored significantly higher than the traditionally-treated cohort on the composite cognition (versus 77 +/- 14, $p = 0.03$). On a linear regression model, age ($p < 0.001$) and patient education ($p = 0.04$) were significantly correlated with cognition with all included. When limited to patients with SCA on hydroxyurea, age ($p < 0.001$) and patient education ($p = 0.006$) remained significant; maternal education ($p = 0.07$), hemoglobin ($p = 0.07$), and fetal hemoglobin ($p = 0.07$) approached significance.

Conclusion: Children with SCA are disproportionately at risk for poor academic performance from their disease process. If started early and maintained during brain development, hydroxyurea may be neuroprotective. Our data provide further evidence to support hydroxyurea's universal prescription for all children with SCA.

Paper # 2015

SURGICAL REVASCULARIZATION REDUCES STROKE RISK IN SICKLE CELL DISEASE AND MOYAMOYA SYNDROME

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Background: Cerebral revascularization surgery (CRS) is a widely used treatment to reduce stroke in patients with Moyamoya disease, an idiopathic progressive cerebral vasculopathy. Patients with sickle cell disease are known to develop moyamoya syndrome, which confers a high risk for stroke,

despite chronic transfusion therapy. These patients have limited proven treatments options to reduce stroke. Recent studies have suggested that CRS may be a safe and effective therapy to reduce risk of cerebrovascular complications in patients with sickle cell disease and moyamoya syndrome (SCD-MMS) but have been limited by small sample size and lack of a control group.

Objective: To investigate whether revascularization surgery reduces the risk of cerebrovascular events (CVEs) in comparison to conservative management alone in a retrospective cohort of children with SCD-MMS.

Design/Method: Sickle Cell Disease Programs offerning both hematological and neurosurgical treatment were recruited. A retrospective review of data of patients with SCD-MMS (≤18 y.o.) was performed. Detailed information on sickle cell disease course, stroke and surgical histories were extracted. The incidence of CVEs (stroke and TIAs) between patients treated with surgical revascularization was compared to those with conservative management alone. Multivariate regression models were generated and logistic regression analyses were performed.

Results: A total of 141 patients with SCD-MMS were studied. 78 (55.3%) were treated with conservative management and revascularization surgery (Surgery group) and 63 (44.7%) were treated with conservative management alone (Conservative group). Compared to the Conservative group, patients in the Surgery group had an earlier onset of moyamoya diagnosis, worse baseline mRS scores and a greater proportion of patients with a history of CVEs before the start of treatment. Despite these, patients in the Surgery group had reduced odds of developing a CVE over the duration of their risk period (odds ratio = 0.27, 95% CI: 0.08-0.94, P = .040). Furthermore, when comparing patients in the Surgery group during their pre-surgical periods and post-surgical periods, patients had markedly reduced odds of developing a CVE after surgery (odds ratio = 0.22, 95% CI = 0.08-0.58, P = .002). 7 patients (8.9%) developed adverse events related to surgery..

Conclusion: This multicenter retrospective study provides strong evidence that revascularization surgery can reduce the risk of CVEs, can be performed safely and is a viable treatment option to reduce stroke in patients with sickle cell disease and moyamoya syndrome. Prospective studies will be needed to futher validate these findings.

Paper # 2016

THE CLINICAL RESPIRATORY SCORE: ASSESSING ACUTE CHEST SYNDROME SEVERITY RISK IN SICKLE CELL DISEASE

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Background: Acute chest syndrome (ACS) remains a leading cause of morbidity and mortality in children with sickle cell disease (SCD). The NHLBI-sponsored Comprehensive Sickle Cell Centers developed a clinical severity index (CSI) to retrospectively classify the outcome of an episode of ACS by clinical features and interventions needed. At our institution, a clinical respiratory score (CRS) was developed for monitoring hospitalized patients with SCD with or at risk for ACS. The

CRS ranges from 0-12, and is determined by a set of objective clinical findings. Per our clinical algorithm, a CRS ≥4 warrants consideration of ICU transfer. During an ACS episode, it would be useful to have a clinical tool that could predict severe ACS. The utility of the CRS in predicting the severity of an episode of ACS has not been established.

Objectives: To identify the relationship between an institution-developed CRS and the CSI. We hypothesize that there is a significant association between pediatric patients with ACS who have peak CRS ≥4 during a hospitalization and having an outcome of severe of worse per the ACS CSI.

Design/Method: We performed a retrospective chart review of patients with SCD (any genotype) admitted to Texas Children's Hospital with ACS between 2015 and 2021. Patients were aged 3-21 years, had ICD-10 codes related to ACS, and had documented CRS scores. Peak CRS was defined as the maximum CRS during admission. CSI designations were converted into a numeric score: Mild = 1, Moderate = 2, Severe or Very Severe = 3. CRS and CSI scores were analyzed using Chi-squared and simple regression tests.

Results: We identified 205 patients who met inclusion criteria. The mean age was 10.5 years (SD 4.9), 55.1% were male, 89.8% identified as Black/African American, and 8.3% identified as Hispanic. Mean and median CRS for the cohort were 1.5 (SD 1.4) and 1.0; mean and median CSI were 1.7 (SD 0.6) and 2.0. There was a significant association between peak CRS ≥4 and a CSI = 3 (OR 8.82 [95% CI 2.87 – 24.24], p <0.001). Similarly, there was a statistically significant, but weak correlation between peak CRS and CSI scores across the population (r^2 0.22 [95% CI 0.16 – 0.27], p <0.001).

Conclusion: Peak CRS during an ACS admission is associated with ACS outcome (CSI), and a CRS ≥4 may suggest an increased risk of severe or very severe ACS. Patients with CRS ≥4 may warrant additional interventions to prevent severe outcomes.

Paper # 2024

SIGNIFICANCE OF THE INSURANCE AUTHORIZATION SYSTEM & THE IMPACT ON A HEMATOLOGY ONCOLOGY SERVICE

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Background: Limited data exists on prior authorizations (PAs) and the impact on medical care for pediatric patients as compared to adults. The PA process not only impacts patients financially but also health-care systems. It is estimated that $631 million a year is spent on PAs. The purpose of this study is to evaluate the PA process. Pediatric oncology patients, in particular, require strict treatment adherence as it is crucial for survival.

Objectives: To evaluate the frequency of PAs completed, non-physician time spent completing PAs, frequency of PAs requiring peer-to-peer evaluation, estimated cost for non-physician/physician time spent on completing PAs, and number of PAs resulting in delay of medical care.

Design/Method: A prospective study evaluating PA requests of pediatric patients (0-28 yrs.) followed in the hematology oncology division at our institution for either a hematology and/or oncology diagnosis over 6 months (August 2021 to February 2022). A PA form, as standard of care, was created to ensure appropriate documentation. The PA form was completed by the department's insurance coordinator and/or the physician who completed a peer-to-peer evaluation. A preliminary analysis of data was performed with final analysis to be completed in February of 2022.

Results: A total of 111 PAs were completed at the time of the analysis. Non-chemotherapy medications were the most frequent PAs (52/119) followed by chemotherapy (44/119). The median time (min.) for non-physician completion of medication PAs was 50 min. The total non-physician time spent to complete 111 PAs was 109 hours. The total non-physician cost was $1 847.27. Of the cohort, 97 PAs (87%) were approved, whereas 14 (13%) were declined. Of the PAs declined, 8 (57%) required peer-to-peer evaluation. All peer-to-peer evaluators were non-pediatric trained (100%). The mean physician time spent completing a peer-to-peer was 16 min. The total physician cost was $232.21. Two PAs were denied after peer-to-peer evaluation (25%), resulting in delay of medical care. Change in clinical management occurred in 4 patients (29%). One limitation included imaging PAs that were completed as per a separate hospital protocol. We suspect denial in PAs would have been more robust if imaging was included.

Conclusion: PAs require a significant time spent by non-physician staff. A non-pediatric trained physician can impact a decision resulting in delay of medical care, overall impacting the morbidity of a pediatric patient. In a small cancer center similar to ours with on average 40 new diagnoses/year, a change in clinical management occurring 20% of the time is significant.

Paper # 2025

TARGETING CD70 USING CAR-NK CELLS TO ENHANCE NK CELLS CYTOLYTIC EFFECT AGAINST OSTEOSARCOMA

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Background: Osteosarcoma (OS) is the most common primary malignant bone tumor among pediatric patients. Effective chemotherapy regimens for refractory OS are scarce, accounting for no improvements in patient survival. Therefore, novel therapies are needed. Although our understanding of the antigenic landscape of OS is nascent, emerging knowledge suggests that CD70 is a viable candidate. CD70 is a transmembrane protein that activates T cells and is hypothesized to cause T-cell exhaustion in solid tumors. CD70 is expressed in primary OS bone tumors with higher expression in lung metastases, the main cause of death in these patients. Pre-clinical studies using an anti-CD70 antibody (ARGX-110) demonstrated indirect anti-tumor effects mediated by NK cells. We hypothesize that direct tumor antigen targeting using specific chimeric antigen receptor (CAR)-Natural Killer (NK) cells directed against CD70 could improve NK cell

cytolytic activity against OS.

Objectives: To evaluate if CD70 directed CAR-NK cells will enhance the therapeutic effect of adoptive transferred NK cells against OS.

Design/Method: Analysis of the cBioportal database (https://www.cbioportal.org) confirmed CD70 expression in OS. Flow cytometry was used to determine surface expression of CD70 on several human OS cell lines (SJSA, OS-17, LM7, CCH-OS-D) and normal human osteoblasts. CD70 CAR constructs were sequenced, verified and transduced into NK cells by collaborators. CD70 CAR-NK cells cytolytic activity against OS-17 cells as compared to NK cells was evaluated by incubating the CD70 CAR-NK cells with OS-17 cells at various effector to target (E:T) ratios. *In vitro* cytokine release was measured upon CD70 CAR-NK cells exposure to OS cells (IsoPlexis).

Results: Database analysis confirmed CD70 gene amplification in sarcomas including OS as compared to other tumors. Flow cytometry demonstrated variable expression of CD70 (MFI) on OS cells and no CD70 expression on human osteoblasts. The cytotoxicity assay revealed an increase in percent lysis at the highest E:T ratios compared to control NK cells. Higher CD70 expression did not correlate with increased cytolysis as cytolysis of CCH-OS-D (lowest CD70 expression) was also achieved. We found a predominant release in the MIP-1a, MIP-1b, and IFN-g cytokines upon OS-17 exposure to CD70 CAR-NK cells.

Conclusion: CD70 is an attractive target with immunotherapy potential against OS. We showed that CD70-CAR NK cells are effective against OS cells *in vitro* compared to control NK cells. CD70-CAR NK killing does not correlate with an increased level of CD70 expression. Increased MIP-1a, MIP-1b, and IFN-g suggest increased CD70-CAR NK cells effector activity and may explain the increased cytolytic effect.

Paper # 2026

COMBINATION AURORA KINASE A AND CDK2 INHIBITION IN RHABDOMYOSARCOMA

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Background: Rhabdomyosarcoma (RMS) is an aggressive childhood cancer for which new therapies are needed. The cyclin-dependent kinases CDK4 and CDK2 regulate cell cycle progression, and are frequently activated and/or overexpressed in RMS. Aurora Kinase A (AURKA) is a cell cycle kinase important in mitosis and cytokinesis, and is overexpressed in RMS. Inhibition of AURKA has been reported to induce cancer cell senescence and polyploidy.

Objectives: We hypothesized that combined inhibition of CDK2/CDK4 and AURKA will be effective in tumor suppression of RMS cells and more effective than either agents alone.

Design/Method: We used the human RMS cell lines, RD and Rh30, and their derived xenografts in immunocompromised NOD-SCID mice, to evaluate the effects of kinase inhibition on RMS cell proliferation, apoptosis, and tumor growth. We also investigated pathways potentially contributing to the drug effects through protein analysis.

Results: Dual inhibition of CDK2 and CDK4 in RMS cell lines showed a significant effect on increased RMS cell death, decreased progression through S-phase, and increased senescence markers. AURKA inhibition also significantly inhibited RMS cell proliferation, and resulted in a increase in polyploid cells. However, this effect was partially alleviated in combination therapy using CDK2/CDK4/AURKA triple inhibition. We therefore reasoned that inhibition of CDK4 may be arresting cells in G1, protecting them from effects of AURKA inhibition. Indeed, reverting to a dual combination of AURKA inhibitor and CDK2 inhibitor alone, we observed a significant effect on cell proliferation arrest and cell senescence. Combination CDK2/AURKA inhibition led to persistent effects on cell numbers, with more effective inhibition of tumor cell survival even after withdrawal of treatment. Dual combination inhibition led to less polyploid cells as compared to AURKA inhibition alone, and arrest of cells in G2/M to a higher extent that with either agent alone. Western blot analysis showed that, as expected, AURKA inhibition increased Cyclin B2 and p21 levels, demonstrating cell cycle arrest in mitosis. Treatment of mice bearing rhabdomyosarcoma xenografts showed significantly improved tumor control in mice treated with the dual combination, comapred to either agent alone. No excess toxicity was observed *in vivo* using dual inhibition.

Conclusion: Utilizing preclinical tumor models, we show that dual CDK2 and AURKA inhibition was more effective than either drug alone in treating RMS tumor cells, both *in vitro* and *in vivo*. Further work is ongoing to validate these combinatory targets in additional preclinical RMS models, and assess downstream pathways impacted by treatment.

Paper # 2027

INCREASED MORBIDITY IS ASSOCIATED WITH INITIAL PARTIAL SHAVE BIOPSY OF PEDIATRIC MELANOCYTIC TUMORS

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Background: Pediatric melanoma accounts for 2-3% of pediatric cancer and is the most common form of skin cancer in children. Appropriate treatment of localized melanoma relies on accurate staging which is largely based on the Breslow thickness of the primary tumor. Although the American Academy of Dermatology recommends excisional biopsy for suspicious skin lesions, partial shave biopsies are often performed in children. Shave biopsies can transect the base of a melanocytic tumor, negatively impacting accurate microstaging, prognostic evaluation, and therapy planning.

Objectives: Evaluate diagnostic biopsy methods in patients with cutaneous melanocytic lesions and their impact on staging, diagnosis, and treatment.

Design/Method: Retrospective analysis of pediatric patients treated for cutaneous melanocytic lesions from 2014 to 2021 at the University of Pittsburgh Medical Center. Variables included patient demographics, biopsy method, presence of positive deep/lateral margins, compromise of microstaging, extension of wide local excision or sentinel lymph node biopsy, need for skin graft, and final diagnosis.

Results: Data was analyzed for 103 patients with lesions that ranged from atypical with unknown malignant potential to melanoma. Of the 103 patients, 55 were female and 48 male with an age range of 1-22. Shave biopsy was performed in 66% of patients, punch in 19%, excisional in 14% and snip in 1%. Of all patients with positive margins, 75% had a positive deep margin and 92% of those patients had an initial shave biopsy. In patients with compromised microstaging due to positive deep margin, 89% had shave biopsy compared to 0% in punch. Twelve patients underwent a larger wide local excision of the primary tumor and seven had sentinel lymph node biopsy due to compromised microstaging, all underwent shave biopsies. Three out of 12 patients with larger excisions required a skin graft and hospital admission. Of patients who had a shave biopsy with compromised microstaging, 44% had a final diagnosis of melanoma compared to 33% in excisional and 0% in punch.

Conclusion: Pediatric patients with suspicious cutaneous melanocytic lesions frequently had shave biopsy as their initial diagnostic evaluation. There was a higher incidence of positive deep margins and compromised microstaging after shave biopsy compared to alternative methods. Increased morbidity associated with definitive surgical management was observed only in the shave biopsy group, including larger wide local re-excisions, skin grafts, hospital admission, and sentinel lymph node biopsy. These findings suggest that patients with shave biopsy had a higher incidence of altered care due to compromised microstaging requiring more invasive surgical treatment.

Paper # 2028

PREVALENCE AND RISK FACTORS FOR PULMONARY EMBOLISM IN PEDIATRIC SICKLE CELL DISEASE.

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Background: Patients with sickle cell disease (SCD) have a high risk for venous thromboembolism (VTE). An adult SCD study identified higher rates of pulmonary embolism (PE) (0.44%) as compared to age and race-matched controls (0.12%) (1). In the general pediatric population, the estimated PE rates are 0.058-0.064% (2). Slightly over half of pediatric PE cases are associated with a deep vein thrombosis (DVT) (3). Studies examining prevalence and risk factors for PE in children with SCD are lacking.

Objectives: Describe the prevalence of PE in children with SCD and identify potential risk factors associated with PE using a nationwide administrative claims data from Pediatric Health

Information System (PHIS).

Design/Method: Children with SCD between 0-21 years of age from January 2010 to June 2021 were included. PE was identified using International Classification of Diseases (ICD)-9 or 10 codes and confirmed with documentation of either an anticoagulant or PE-related imaging study. SCD, DVT and risk factors such as obesity, pregnancy, acute chest syndrome (ACS), Central nervous system (CNS) vasculopathy were identified using ICD codes. Billing codes were used to identify presence of central venous line (CVL), apheresis, use of hormonal therapy, anticoagulants and hydroxyurea. Logistic regression analysis was performed to assess association between risk factors and PE.

Results: We identified 22,631 unique patients with SCD with a median age of 10.8 years (range: <0.1-20.9) from PHIS. A total of 120 (0.53%) patients developed a PE with median age of 17.4 years (range: 6.6-20.9). A concurrent diagnosis of ACS was documented in 58% of patients with PE. Prior history of CVL, recurrent ACS (> 1 episode prior to PE diagnosis), hydroxyurea use, older age, CNS vasculopathy, apheresis, number of total hospital and ICU admissions were significantly associated with PE on bivariate logistic regression analysis. The diagnosis of DVT was significantly more common among patients with admissions for PE compared to those without PE (28% vs 0.6%; p<.0001).

Conclusion: The prevalence of PE in children with SCD is 0.53%. Over half of these patients had ACS at time of diagnosis of PE (58%) and 28% had DVT. Factors significantly associated with PE such as prior history of CVL, recurrent ACS, use of hydroxyurea, older age, CNS vasculopathy, apheresis and number of total number of hospitalizations suggest that the risk for PE in SCD is related to the severity of disease state.

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Paper # 2029

THE EFFECT OF HEMOGLOBIN ON OXIDATION OF HMGB1 AND PLATELET ACTIVATION

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Background: Inflammation plays a key role in propagating the pathogenesis of hemolytic diseases. Patients with elevated cell-free hemoglobin (Hb) are at significantly higher risk of thrombosis, which can lead to life-threatening complications such as pulmonary emboli and stroke. On a cellular level, it is well established that in hemolytic states, platelet activation is elevated and correlates with hemolysis, and that platelet activation stimulated by Hb is driven by mitochondrial reactive oxygen species (mtROS) generation. However, the contribution of inflammatory signaling to platelet activation and its cross-talk with hemolysis remain unknown. High-mobility group box 1

(HMGB1), an inflammatory mediator released by cells, has been shown to be elevated in sterile inflammatory conditions and to stimulate platelet activation. Notably, the ability of HMGB1 to mediate platelet activation is dependent on the oxidation state of critical cysteine residues in the protein.

Objectives: We hypothesize that in hemolytic conditions, Hb and its derivatives oxidize HMGB1 to increase platelet mtROS production leading to platelet activation.

Design/Method: Recombinant HMGB1 was incubated in vitro with metheme derived from Hb and quantified by spectroscopy. Carbonyl groups attached to protein side chains on HMGB1 were derivatized to 2,4-dinitrophenylhydrazone (DNP-hydrazone) and quantified by Western blot immunodetection. Protein oxidation of HMGB1 was quantified by signal intensity of DNP ab (OxyBlot protein oxidation detection kit, Millipore) co-localized to signal from anti-HMGB1 ab (Biolegend). Platelets were isolated from the whole blood samples of human participants, and platelet activation was measured by flow cytometry using PE antibody to GPIIb (CD41) to mark platelets and APC to detect exposure of surface CD62P (p-selectin) upon activation. Platelet mtROS were estimated using MitoSOX Red and fluorescence spectroscopy. Data was analyzed using FlowJo software and nonparametric statistical tests.

Results: We found that exposure of HMGB1 to metheme produced a 4-fold increase in the oxidation signal of HMGB1 compared with untreated HMGB1. Additionally, the presence of cell-free Hb in solution with HMGB1 significantly enhanced HMGB1-mediated platelet activation in a dose-dependent manner as the concentration of Hb increased (P=0.0211). We confirmed that treatment of isolated human platelets with Hb or with HMGB1 each independently increased platelet mtROS production by 2-fold (P=0.0004) and 4-fold (P=0.0008), respectively. Scavenging mtROS using MitoTEMPO attenuated platelet activation by HMGB1 + Hb by 2-fold.

Conclusion: Together, these studies suggest a mechanism of synergy between hemolysis and inflammatory and redox signaling in potentiating platelet-driven thrombosis.

Paper # 2030

STANDARDIZED THROMBOPROPHYLAXIS PROTOCOL IN MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

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Background: Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) exhibit laboratory evidence of hypercoagulability and are at risk of experiencing thrombotic complications. We developed and implemented a standardized multidisciplinary treatment approach which encompassed a thromboprophylaxis protocol and a computerized clinical decision support system including a provider order set to guide and unify practice. In high-risk patients defined as critically ill and/or having additional risk factors for thromboembolism, prophylactic-

dose enoxaparin (target anti-Factor Xa of 0.1–0.3 U/mL) was added.

Objectives: To evaluate impact of implementation of a standardized thromboprophylaxis protocol in hospitalized patients with MIS-C.

Design/Method: We conducted a retrospective study of patients who were admitted to our center between March 2020 and December 2021 with confirmed MIS-C based on Centers for Disease Control and Prevention case definition. Relevant data were extracted from prospectively maintained institutional databases and the electronic medical records and were summarized using descriptive statistics. Key outcome measures included frequency of objectively confirmed venous and/or arterial TE during hospitalization and within 30 days after discharge and frequency of major bleeding and/or clinically relevant nonmajor bleeding (CRNMB) defined according to the International Society on Thrombosis and Haemostasis criteria.

Results: A total of 136 patients (59 females, median age 8 years) with confirmed MIS-C were included in this study. Forty-five patients (33%) were ≥12 years of age. Of 136 patients, 124 patients (91%) required intensive care unit (ICU) stay and 64 patients (47%) required a central venous catheter for a median duration of 5 days [Interquartile range (IQR) 4-7]. The median total hospital and ICU length of stays were 11 days [IQR 6-14] and 3 days [IQR 2-6], respectively. Prophylactic-dose enoxaparin was initiated in 119 patients (88%) who were deemed high-risk per our protocol at a median of 1 day after admission [IQR 0-3] achieving target levels at a median of 1 day [IQR 1-2]. The median first anti-Factor Xa level was 0.13 u/mL [IQR 0.05-0.19]. Only 1 patient (0.7%) developed symptomatic non-catheter related superficial vein thrombosis requiring therapeutic anticoagulation. There were no other TEs encountered in our cohort. Bleeding events occurred in 5 patients (4.2%). All bleeding events were considered CRNMB (gastrointestinal bleeding in 4 patients and epistaxis in 1 patient). There were no mortalities.

Conclusion: Implementation of an institutional standardized thromboprophylaxis protocol in patients with MIS-C was feasible and led to timely initiation of prophylactic anticoagulation and low rates of TEs and bleeding complications.

Paper # 2031

CRISPR TARGETING OF SBDS IN MAMMALIAN CELL LINES REVEAL INCREASED TP53/CDKN1A AND SLOW GROWTH

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Background: Shwachman-Diamond syndrome (SDS) is an inherited bone marrow failure syndrome associated with a significant risk for transformation to myeloid neoplasia. Biallelic mutations in the Shwachman-Bodian-Diamond-Syndrome (*SBDS*) gene account for 90% of cases and result in impaired ribosomal assembly. The molecular pathogenesis of SDS and its transformation to neoplasia in some patients is poorly understood. Based on RNA-Seq and western blotting analysis in our zebrafish model of SDS (*JCI Insight*, 2020), we hypothesize that stress

responses that lead to metabolic reprogramming cause the syndrome and its neoplastic complication.

Objectives: Characterize the biochemical pathways involved in pathogenesis of SDS using CRISPR-Cas9 edited *SBDS* mammalian cell lines.

Design/Method: We created *SBDS* knockdown HeLa cell line using CRISPR genome editing. We designed our guide RNA to create indels in exon 2, which would approximate the K62X truncations in *SBDS*. We analyzed the expression of *TP53* pathway markers and lipid metabolism markers in the edited cell lines using real-time polymerase chain reaction (RT-PCR).

Results: While we did not identify any clones with complete knockout of *SBDS*, we did isolate clones with less than 10% protein expression. We correlated decreased *SBDS* protein expression with a 3-fold decrease in cellular growth rate. Doubling time was 36 hours in the *SBDS* knockdown clones compared to 22 hours in parent cell. *TP53* showed a 4-fold increase while *CDKN1A* showed a 12-fold increase in the clone with 90% reduction of *SBDS* relative to parental cells. We observed a 2.5-fold increase in *BAX,* and corresponding decrease in MDM2. These results were similar to those in the zebrafish KO model published by our group in 2020. Interestingly, unlike the *sbds* $^{-/-}$ zebrafish, we observed a 2-fold decrease in *FASN, PPARG* and *SREBP1* in the clones relative to the parental cell.

Conclusion: To our knowledge, we generated the first mammalian cell line deficient in *SBDS* based on CRISPR. Levels of *CDKN1A* and *TP53* were significantly increased in *SBDS* knockdown clones, which would lead to cell cycle arrest and slow growth as observed in these clones. We found a decrease in markers of lipid metabolism, which could be due to lack of fatty acids in the tissue culture media, unlike zebrafish which are fed a lipid-rich diet. We are currently creating other mammalian cell lines using our CRISPR /Cas9-mediated genome editing model, which can be used to provide new insights into the pathogenesis of SDS and validate biochemical findings in other experimental systems such as zebrafish and yeast.

Poster # 001

ANALYSIS OF BLOOD TRANSFUSION REACTIONS IN A TERTIARY CARE CENTER: A RETROSPECTIVE ANALYSIS

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Background: Transfusion of blood components such as packed red blood cells, platelets, fresh frozen plasma and cryoprecipitate is very commonly encountered in pediatric practice. Although it is considered a life-saving treatment and is an essential part of treatment for critically ill patients, it may be complicated by various transfusion reactions like allergic, anaphylactic, acute hemolytic, delayed hemolytic, febrile non-hemolytic, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), bacterial contamination, disease transmission and reactions unrelated to transfusions. Here we present analysis of blood transfusion reactions over a 5

year period at a pediatric tertiary care center.

Objectives: This study aimed to determine the frequency and type of acute adverse reactions in children receiving transfusions.

Design/Method: A retrospective analysis was conducted using blood bank records of Children's Hospital of Michigan, where we examined all transfusion reaction evaluations documented during a 5-year-period spanning from January 1, 2016 till December 31, 2020.

Results: During the 5-year period of 2016-2020, 44,799 transfusions were given at our hospital, (27959 pRBCs, 10719 platelet units, 4479 FFP and 1788 cryoprecipitate units). There were 223 transfusion reactions reported during this time (0.50%). Of these, 104 were allergic/anaphylactic (0.23% of all transfusions), and the rest were nonspecific reactions, febrile non-hemolytic, transfusion-associated circulatory overload and delayed hemolytic reactions. TRALI, acute hemolytic transfusion reaction and bacterial sepsis were not encountered. The risk of for an allergic/anaphylactic reaction was highest for platelet units (0.38%) and FFP (0.36%) as compared to pRBCs (0.16%, p= 0.001). Reactions occurred despite premedication in 42%. Skin, airway and respiratory findings were seen in 96%, 14% and 36% of the allergic reactions, respectively. None of the allergic reactions were fatal, and all resolved within 24 hours.

Conclusion: In this study of pediatric transfusions, we observed acute transfusion reactions in <1% of transfusions. Allergic reactions comprise an important share of these reactions and are seen more often with platelet and FFP transfusions. The role of premedications in preventing allergic reactions remains controversial as allergic reactions can occur even after premedications.

Poster # 002

SAFETY OF AMOTOSALEN-UVA PATHOGEN REDUCED PLATELETS IN THROMBOCYTOPENIC PEDIATRIC PATIENTS

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Background: Platelet (PC) transfusion is a critical supportive therapy for pediatric patients with risk of transfusion-transmitted infection (TTI). Amotosalen-UVA pathogen reduction (PR) of PC is FDA approved for patients of all ages to reduce the risk of TTI.

Objectives: To conduct a subset analysis of pediatric patients enrolled in a Phase 4 study of PRPC.

Design/Method: An open-label prospective sequential cohort study compared the safety of PRPC with conventional PC (CPC) for adults and children with hypoproliferative thrombocytopenia requiring PC support up to 21 days with 7 days surveillance after last PC. The CPC cohort was enrolled first followed by the PRPC cohort without crossover and with matched primary therapy stratification. This subset analysis only included enrolled children (≤ 18 years of age). The primary

endpoint was the incidence of treatment emergent assisted mechanical ventilation (TEAMV). Secondary endpoints included treatment emergent acute respiratory distress syndrome (ARDS) by a blinded adjudication panel, TEAMV for clinically significant pulmonary adverse events (CSPAE = CTCAE Grade ≥ 2), CSPAE, peri-transfusion AE, transfusion reactions (TR), and mortality.

Results: By intention to treat (ITT) analysis 1068 PRPC and 1223 CPC patients were enrolled including 207 pediatric patients (38 PRPC and 169 CPC). For all patients the cumulative incidence of TEAMV was reduced for PRPC versus CPC (2.9% vs 4.6%, p = 0.039). PRPC pediatric patients (0/38) had less TEAMV than CPC patients (11/169, p =0.11). There were no differences in the following outcomes: mean PRPC transfusions, 4.8±4.9 versus 6.6±6.7 (CPC), p=0.217, adjudicated ARDS for PRPC versus CPC (0%, 1.4% p = 0.454), CSPAE for PRPC (5.9%) versus CPC (8.0%, p = 0.653). The incidence of adjudicated TEAMV for CSPAE was numerically less for PRPC (0% versus 2.4% for CPC: 95% CI: -4.7%, -0.1%, p = 0.061). The overall incidence of AE was not different for PRPC (34.2%) versus CPC (42.0%), (p = 0.394). Acute TRs were not significantly different for PRPC and CPC cohorts (8.8% versus 11.6%), (p = 0.656). Serious AEs were not different between PRPC and CPC cohorts (15.8% versus 16.6%), (p = 0.883). AEs resulting in death were not different between PRPC and CPC cohorts (2.6% versus 4.7%, p = 0.658).

Conclusion: In this Phase 4 study, PRPC trended towards reduced TEAMV in children with hypoproliferative thrombocytopenia, and no safety signals were observed. The small sample size limits generalization of these findings. Larger post market experience is required for definitive conclusions.

Supported by a grant from Cerus.

Poster # 003

TO PREMEDICATE OR NOT? A CLOSER LOOK AT PREMEDICATIONS FOR BLOOD PRODUCT TRANSFUSIONS AT MSK KIDS

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Background: Blood product transfusions are a common supportive care measure among pediatric oncology patients during therapy. Though uncommon, some patients have transfusion-related adverse reactions. Such reactions range in severity and include mild, allergic; febrile, non-hemolytic; hemolytic; and anaphylactic reactions. In an attempt to reduce transfusion reactions, many patients are prophylactically premedicated with antipyretics, antihistamines, and/or corticosteroids. However, the use of premedications remains controversial as it is not always evidence-based and leads to significant practice variability, unnecessary treatments, and additional costs.

Objectives: Our goal was to analyze current blood product premedication practices at MSK Kids.

Design/Method: We conducted a retrospective single-institution review of all pediatric patients treated at MSK Kids who received a blood product transfusion from January to April 2021. Patients with a history of complex transfusion reaction(s) were excluded. Data extracted included: demographics, type of transfusion (platelet and/or red blood cell (RBC)), prior history of transfusion reaction(s), premedication(s) administered prior to current transfusion (acetaminophen, antihistamine, and/or hydrocortisone), and signs/symptoms of transfusion reactions. Descriptive statistics were used for analysis.

Results: Of 116 MSK Kids patients who received a blood product transfusion between January and April 2021, 112 met inclusion criteria. Median age at transfusion was 8.2 years (range 0.6 – 17.8) with 44.6% (n=50) female patients. Each patient received a median of 3 transfusions (IQR 2-7). There were a total of 603 transfusions, of which 52.2% (n=315) were platelets and 47.7% (n=288) were RBCs. Premedications were given for 434 (72.0%) transfusions: acetaminophen only (n=77), diphenhydramine only (n=11), or a combination of 2 or more medications (n=346). 34 patients had a previous history of a transfusion reaction; 212/217 (97.7%) transfusions in these patients were premedicated. 78 patients did not have a history of a previous transfusion reaction; 222/386 (57.5%) transfusions in these patients were still pre-medicated. 19/603 (3.2%) transfusions resulted in a reaction. Reactions included: rash/pruritus (n=17), fever (n=6), respiratory symptoms (n=3), and/or hypotension (n=1). No transfusions led to anaphylaxis. There was no difference in the incidence of transfusion reactions between those that were premedicated (3.2%) versus those that were not (3.0%). None of the transfusion reactions led to severe sequelae or admission to the intensive care unit.

Conclusion: Despite the low overall incidence of transfusion reactions in our cohort, most patients still received premedication, even without a history of transfusion reactions, with no clear benefit. Standardization of an evidence-based algorithm and provider education is needed for blood product transfusion premedication in pediatric oncology patients.

Poster # 004

TRANSFUSION-RELATED HYPERKALEMIA AFTER ERYTHROCYTAPHERESIS IN PATIENTS WITH SICKLE CELL DISEASE

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Background: Erythrocytapheresis is one of the few treatment options for patients with sickle cell disease that can significantly reduce morbidity and mortality by decreasing the amount of hemoglobin S in the patient's blood. The procedure typically consists of removing some of the patient's blood (using apheresis) and then transfusing multiple units of sickle-negative, leuko-reduced, non-irradiated, and phenotypically matched red cell units. Hyperkalemia is one potential complication of transfusion of multiple red cell units. The high levels of potassium in stored red cell units can contribute to post-transfusion hyperkalemia, as can several other factors such as impaired renal function, irradiation of unit, age of unit, and total volume of units used.

Objectives: Due to the life-threatening nature of hyperkalemia, we elected to evaluate for post-apheresis hyperkalemia in this patient population.

Design/Method: This observational study focused on patients with sickle cell disease maintained on long-term erythrocytapheresis. Serum potassium levels were measured prior and immediately after each erythrocytapheresis session. In addition, potassium levels were measured from stored red cell units previously. We also recorded patient information including age, sex, serum creatinine level and volume of red cell units received during each procedure.

Results: A retrospective chart review for 28 patients were performed between November 2020 to July 2021. A total of 86 timepoints for pre- and post- apheresis potassium levels were obtained. Prior testing on stored red cell units with CPDA-1 showed potassium levels ranging 6.6-8.5 mmol/L on day 8 of storage. However, as shown in the graph below, there were no significant changes noted in pre- and post- apheresis serum potassium levels. Various blood volumes were used (range: 640-2300 mL) and we found no correlation between volume of red cell units used and potassium levels measured post- procedure. In addition, each patient was noted to have normal serum creatinine levels prior to each erythrocytapheresis session.

Conclusion: While there have been case reports of transfusion- related hyperkalemia in pediatric patients, to date, little has been published that evaluate hyperkalemia in patients with sickle cell disease undergoing erythrocytapheresis. Despite the high potassium load from red cell units, there is a rapid redistribution of potassium without laboratory evidence of hyperkalemia at the completion of the procedure. This data shows that potassium levels in patients with sickle cell disease maintained on erythrocytapheresis remain stable and are not adversely affected. This provides further reassurance that routine monitoring of potassium levels post erythrocytapheresis is not necessary.

Poster # 005

INTRODUCING A BIOPHYSICAL PLATELET FUNCTION PANEL TO INVESTIGATE BLEEDING OF UNKNOWN CAUSE

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Background: A subset of patients with chronic bleeding remain undiagnosed and even after extensive diagnostic evaluation are labeled as "bleeding of unknown cause" (BUC). The key barrier to treating these patients is that they have a clinical bleeding tendency in the presence of normal diagnostic tests, and optimal methods for monitoring and treating patients with BUC remain unknown.

Objectives: While patients with BUC have symptoms of a primary hemostatic disorder, there is no diagnostic test or biomarker that can accurately identify which patients are at risk for bleeding. In order to fill this diagnostic gap and address the clinical need for more assays of platelet function,

we have engineered a biophysical platelet function panel of assays.

Design/Method: We have engineered multiple new biophysical assays to assess disorders of primary hemostasis to potentially define new bleeding disorders and characterize platelet phenotypes in patients with BUC. Our panel collectively enables us to simultaneously assess different facets of primary hemostasis from the microscopic level of single-platelet physiology to hemostatic plug formation, thereby capturing various aspects of platelet function with a single blood sample. Our panel ranges from platelet adhesion and bulk clot contraction assays to spatially-regulated platelet granule secretion assays, single-platelet contraction cytometry, microfluidics, and a microengineered vascularized bleeding model. As such, we are leveraging these assays to correlate platelet function with bleeding phenotype severity and establish the dynamic range of this diagnostic panel.

Results: In studying BUC, we have begun to characterize biophysical platelet signatures and cellular phenotypes. Using the bulk clot contraction assay to measure kinetics, we demonstrated over time that there was an overall 10% decrease in contraction than that of a healthy control. Additionally, platelets in BUC spread an average of 24% less on smaller microdot patterns using the spatially-regulated granule release assay. This suggests that there may be limitations in cytoskeletal extension or granule release in BUC. As such, our preliminary data supports the hypothesis that our assays collectively enable us to simultaneously assess different facets of primary hemostasis and platelet function in BUC.

Conclusion: The versatility of our biophysical assays in capturing platelet function allows for a thorough investigation into primary hemostatic disorders and BUC. Here we demonstrate the translational utility of our panel in providing a deeper understanding of platelet biophysics as it relates to BUC. As such, ongoing research is being conducted using our panel to investigate biophysical properties in BUC and correlate these properties with bleeding phenotype severity.

Poster # 006

PROGNOSTIC ROLE OF POSITIVE DIRECT ANTIGLOBULIN TEST IN PEDIATRIC IMMUNE THROMBOCYTOPENIC PURPURA

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Background: The most common cause of acute thrombocytopenia in otherwise healthy children is immune thrombocytopenia (ITP). Phases of disease are used to classify ITP into acute (<3 months of thrombocytopenia), persistent (between 3-12 months), and chronic (≥ 12 months). Although the majority of pediatric patients with ITP will have resolution, 20% will develop persistent thrombocytopenia refractory to first-line treatments. The International Working Group addressed standards for diagnostic approach recommendations in 2009 and advised that in addition to clinical data and traditional diagnostics (complete blood count, peripheral blood smear), direct antiglobulin test (DAT) and Rhesus (Rh) factor be obtained during initial evaluation. In a study by Kim et al., researchers demonstrated that independent of concurrent autoimmune hemolytic anemia, a positive DAT was associated with development of chronic ITP and use of second-line therapy, suggesting

that autoimmune dysregulation predisposes to development of chronic ITP. We sought to evaluate the prognostic role of a positive DAT test in pediatric ITP.

Objectives: 1) To evaluate the relationship between a positive DAT and development of persistent or chronic ITP in pediatric patients. 2) To determine the prognostic role of a positive DAT and use of second-line agents for pediatric ITP.

Design/Method: A retrospective chart review of patients treated at Norton Children's Cancer Institute with a diagnosis of ITP between 2016 and 2020.

Results: A total of 114 charts were reviewed, of which 42 met inclusion criteria. Of these, 5 had a positive DAT at time of diagnosis. Of the positive DAT cohort, 2 developed persistent ITP, and 3 developed chronic ITP. None of the patients with positive DAT at diagnosis remained acute. Of the patients with negative DAT at diagnosis, 24 remained acute, and 13 developed persistent or chronic ITP. The association between positive DAT and persistent or chronic ITP was statistically significant (P=0.0101). Of the positive DAT cohort, 2 required use of second-line therapy. Of the negative DAT cohort, 6 required use of second-line therapy. The association between positive DAT and use of second-line therapy was not statistically significant (P=0.2368).

Conclusion: A positive DAT at time of ITP diagnosis is significantly associated with development of persistent or chronic ITP but not with second-line agent use.

Poster # 007

TWO-YEAR OUTCOMES OF OLIPUDASE ALFA THERAPY IN CHILDREN WITH CHRONIC ACID SPHINGMYELINASE DEFICIENCY

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Background: Acid sphingomyelinase deficiency (ASMD) is a rare debilitating lysosomal storage disease with no approved treatment. Deficient ASM activity results in progressive visceral, hematologic, and pulmonary dysfunction across a disease spectrum with onset from infancy to adulthood that includes central nervous system manifestations in the most severe patients. Disease awareness is low and diagnostic delays in children are common. Undiagnosed children with ASMD who have thrombocytopenia/bleeding issues may be referred to hematologists. Olipudase alfa, intravenous recombinant human ASM, is in late-stage development (Sanofi Genzyme) for the non-central-nervous-system manifestations of ASMD in children and adults. A 1-year open-label trial of dose-escalated olipudase alfa in 20 children with chronic ASMD (ASCEND-Peds, NCT02292654, primary outcome, safety) demonstrated significant clinical improvements. All 20 patients continue to be treated in a long-term study (LTS/NCT02004704).

Objectives: We report cumulative 2-year safety and efficacy outcomes in these 20 patients.

Design/Method: Two-year changes from baseline are reported as means ±SD.

Results: At baseline, age ranged from 1.7-17 years; mean spleen volume was 19.0±8.8 multiples of normal (MN); mean liver volume was 2.65±0.74 MN; mean platelet count was 137.74±62.32x10^9/L; mean percent-predicted carbon dioxide diffusing capacity (DL_{CO}) (n=9 children able to perform the test) was 54.79±14.23% and mean height z-score was -2.1±0.84. Olipudase alfa was generally well-tolerated; >99% of adverse events were mild or moderate. Four patients (three in Year-1; one in Year-2) had seven treatment-related serious adverse events. One infant had an anaphylactic reaction but was successfully desensitized and reached the target dose. One patient had increased alanine aminotransferase twice (both transient, asymptomatic); one had urticaria and rash; and one had two hypersensitivity reactions. No patient discontinued. During Year-2, splenomegaly and hepatomegaly further improved in all patients (n=19) (mean percent decrease in MN: 60.9%±8.7% and 49.0%±10.1%, respectively, P<0.0001) and percent improvements in platelet count were sustained (n=14) (28.7%±28.3% increase, P=0.0032). Mean percent-predicted DL_{CO} (n=9) continued to improve (46.6%±25.5% increase, P<0.0001). High-resolution-computed lung tomography scores for ground glass appearance, interstitial lung disease, and reticulonodular density (n=19) further improved (mean decrease of 0.44 ±0.50, 0.70±0.63, and 0.58±1.18, respectively). Mean height Z-scores (n=16) further improved (1.17±0.50 increase, P<0.0001). Improvements in atherogenic lipid profiles, abnormal liver function tests, and the plasma biomarkers lyso-sphingomyelin and chitotriosidase were sustained.

Conclusion: Clinical improvements noted at 1 year in the ASCEND-Peds trial of 20 children with chronic ASMD were sustained or amplified with no new safety issues after 2 years of olipudase alfa enzyme replacement therapy.

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Poster # 008

CLINICAL SPECTRUM OF DIAMOND-BLACKFAN ANEMIA, A SINGLE CENTER EXPERIENCE

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Background: Diamond-Blackfan anemia (DBA) is a rare congenital bone marrow failure syndrome, characterized by macrocytic anemia and reticulocytopenia. A sporadic or familial mutation in the genes responsible for ribosomal synthesis results in DBA. DBA is associated with failure to thrive, premature birth, growth retardation, cardiac anomalies, limb abnormalities, craniofacial abnormalities, renal anomalies, and increased risk for malignancy. Classical DBA presents as a transfusion dependent anemia in infancy, but presentation later in life is possible.

Objectives: The study aim was to understand the spectrum of presentation and outcomes of patients with DBA at a single institution.

Design/Method: A retrospective chart review of patients diagnosed with DBA from 2000 to 2020, at a tertiary care referral center.

Results: Twenty-nine patients were diagnosed with DBA over a twenty-year period. Median age at diagnosis was 2 months (mean 1.6 years, range 2 days to 15 years), with 10 patients (34.5%) presenting after infancy. Sixteen females (55.2%) were diagnosed. Congenital malformations included ten patients (35.7%) with cardiac defects, eleven (37.9%) with craniofacial abnormalities, three (10.7%) with limb abnormalities, and 16 (55.2%) with short stature. Diagnosis was after an illness in three patients (10.7%). All patients diagnosed after 2 years of age had congenital abnormalities noted prior the diagnosis of DBA. Laboratory values at diagnosis included average hemoglobin was 6.13 g/dL (range 1.7-12.1), average reticulocyte count 1.68% (range 0.1-2.6), and erythrocyte adenosine deaminase was elevated in 37.9% of patients (not available for 11 patients). Six patients have a family history of DBA, including a father and his two children and another sibling pair. Fifteen patients were found to have mutations in one of their ribosomal protein genes. Steroids +/- leucine were used as treatments for these DBA. Seventy-two percent were prescribed oral steroids during their therapy. Eighteen of patients (62.1%) required chronic transfusions. Three patients previously requiring chronic transfusions, were cured with hematopoietic stem cell transplant. Four patients had spontaneous remission. No patients progressed to malignancy.

Conclusion: This high volume of patients with DBA at a single center demonstrates a wide spectrum of phenotypic variability for age at presentation, steroid responsiveness, need for chronic transfusion, and spontaneous remission rate, even between individuals with the same genetic mutation. It is important to consider DBA in patients with unexplained macrocytic anemia, especially in patients with congenital abnormalities, even if presenting after infancy and not transfusion dependent. Wide range of presentations and clinical course make it challenging to formulate universal therapy guidelines.

Poster # 009

NEUROCOGNITIVE OUTCOMES AMONG PATIENTS WITH SHWACHMAN-DIAMOND SYNDROME

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Background: Shwachman-Diamond Syndrome (SDS) is a rare inherited bone marrow failure syndrome characterized by exocrine pancreatic dysfunction, skeletal abnormalities, infections and neurocognitive developmental issues. Data on cognitive, behavioral and adaptive functioning are limited for this disease.

Objectives: To understand the spectrum of cognitive, behavioral and adaptive functioning of SDS patients with biallelic mutations in the *SBDS* gene.

Design/Method: We performed a retrospective cohort study of 133 subjects with confirmed biallelic *SBDS* mutations enrolled on the Shwachman Diamond Registry and Study. To evaluate

neurocognitive outcomes, we analyzed education level, results of deveopmental testing, needed supplemental educational programs, school issues, therapy services, applicable developmental testing and work status.

Results: Highest education level data was available for 96 patients, with eight patients over 18 years of age having completed school at all levels including college and post-graduate training. For patients who required additional educational programing (n=89), special education was required by 39% (n=37), homebound school by 2% (n=3). Advanced placement programs were reported in 6% (n=6) of patients. Seventy-two patients were evaluated for an individualized education plan (IEP of which 50% required IEP services. School related issues were reported by 98% of families. Learning disability and problem concentrating were the most common issues observed (26%, n=28). Developmental testing was performed in 36% (n=34) out of 97 patients, with delays and early development issues being the most commonly reported concerns (70.5%, n=24). No concerns on developmental testing were observed in 17.6% (n=6) of patients of patients who had had such testing. For the patients with available data on working status (n=65), a majority of patients (83%, n=53) were in school at their last follow-up visit. Of those who were at the appropriate age for work (>16 years old) and not attending school (n=13), 64% (n=7) were working full-time, 27% (n=3) were working part-time and only 9% (n=1) were unable to successfully find work. Additional neurological medical diagnoses were also queried within the registry and 22 patients had other concurrent diagnoses. Attention-deficit hyperactivity disorder was the most common disorder, observed in 45% (n=10) of patients. Neuroimaging findings were performed in 27 patients, and normal exam was the most commonly reported (48%, n=13), along with Chiari malformation (11%, n=3) and delayed myelination (11%, n=3).

Conclusion: Neurocognitive outcomes are variable among patients with SDS, 50% (n=49) of school-age patients did not require special education services. These data help inform the range of neurocognitive outcomes in SDS patients.

Poster # 010

EFFICACY/SAFETY IN CHILDREN ON 2/4-WEEKLY EMICIZUMAB PROPHYLAXIS: 52-WEEK OUTCOMES IN HAVEN 2

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Background: The phase III HAVEN 2 trial established the efficacy and safety profile of emicizumab prophylaxis in children with hemophilia A (HA). At primary analysis, median emicizumab exposure for the weekly dosing arm was 57.2 weeks. Two- (Q2W) and four- (Q4W) weekly dosing arms were added later, resulting in a shorter exposure at primary analysis (median 20.1 and 18.1 weeks, respectively).

Objectives: We present 52-week efficacy and safety data for Q2W/Q4W emicizumab prophylaxis in children with HA.

Design/Method: HAVEN 2 (NCT02795767) enrolled children with HA aged <12 years, with a history of high-titer inhibitors (≥5 BU/mL), previously receiving bypassing agents. Children with ongoing or planned immune tolerance induction therapy were excluded. Annualized bleed rates (ABRs) were calculated for treated bleeds using negative binomial regression.

Results: At the last patient visit (11 November 2020), children with HA receiving emicizumab Q2W (n=10) and Q4W (n=10) had a median exposure (range) of 67.1 (54.7–129.4) and 66.6 (8.1–140.4) weeks, respectively. Treated bleed ABRs (95% CI) were 0.2 (0.1–0.5; Q2W) and 1.8 (0.3–10.6; Q4W), with 70% (Q2W) and 60% (Q4W) of children experiencing zero treated bleeds. The numerically higher ABR for Q4W was mainly driven by two children: one with four target joint bleeds both in the 24 weeks prior to study entry and over approximately 28 weeks following study entry; the other developed Grade 3 neutralizing antibodies (nAbs) associated with loss of efficacy. This child had his dose up-titrated before withdrawing from treatment.
AEs occurred in 90% and 100% of children receiving emicizumab Q2W and Q4W, respectively, with 20% and 60% experiencing AEs related to emicizumab. Most (25/31, 80.6%) related AEs were injection-site reactions (ISRs), all of which were Grade 1–2. The remaining related AEs were three incidences of erythema in one child (Q4W; two occurred after up-titration), two of indeterminable blood type (Q2W and Q4W), and one case of Grade 3 nAbs (detailed above). Serious AEs occurred in 10% and 30% of children receiving emicizumab Q2W and Q4W, respectively. No thrombotic events or thrombotic microangiopathic events occurred.

Conclusion: Emicizumab Q2W/Q4W efficacy/safety outcomes for children in HAVEN 2 were consistent with QW dosing and the other HAVEN trials.

Acknowledgements: The HAVEN 2 trial was sponsored by F. Hoffmann-La Roche, Ltd. Third party medical writing assistance, under the direction of all authors, was provided by Phoebe Tate, MSc, of Ashfield MedComms, and was funded by F. Hoffmann-La Roche Ltd/Genentech, Inc.

Poster # 011

EMICIZUMAB PROPHYLAXIS IN INFANTS WITH SEVERE HEMOPHILIA A: MANAGEMENT OF 6 CASES

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Background: Over the last several decades, limitations of standard factor therapies for patients with severe hemophilia A (SHA) have led to the development of novel therapies. Emicizumab is a subcutaneously administered, bispecific monoclonal antibody that mimics factor VIII (FVIII) and has been shown to be safe and effective in the pediatric population. However, data regarding its use for prophylaxis in infants is limited.

Objectives: The objective of this study is to share the management of prophylaxis with emicizumab in infants with SHA.

Design/Method: Six infants with SHA on emicizumab were selected to comprise a descriptive case series.

Results: Two of the 6 cases were prenatally diagnosed based on family history. Despite the absence of bleeding episodes, both patients' parents were concerned about bleeding complications and emicizumab prophylaxis was started early in one (at 3 months of age) and a more typical age for prophylaxis initiation at 10 months of age, respectively. Case 3 was diagnosed with SHA at birth based on family history and was subsequently started on emicizumab at day 7 of life to treat a postnatal intracranial hemorrhage (ICH) following 7 days of factor therapy. Cases 4 and 5 were diagnosed with SHA after a severe post-circumcision bleeding necessitating treatment with FVIII. After extensive discussion regarding the risks for ICH in infants and the lack of data on emicizumab on infants, both were prescribed emicizumab at 5 weeks and 3 months of age, respectively. Case 6 was diagnosed with SHA after an ankle bleed. A high titer inhibitor was detected after a prolonged bleed following port replacement. Emicizumab prophylaxis was started at 11 months of age. Emicizumab was dosed at 3 mg/kg every two weeks as maintenance dosing for all cases. Five of the 6 cases did not have any bleeding episodes after the initiation of emicizumab prophylaxis. Case 4 had a shin hematoma which resolved after one dose of FVIII at 23 months of age. No safety issues were identified.

Conclusion: As a subcutaneous drug, emicizumab can be feasibly initiated shortly after birth or at any time during infancy. However, there is limited data on emicizumab prophylaxis in infants with SHA. Intracranial hemorrhage and other forms of major bleeding might occur in infants before the typical age at initiation of intravenous factor prophylaxis, suggesting a role for emicizumab in infants. These data demonstrate the efficacy and safety of emicizumab even when started at very young ages.

Poster # 012

THE IRON LADIES: HIGH PREVALENCE OF IRON DEFICIENCY IN WOMEN WITH BLEEDING DISORDERS

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Background: Iron deficiency (ID) is a major public health problem with physical and cognitive impairment in adolescent and adult women. Women with heavy menstrual bleeding (HMB) are at higher risk for ID, with HMB in over half of WBD, yet ID prevalence in WBD is unknown. Furthermore, no screening or treatment guidelines exist, and the literature suggests less frequent supplementation improves iron absorption.

Objectives: We aimed to describe screening practices for and management of ID in WBD by medical providers within hemophilia treatment centers (HTCs).

Design/Method: We collected data on practices related to screening and management of ID using electronic surveys distributed to medical providers who treat WBD within HTCs. We then abstracted data from 01/2015-12/2019 through the ATHNdataset, a de-identified national database, to determine prevalence and incidence of ID in WBD age 13-40 years.

Results: Responses were collected from 62 providers within 142 HTCs. Providers saw an average 70 WBD/year, with ID identified in an average 38 WBD/year. Screening is part of routine practice for 69.4% of providers, while 32.3% of respondents limit screening to women with bleeding symptoms. Oral or intravenous supplementation is prescribed by 96.8% and 80.6% of respondents, respectively. The most used oral supplement is ferrous sulfate, daily or alternate day dosing is employed by 54.8% and 51.6% of providers. Indications for IV supplementation include refractoriness (75.8%) or non-compliance with oral iron (69.4%). The most used form of IV iron is iron sucrose (43.5%). Repeat labs are obtained to monitor iron repletion by 96.8% of providers, typically after three months.

The ATHNdataset included 10 527 WBD meeting inclusion criteria. ID screening was completed in 1.21%-2.92% of women per year, and screening increased over time. Overall, 2.56% of WBD (n=270) had ID. Among women undergoing lab testing (n=375, 3.6%), ID was present in 58.62%-71.97%. WBD with ID were primarily white (77%), average age at initiation of the study was 19.7 years. Von Willebrand disease was the most common diagnosis among all age groups and races, and in women with ID (44.1%). There was no difference in percentage of women with ID by age.

Conclusion: Over half of screened WBD have ID. Yet, while all medical providers report screening for ID in WBD, only a minority of WBD undergo ID screening. As most of those screened have ID, our findings suggest ID screening should be performed in all WBD, and studies are needed to establish optimal treatment.

Poster # 013

ADAMTS13 LEVELS IN A PD FVIII CONCENTRATE: A POTENTIAL OPTION FOR PEDIATRIC PATIENTS WITH cTTP

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Background: Treatment of congenital thrombotic thrombocytopenic purpura (cTTP), a disease characterized by the deficiency of ADAMTS13, remains a challenge since the mainstay of therapy is the use of Fresh Frozen Plasma (FFP). No specific treatment is available yet. A few published reports highlight plasma-derived (pd) FVIII concentrates that proved to be efficacious for the off-label treatment of acute microangiopathy episodes and their prevention in cTTP. The successful use of FVIII plasma derived products in pediatric and juvenile cTTP patients was reported recently in a study involving 7 children diagnosed with cTTP, and in a further work reporting the administration of such drugs in an adolescent who was intolerant to FFP infusions. Among the different pdFVIII concentrates used/tested, Koate® was shown to have the highest content of

ADAMTS13.

Objectives: On the basis of this information, we decided to evaluate the levels of ADAMTS13 in several batches of Koate®, to evaluate its use as a potential option for possible replacement therapy in cTTP.

Design/Method: Eight Koate® lots were analyzed: 6 lots of 1000 IU /vial FVIII and 2 lots of 500 IU/vial). The determination of ADAMTS13 activity levels in the product were carried out by three different methodologies: a Fluorescence Resonance Energy Transfer (FRET) assay, a chemiluminescence test, and a chromogenic ELISA test. ADAMTS13 protein antigen levels were measured by means of a FRET technique as well. In addition, the activity and antigen of von Willebrand factor protein, contained within the concentrate, were determined using chemiluminescence assays. To increase the robustness of obtained results, qualification protocols were applied to the methods used in the characterization study.

Results: The results confirmed high levels of ADAMTS13 in all Koate® lots (n=8) analyzed, with antigen and activity levels respectively of 10.72 IU/ml ± 1.39 and 5.62 IU/ml ± 0.49.

Conclusion: Our results confirm literature findings showing the presence of ADAMTS13 at significant levels in Koate®, exhibiting a concentration 10 times higher and an activity 5 times higher compared to plasma levels (≈ 1 IU/ml). High content of ADAMTS13 in Koate® could help in restoring this protein to physiological levels, while providing the advantage of reduced infusion volume (as compared to FFP), thus possibly improving the quality of life, especially in pediatric patients allowing for home therapy. These findings and published case studies suggest that Koate® could be a potential candidate for the treatment of cTTP, warranting evaluation in a clinical trial

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Poster # 014

A PILOT STUDY OF APIXABAN AS SECONDARY PROPHYLAXIS OF VENOUS THROMBOEMBOLISM IN PEDIATRIC PATIENTS

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Background: Venous thromboembolism (VTE) is a major complication in hospitalized children and adolescents secondary to its association with increased morbidity and mortality. Historically, the standard of care for children and adolescents with primary VTE is the use of coumadin or low molecular weight heparin for secondary VTE prophylaxis. However, these medications require frequent laboratory testing and subcutaneous injections.

Novel oral anticoagulants (NOACs) are approved in adults for secondary VTE prophylaxis with established efficacy and safety. Apixaban, a selective inhibitor of FXa, has a rapid onset of action, few drug interactions and a predictable anticoagulant response that enables fixed dosing and does

not require injections or frequent monitoring.

Objectives: We hypothesized that secondary prophylaxis with apixaban (Eliquis®) would be feasible, safe, and prevent secondary VTEs in children and adolescents with a newly diagnosed primary VTE.

Design/Method: We conducted a phase II pilot open label study of apixaban as secondary VTE prophylaxis in children and adolescents. (NCT04041843)

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 (NCT04041843).

Participants had a chest CT angiogram and Doppler US of affected areas and anti-Xa levels were monitored throughout.

Results: Twenty-four patients have been enrolled. Thirteen patients had isolated new onset deep venous thrombosis, seven patients had isolated pulmonary emboli, and 4 patients had both DVT and PE upon study entry. Of the 20 patients with evaluable thrombi at day 30, 40% showed complete response and 45% showed a partial response. Patients with evaluable disease by day 90, 64% had a complete response with 32% of patients having a partial response.

Importantly, there were no patients that experienced a new VTE, which equates to 100% successful VTE secondary prophylaxis. There were no episodes of bleeding, (Grade I-IV hemorrhage CTCAE 4.0) and no patients required dose modifications.

Conclusion: Our results suggest that apixaban administered in children and adolescents with a primary VTE for secondary prophylaxis is feasible, is safe and well tolerated in children and adolescents for the secondary prophylaxis of patients with a newly diagnosed primary VTE and no adverse events of bleeding reported. Apixaban secondary prophylaxis resulted in 100% prevention of secondary VTE. Multiple studies are underway establishing the safety and efficacy of apixaban in the pediatric population hopefully leading to it's eventual FDA approval.

Poster # 015

PERSISTENT PULMONARY EMBOLISM SYMPTOMS IN CHILDREN AND ADOLESCENTS

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Background: Pulmonary embolism (PE) is a rare thrombotic event in the pediatric population, however has increased in incidence over the past two decades. This increase is hypothesized to be due to a combination of increased diagnostic testing and an increasing population of medically complex children. As is the case with many uncommon pediatric conditions, the diagnostic and treatment strategies for pediatric PE are based on small pediatric studies or extrapolated from adult

data. A particular area that requires further investigation is the long-term outcomes of children with PE. The rates of persistent PE symptoms in children have not been examined.

Objectives: The goal of this study is to identify the incidence of persistent symptoms in pediatric patients following pulmonary embolism that prompt return to emergency care. This study also evaluates the frequency with which repeat computed tomography angiography (CTA) is obtained in patients with persistent symptoms, as well as the rate of PE recurrence.

Design/Method: A retrospective chart review of patients diagnosed with PE at the Children's Hospital of Pittsburgh from January 1, 2012-June 1, 2021 was completed. Data was collected from the initial PE presentation as well as any subsequent visits.

Results: Ninety-six patients were diagnosed with PE during the study period. Forty patients (42%) returned to the ED for recurrent or persistent symptoms at least once. A total of 110 return ED visits were identified, and 64 repeat CTAs were completed. Recurrent or worsening PE was identified in 8% of patients. Of these patients, two were diagnosed with May-Thurner Syndrome and one with antiphospholipid antibody syndrome. An additional five patients had chronic illnesses including lupus, poorly controlled type 1 diabetes, a mitochondrial disorder, chronic pancreatitis and substance use disorder.

Conclusion: Persistence of PE symptoms following hospital discharge is common in the pediatric population and results in frequent ED visits and repeat imaging. The rate of PE recurrence of 8% in this study is similar to prior studies. Although this rate is not insubstantial, it should be noted that all recurrences occurred in patients with significant thrombotic risk factors. Future work will focus on identifying risk factors for symptom persistence and further elucidating the risks for PE recurrence. The identification of patients at low risk for PE recurrence will allow for minimization of repeat CTAs in this population, reducing cumulative exposure of ionizing radiation.

Poster # 016

IMPROVING VENOUS THROMBOEMBOLISM PROPHYLAXIS IN HOSPITALIZED PEDIATRIC PATIENTS: A QI INITIATIVE

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Background: Venous thromboembolism (VTE) remains the most preventable cause of death in hospitalized patients. The prevalence of VTE is 1 in 200 pediatric hospital admissions, which increases in-hospital mortality between two and six-fold. The increasing rate of VTE in children requires pediatricians to be aware of the common signs and symptoms of VTE. Pediatricians must identify at-risk patients and choose appropriate anticoagulation based on risk factors for VTE.

Objectives: To optimize prevention and reduce incidence of VTE in acutely ill, hospitalized, pediatric patients less than 18 years of age by 10% and increase process reliability to a VTE

prevention bundle to 90% within one year of implementation at our institution.

Design/Method: Utilizing current pediatric VTE guidelines, we developed an educational program for our pediatric residency consisting of lectures and periodic reviews of current clinical practice guidelines with attendings to educate residents on the prevalence and prevention of pediatric VTE. We integrated a standardized template into the electronic medical record (EMR) so that the VTE prophylaxis scoring tool was included in the initial history and physical for all pediatric admissions. We retrospectively reviewed 5-6 patient charts per week (4 in the pediatric inpatient unit, 2 in the pediatric intensive care unit) over one year to monitor process reliability, determine whether each VTE score was appropriate and determine whether the prophylactic measures taken based on the risk assessment were adequate. Prior to the implementation of our quality improvement initiative, the incidence of non-central venous catheter-associated VTE was one per year.

Results: A retrospective chart review of 230 patients found that 88.6% demonstrated adequate VTE assessment and 88.2% (n=202) exhibited appropriate prophylactic measures based on the assessment. Process reliability increased from baseline of 75 to 95% over one year. There was an incidence of 1 VTE over 12 months, though appropriate risk-assessment and anticoagulation had been determined by the primary team.

Conclusion: The implementation of a standardized assessment tool for VTE resulted in appropriate and effective use of VTE prophylaxis for pediatric patients. The objective to increase process reliability to 90% was met. The project heightened general awareness of VTE risk in the pediatric population and aided in clinical decision making geared toward prevention and treatment of VTE in children. Ongoing improvement efforts include continuing resident education, expanding the use of clinical decision support in the EMR, team meetings once a VTE is identified, and integrating process changes to the housestaff and nursing workflow.

Poster # 017

ASCORBIC ACID AND OXIDATIVE STRESS IN PEDIATRIC SICKLE CELL DISEASE

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Background: Oxidative stress plays a significant role in sickle cell disease (SCD). Critically ill adults with extreme oxidative stress demonstrate low concentrations of antioxidant vitamins, such as ascorbic acid (AA). However, AA and oxidative stress in pediatric patients with SCD remains largely unexplored. Additionally, no prior studies explore oxidative stress and AA in various states of the disease.

Objectives: The primary aim was to compare AA concentrations in pediatric patients with SCD in steady-state of disease versus hospitalized patients with either vaso-occlusive crisis (VOC) or acute chest syndrome (ACS). The secondary aim was to compare oxidative stress between both groups and determine whether increases in oxidative stress correlate with changes in AA.

Design/Method: We conducted a prospective, single-center study that enrolled 21 steady-state and 18 hospitalized pediatric aged patients with SCD. Markers of oxidative stress included malondialdehyde (MDA), RBC glutathione (GSH) and glutathione disulfide (GSSG), superoxide dismutase (SOD) activity, and catalase activity in blood samples collected with IRB consent. AA and GSH concentrations were measured via HPLC. Plasma MDA, SOD, and catalase activities were determined using commercial assay kits.

Results: Median age for patients in steady-state was 11 years (IQR 4.5, 15.0) and for hospitalized patients 14.4 years (IQR 12.5, 18.0; $p = .02$). Percent with genotype HbSS was 81.0 and 72.2, respectively ($p = .96$). Median plasma AA concentration for patients in steady-state was 34.3 μM (IQR 6.6, 57.2) and for hospitalized patients was 17.1 μM (IQR 8.6, 31.3; $p = .24$). Seven patients had AA concentrations < 10.0 μM. Median RBC AA concentration for patients in steady-state was 10.7 μM (IQR 5.5, 37.1) and for hospitalized patients was 9.5 μM (IQR 4.7, 31.7; $p = .56$). There were no differences in MDA ($p = .56$), GSH ($p = .64$), GSSG ($p = .25$), or catalase activity ($p = .33$). SOD activity was significantly lower in the hospitalized group ($p = .02$). RBC AA was negatively correlated with MDA ($r = -.454$; $p = .007$) and GSSG ($r = -.620$; $p = <.001$) and positively correlated with GSH ($r = .395$; $p = .021$).

Conclusion: Our findings suggest that there is no significant difference in AA between the different states in pediatric SCD. Some patients were AA deficient based on normative values. Additionally, RBC AA concentrations may reflect a degree of oxidative stress. Further studies are needed to elucidate effects of low AA on oxidative stress and its clinical consequences in SCD.

Poster # 018

SICKLE CELL DISEASE SEVERITY AND NEUROCOGNITIVE FUNCTIONING IN A PEDIATRIC COHORT

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Background: Sickle cell disease (SCD) manifests as hemolytic anemia and periodic occlusion of the vessels leading to tissue ischemia that can lead to silent cerebral infarcts, stroke, cerebral hemorrhage, and other cerebral blood flow abnormalities. Lower IQ scores, diminished working memory, and decreased school performance are associated with disease severity, including stroke, lower levels of hemoglobin, and abnormal transcranial ultrasound findings. Neurocognitive deficits were still present when controlled for stroke.

Objectives: There is less research on neurocognitive deficits in pediatric SCD. Our aim was to understand if impairments in neurocognition are correlated with disease severity and which neurocognitive domains are affected most by SCD.

Design/Method: The Yale Sickle Cell Program follows children with SCD from birth to 21 years. From this cohort we identified children who had completed neuropsychological testing. Patients with history of stroke, seizures, or other neurological disorder were excluded from analyses. Patient charts were reviewed for clinical data on type of SCD, hospitalizations for pain crisis, stroke

history, hydroxyurea use, and laboratory parameters collected within 1 year of neuropsychological testing. Neuropsychological evaluations included the Weschler Scales of Intelligence, Children's Memory Scale, Delis-Kaplan Executive Function System, and Behavior Assessment System of Children. Bivariate Spearman r correlations were performed to identify factors associated with poor neurocognitive function.

Results: Fifty-seven children with SCD had neuropsychological testing. Nine were excluded due to a history of stroke (n=7) or underlying neurological disorder (n=2). The 48 patients (28 males, 20 females) had a mean age of 11.7 years (SD=4.11) at evaluation. Thirty-one patients had SS disease=31, SC disease=12 SB+=3, SBo=2. Twenty-two patients had a history of acute chest syndrome. At the time of evaluation, 23 patients were on hydroxyurea therapy and 4 patients had monthly transfusions (3 for abnormal Transcranial Doppler velocities, 1 for recurrent vaso-occlusive crises (VOC)). Neurocognitive outcomes differed significantly from normative expectations (full scale IQ=83.19 $\pm$ 12.19, working memory index=90.02 $\pm$ 13.28, and processing speed index = 84.5 $\pm$ 12.82). Hemoglobin, hematocrit and bilirubin were correlated with working memory ($r=-0.387$, $p< 0.01$; $r=-0.370$, $p=0.01$; $r=0.629$, $p<0.01$). Reticulocyte count was negatively correlated with processing speed ($r =-0.393$, $p=0.043$). Parent-reported child anxiety was associated with more hospitalizations for VOC ($r=0.416$, $p<0.05$).

Conclusion: Patients with SCD without overt stroke perform more than 1 SD from the normative mean on tests of general intelligence and information processing speed. Hemolysis was not associated with worse neurocognitive outcomes in our cohort.

Poster # 019

COGNITIVE AND ACHIEVEMENT FUNCTIONING IN CHILDREN & ADOLESCENTS WITH SICKLE CELL DISEASE

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Background: Sickle cell disease, and its increased risk of strokes, negatively impacts the cognitive and academic functioning of patients causing missed school days and socioeconomic disparities. Recent evidence suggests that patients may suffer cognitive impairment without a history of infarction.

Objectives: The aim of this study was to report on our institutional efforts to screen and identify cognitive impairments so earlier interventions could be made.

Design/Method: We performed a retrospective study of all sickle cell patients who had received cognitive testing and/or achievement testing through services offered in our clinic from December 2020 through October 2021. Sociodemographic data, cognitive and achievement testing results, psychological diagnoses, hospital utilization, and use of IEP/504 plans were reviewed.

Results: Sixteen children with sickle cell anemia (SS) who completed cognitive and achievement testing through our clinic were identified. The median age at time of testing was 9 years (range 4-16). All but one child self-identified as African American or Black, with one participant identifying as Mixed.This group included 12 females and 3 males. Eleven patients were prescribed hydroxyurea, 5 patients underwent scheduled therapeutic erythrocytapheresis (2 for history of clinical stroke, 2 for history of silent infarctions, one for abnormal TCD). Eight (50%) children had been hospitalized within the past two years for pain crises with a mean of 2.66 hospitalizations.

We identified 5 (31%) children who met criteria for a Specific Learning Disorder, 3 of whom had a history of stroke, 2 (12.5%) with an Intellectual Disability, one of whom had a history of stroke, and 1 (6%) with an Unspecified Intellectual Disability. Only 1 (6%) caregiver reported their child had an established Individualized Education Plan at school, with 9 (56%) reporting a 504 plan had been established. Two caregivers reported their child had been diagnosed with ADHD, and one reported a history of anxiety and trauma.

Conclusion: Our data shows that potential learning disabilities are likely going un-identified and educational needs unmet by parents and school. It is unclear whether these shortcomings are caused by the lack of education or established stigma around utilization of special needs courses and therapy in children. Future more in-depth studies are needed to identify solutions to providing cognitive and academic resources in children with sickle cell disease.

Poster # 020

THE SPECTRUM OF SLEEP DISORDERS IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Patients with sickle cell disease (SCD) are vulnerable to hypoxia, which triggers hemoglobin sickling and manifests with vaso-occlusive events (pain and respiratory distress). Chronic hypoxia in patients with SCD is responsible for long-term neurological, renal, skeletal, and cardiopulmonary complications. Recent data suggest that patients with SCD are at higher risk of developing sleep-disordered breathing (SDB), most commonly obstructive sleep apnea (OSA), which in turn exacerbates hypoxia and its downstream effects. However, other disorders of sleep, such as sleep fragmentation, have similar cardiopulmonary and neurocognitive sequelae, yet their characteristics and clinical significance in patients with SCD remain unclear.

Objectives: To describe the spectrum of sleep disorders experienced by children with SCD. We hypothesized that a range of sleep disorders exist in patients with SCD, which are not limited to SDB.

Design/Method: We included all participants from the Sickle Cell Clinical Research and Intervention Program (SCCRIP), a longitudinal lifetime cohort of patients with SCD, who had undergone a polysomnographic exam for a clinical indication from 2016 to 2020. All SCD

genotypes were included. Sleep architecture, respiratory function, and limb movements were abstracted from the sleep studies and scored according to the American Academy of Sleep Medicine guidelines.

Results: One hundred and fourteen patients met inclusion criteria. Sixty patients were male and 54 were female. The mean age at the time of sleep study was 9.3 years (range 2-23). Eighty-four patients had genotype HbSS/Sβ0 (73.7%), 23 (20.2%) HbSC, 5 (4.4%) Sβ+, and 2 (1.8%) other. Of the 114 patients, 62 (54.4%) were found to have OSA (Apnea Hypopnea Index >1/hour). Seventy-three patients (64%) had abnormal nocturnal oxygen desaturation index (>5/hour). Sixty patients (52.6%) exhibited an abnormal total arousal index (>10/hour), a marker of sleep fragmentation. Of the arousal events, 65% were not respiratory-related. Seventy-eight patients (68.4%) demonstrated decreased REM sleep (<20%), and 59 patients (51.8%) had abnormal sleep efficiency (<90%). Twelve patients (10.5%) had abnormal periodic limb movements (PLM index>5/hour), but only two of these patients (1.8%) had PLM events that led to arousals. None of the sleep study parameters showed significant differences among genotypes.

Conclusion: Children with SCD suffer from a variety of sleep disorders which are not limited to SDB. Disorders of sleep architecture, including sleep fragmentation with and without concomitant SDB appear common in patients with SCD. The significance of disorders of sleep architecture, with or without SDB warrants future investigation for their effects on organ function.

Poster # 021

MANAGEMENT OF SICKLE CELL DISEASE: A CLINICAL PRACTICE SURVEY

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Background: Therapeutic options for Sickle Cell Disease (SCD) have increased recently as well as the development of updated national guidelines. It is not known how these options are being offered or to what degree guidelines are incorporated into clinical practice.

Objectives: To assess the clinical practice patterns of providers treating children with SCD.

Design/Method: A survey study was performed which included nine sections: clinic structure, prophylaxis, immunizations, hydroxyurea, splenic sequestration, stroke, novel therapies, potential curative therapies, and transition. Survey was disseminated over a three-month period via SurveyMonkey, to members of the American Society of Pediatric Hematology-Oncology Hemoglobinopathy Special Interest Group.

Results: There were 86 respondents; most were attending/faculty (85%, 73/86) who were part of a university/academic practice (65%, 56/86). Program size was most commonly 50-250 patients (44%, 37/86). Accessibility to support staff in clinic included 95% (81/86) social work; 76% (65/86) child life; 68% (58/86) nurse coordinator and 34% (29/86) school liaison and 15% (13/86) transition navigator.

For preventive care, 72% prescribe penicillin prophylaxis before 2 months of age recommending 100% (83) for HbSS and Sβnull, 72% (60/83) for HbSC and 70% (58/83) for HbSβplus. Influenza was the most common vaccine offered in clinic at 96% (76/79) with 91% (72/79) offering pneumococcal vaccines, 84% (67/79) offering meningococcal vaccines and 50% (40/79) offering COVID vaccines.

Transcranial doppler screening was offered in 95% (69/73) but only 42% (31/73) performed MRI screening for silent stroke. Transfusion therapy was recommended for primary stroke prevention by 90% (65/72) and 84% (59/70) attempt to transition to hydroxyurea following TWITCH guidelines. For secondary stroke prevention, 88% (63/72) recommend chronic transfusion therapy.

Regarding disease-modifying therapy, 90% (70/78) report starting hydroxyurea routinely in patients with HbSS and Sβnull; initiated at 9 months of age by 69% (54/78). Laboratory monitoring recommended every 3 months for stable dosing by 62% (49/78) and hydroxyurea held by 56% (44/78) if platelets <75,000, 73% (56/78) for neutrophils <1000. New therapies were recommended for patients on hydroxyurea who were still experiencing SCD complications: L-glutamine 68% (37/54; crizanlizumab 93% (54/58). Voxelotor was recommended for patients on hydroxyurea with low hemoglobin 65% (43/66). Matched sibling transplant was considered for any disease severity by 55% (38/69). Gene therapy trial is offered on-site by 29% (20/69).

Transition programs were endorsed by 61% (42/69), but only 45% (31/68) had dedicated staff.

Conclusion: This survey is the only assessment of the application of SCD guidelines in clinical practice.

Poster # 022

NEWBORN SCREENING FOR SICKLE CELL DISEASE IN KANO, NIGERIA: A PILOT PROGRAM

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Background: Nigeria has the highest burden of sickle cell disease (SCD) in the world, with approximately 150 000 babies born with SCD annually, and a mortality rate between 50-90% for children with SCD under age five. Universal newborn screening (NBS) leading to provision of antibiotic prophylaxis has significantly reduced mortality for children with SCD in high-income settings. However, universal newborn screening does not exist in Nigeria.

Objectives: The primary objective of this pilot program was to establish and evaluate NBS for SCD in Kano, the second largest city in Nigeria. Secondary objectives included describing the birth prevalence of SCD in Kano and establishing a genetic counseling program for parents with children with trait phenotypes.

Design/Method: Aminu Kano Teaching Hospital (AKTH) started NBS for SCD in September 2020. Dried blood spot samples were collected and tested for SCD using high performance liquid chromatography (HPLC). Infants were screened in the labour room, postnatal ward, neonatal intensive care unit (NICU), pediatric clinic, and immunization clinic. If NBS was positive for homozygous SCD (HbSS), families were counseled, and patients were enrolled into the sickle cell clinic at AKTH. If newborns were identified to have a trait phenotype, families were invited to group genetic counseling.

No newborns were screened between 1 November 2020 to 30 March 2021 while validation of prior results took place.

Results: These results include infants enrolled up to 30 November 2021. Screening was performed on 2818 infants, including 2568 (91.1%) born at AKTH. 46.8% were screened soon after birth in the labour room, postnatal ward or NICU, and 35.6% of patients were screened at their first visit to the immunization clinic. 17.6% of patients were screened at the pediatric clinic.

Fourty-four infants (1.6%) had homozygous SCD and 28 (63.6%) of them were enrolled into clinic. Five-hundred eighty-four (20.7%) infants had sickle cell trait, and 164 (28.1%) of their families received group genetic counseling.

Three-hundred fifty-eight newborns (12.2%) born at AKTH were not screened. Reasons included family refusal, instability of patient, and missed patients.

Conclusion: Homozygous SCD birth prevalence in the pilot population Kano is approximately 1.6 per 100 births. This pilot NBS screening program in Kano demonstrates the importance of screening infants beyond the immediate delivery setting, over half of all infants were screened at immunization and pediatric clinics. Next steps include expanding NBS to other hospitals in Kano and developing strategies to increase trait genetic counseling.

Poster # 023

A COMPREHENSIVE EVALUATION OF MEDICATION ADHERENCE BARRIERS IN SICKLE CELL DISEASE USING COM-B MODEL

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Background: Sickle cell disease (SCD) is an inherited hemoglobinopathy that affects >100,000 Americans. Common SCD-related complications include vaso-occlusive pain episodes and acute chest syndrome. Despite the efficacy of hydroxyurea in reducing these complications, adherence remains suboptimal and the association between specific barriers and adherence behavior is unclear.

Objectives: To examine the prevalence of different barriers to hydroxyurea adherence among patients and their caregivers, and to evaluate the relationship between different barriers and their

impact on adherence rates.

Design/Method: In this cross-sectional study, patients and their parents/caregiver were enrolled in clinic at Lurie Children's Hospital of Chicago if they had SCD (all genotypes) and were taking hydroxyurea. Study measures included demographics, self-report of adherence using visual analogue scale (VAS), and an adapted version of the Disease Management and Barriers Interview (DMI) – SCD. The DMI-SCD was mapped to the **C**apability, **O**pportunity, **M**otivation, and **B**ehavior (COM-B) model of the Behavior Change Wheel. The number of different COM-B categories and total number of barriers reported were analyzed in relation to adherence markers. Laboratory markers of adherence were collected from chart review, including fetal hemoglobin (HbF%) and mean corpuscular volume (MCV).

Results: Forty-eight parents/caregivers (females 83%, median age 38 [34-43]) and 19 patients (male 53%, median age 15 [13.5-18]) participated. Overall, parents' and patients' VAS scores significantly correlated with MCV and HbF%. Using VAS, many patients (73%) reported low hydroxyurea adherence, while most caregivers (83%) reported high, not low, adherence. The majority of patients (84%) and parents (69%) reported ≥1 adherence barrier. Parents endorsed barriers across multiple components of COM-B, with physical opportunity (e.g., cost, access, physical characteristics of hydroxyurea as a medicine) and reflective motivation (e.g., perceptions of SCD, beliefs about hydroxyurea, self-efficacy) being the most commonly reported categories (48% and 42%), respectively. Patients most commonly identified psychological capability (e.g., forgetfulness, understanding of SCD and hydroxyurea,
cognitive and executive function) and reflective motivation (84% and 68%), respectively. Patients' and parents' VAS scores negatively correlated with the total number of adherence barriers (r=–0.53, *P*=0.01; r=–0.28, *P*=0.05) as well as different COM-B categories (r=–0.51, *P*=0.02; r=–0.35, *P*=0.01), respectively, suggesting lower hydroxyurea adherence with more endorsed barriers.

Conclusion: Patients with SCD and their caregivers endorsed multiple barriers to hydroxyurea adherence, indicating that adherence is multifactorial. Fewer barriers to hydroxyurea adherence were associated with higher adherence. Understanding barriers to medication adherence is essential to address these challenges and develop tailored interventions aimed at improving adherence.

Poster # 024

HEALTH-RELATED QUALITY OF LIFE OF ADOLESCENTS WITH SICKLE CELL DISEASE: A US CROSS-SECTIONAL SURVEY

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Background: Children and adolescents with sickle cell disease (SCD) experience disease-related complications such as chronic pain, vaso-occlusive crises, anemia, acute chest syndrome, and splenic sequestration. These complications, and their long-term effects, likely contribute to impairments in health-related quality of life (HRQoL).

Objectives: To compare the HRQoL of adolescents with SCD with a normative sample of adolescents from the US general population.

Design/Method: An online cross-sectional observational survey was administered to US adolescents with SCD, ages 12-17 years (n=247). Adolescents provided assent to participate, and their guardians provided permission. Adolescents completed the Child Health Questionnaire-Child Form 45 (CHQ-CF45) and the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) Pain and Sleep Impact domains. Average CHQ-CF45 scores were compared to developer-provided normative scores from a sample of adolescents ages 11-18 representative of the US adolescent population. Adolescents' ASCQ-Me Pain and Sleep Impact scores were compared to benchmark scores from a sample of US-based adults with SCD. Differences between adolescent and normative/benchmark sample means were evaluated using Welch's t-tests. Differences were also compared to a minimally important difference (MID) threshold, calculated as ½ standard deviation of the normative/benchmark sample mean.

Results: Adolescents with SCD reported CHQ-CF45 scores that were significantly lower than normative scores ($p<0.001$ for all domains). For 8 of the CHQ-CF45 domains, differences between the adolescent SCD sample and the normative sample were meaningful, as they exceeded the MID threshold. The greatest impacts were observed for the Physical Functioning, Role/Social Limitations due to Physical Health, and General Health domains. Differences for the Getting Along/Behavior and Family Cohesion domains were not meaningful, as they did not exceed the MID threshold. Adolescents reported ASCQ-Me Pain Impact scores that did not differ significantly from the benchmark sample of adults with SCD ($p=0.079$). While adolescents' ASCQ-Me Sleep Impact scores were significantly higher than those of the adult SCD benchmark sample (indicating that the adolescent sample experienced fewer sleep impacts, $p<0.001$), the difference did not exceed the MID threshold.

Conclusion: Using adolescent-self report, these results demonstrate the significant detrimental impact of SCD on adolescents, relative to a normative sample of US-based adolescents of a similar age. Impacts were observed across many different areas of HRQoL. Results also indicate that adolescents with SCD experience pain and sleep-related impacts that do not meaningfully differ from those experienced by adults with SCD. Treatments and services for adolescents with SCD should focus on improving HRQoL.

Funding: Novartis Pharmaceuticals Corporation

Poster # 025

QUALITY OF LIFE IN CHILDREN WITH SICKLE CELL DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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Background: Sickle cell disease (SCD) is a severe genetic disorder that is associated with numerous physiological and psychosocial challenges that may impact individual's health related quality of life (HRQL). Monitoring HRQL among children diagnosed with SCD allows for better understanding of health status fluctuations, can be an indicator of SCD related issues, and can be an index and advisor of clinical care needs. Yet, while the literature on HRQL in adults with SCD is relatively well-established, there remains a gap concerning the HRQL among children diagnosed with SCD, and more importantly, the critical factors that might contribute to a better or worse HRQL.

Objectives: This review aimed to: 1) examine the operationalization of health-related quality of life (HRQL) in pediatric patients diagnosed with sickle cell disease (SCD); 2) document the biopsychosocial factors related to HRQL in pediatric patients diagnosed with SCD; and 3) complete a meta-analysis comparing HRQL in pediatric patients diagnosed with SCD compared to controls.

Design/Method: Existing articles and abstracts published from January 2000 to March 2021 were collected from MEDLINE, PsychINFO, EMBASE, and CINAHL databases. Eligible studies: 1) were original research, 2) had a quantitative assessment of HRQL, 3) were published in English, 4) had participants with a mean age $\leq$ 21 years, 5) had HRQL as primary aim, 6) were published in 2000 or later, 7) had a sample size > 20, and 8) included participants who have not undergone hematopoietic stem cell transplant. Risk of bias was assessed using the Cochrane risk of bias tool. Two independent raters completed the data abstraction and quality assessment for each published study. The quality of evidence was graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) tool.

Results: The final review included 66 articles. Meta-analyses revealed children with SCD had significantly lower HRQL compared to healthy controls by self- and parent-proxy report (standardized mean difference=-0.93, 95% CI=-1.25, -0.61, p <0.00001; standardized mean difference=-1.34, 95% CI=-1.79, -0.89, p <0.00001). Poorer HRQL was associated with more severe SCD, female sex, and pain.

Conclusion: The findings of this review indicate that children with SCD may be at risk for poorer HRQL compared to their healthy peers and may be impacted by several biopsychosocial factors. Future research is needed to examine how sociocultural factors uniquely impact this population and their overall life quality.

This work was supported by the Sickle Cell Disease Association of Canada.

Poster # 026

DISEASE KNOWLEDGE OF PARENTS OF CHILDREN WITH SICKLE CELL DISEASE IN BENIN

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Background: Sickle cell disease (SCD) is a genetic blood disorder that disproportionately affects people from sub–Saharan Africa and of African descent. This condition is often marked by episodes of excruciating pain and severe anemia, therefore, necessitating frequent hospital visits. SCD knowledge is thought to have important outcomes such as frequency of occurrence of painful episodes and hospitalizations. Parents of children with SCD are tasked with managing the condition of their children from infancy until adolescence where some of this responsibility is shared with the patients. Thus, empowering parents of children with adequate knowledge could ensure that they are better equipped to manage their children's condition.

Objectives: The aim of this study was to assess the disease knowledge levels of parents of children with SCD and examine its relationship with the number of hospitalizations.

Design/Method: In this study, we have adopted a cross-sectional and observational approach. Parents of children attending routine consultations at the Integrated Care Centre for Children and Pregnant Women with Sickle Cell Disease (CPMI-NIFED) in Benin, were invited to complete a questionnaire. SCD knowledge was assessed using a locally developed questionnaire. In addition, we collected information on socio-demographic characteristics, healthcare utilization frequency of annual hospitalizations and occurrence of painful episodes. Regression analysis was used to examine the relationship between SCD knowledge, number of hospitalizations, occurrence of painful episodes and socio-demographic characteristics. The study is ongoing, and we aim to include at least 105 parents of children with SCD.

Results: To date, a total of 66 parents of children with SCD have been recruited for the study. About half of the participants had at least secondary level education (n=32; 47%) and had male children (n=42; 65 %). Few participants demonstrated good SCD knowledge (N=19; 29%) answering correctly over 70 per cent of the questions. Higher SCD knowledge scores were associated with fewer of hospitalizations (p=0.052) and older age of the children (p=0.037). However, no association was found between SCD knowledge and the frequency of occurrence of painful episodes.

Conclusion: Our study underscores the importance of having adequate disease knowledge especially for parents of children with SCD. With increasing age of their children, parents might have gained more knowledge due to more consultations with healthcare professionals or experiential learning from managing their children's condition. Healthcare practitioners should pay more attention to the disease knowledge levels of parents with young children who have SCD.

Poster # 027

SOCIAL DETERMINANTS OF HEALTH AND MISTRUST IN CHILDREN WITH SICKLE CELL DISEASE TAKING HYDROXYUREA

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Background: Hydroxyurea reduces the occurrence of complications such as pain crises, acute chest syndrome, and hospitalizations in children with sickle cell disease (SCD). However, adherence to a long-term medication can be difficult for patients and their caregivers. Hydroxyurea treatment requires daily dosing, laboratory monitoring, regular hematology appointments, and securing medication from the pharmacy. Given the complexity social determinants of health (SDoH; race, socio-economic status, education level, insurance type, health literacy, social support, and food security) and mistrust in the healthcare system may impact adherence to hydroxyurea as well as disease knowledge and health care utilization.

Objectives: The primary objective of this study was to determine associations between SDoH and contextual factors and adherence with hydroxyurea. Secondary objectives were to evaluate associations between SDoH and contextual factors on disease knowledge and health care utilization.

Design/Method: The study population included parents of children with SCD prescribed hydroxyurea and followed within the comprehensive SCD center at Rady Children's Hospital San Diego. Clinical characteristics and socio-demographics were collected. Patient-reported adherence to hydroxyurea was assessed using the Modified Morisky Scale. Health literacy (HL) was assessed with the Short Test of Functional Health Literacy for Adults (S-TOFHLA) and New Vital Sign (NVS), and food insecurity was assessed via the USDA Food Security Module. To assess mistrust in the healthcare system and social support, we used the Pediatric Trust Scale (Pedi-TIPS) and the Duke-UNC Functional Social Support Scale, respectively. Disease knowledge was assessed using the Georgia Department of Public Health SCD Knowledge Quiz, and calls/visits regarding pain crises and other SCD-related complications were assessed via chart review, and Descriptive statistics were used to characterize the population. Associations were assessed using linear regression models.

Results: Forty-eight parents of children with SCD at Rady Children's Hospital San Diego were enrolled. None of variables assessed were significantly associated with lower self-reported adherence, likely due to the small sample.
Limited health literacy was associated with lower disease knowledge ($p = 0.006$). Higher mistrust and food insecurity were associated with more calls/visits for SCD-related care ($p = 0.036$ and <0.001, respectively).

Conclusion: Health literacy clearly impacts disease knowledge. Further research including SDoH and comprehensive assessment of contextual factors in a larger sample can help elucidate factors contributing to lower adherence and inform interventions aimed at improving adherence and reducing complications in children with SCD.
Poster # 028

FACTORS ASSOCIATED WITH ERYTHROPOIETIN IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is an inherited red blood cell disorder caused by a structural abnormality of hemoglobin called sickle hemoglobin (HbS). Deoxygenation of HbS causes polymerization, leading to the generation of sickled cells and dense erythrocytes. Clinical manifestations of SCD are related to chronic hemolysis and vaso-occlusion, which lead to ischemia and chronic organ damage. Kidney disease is a common sequalae of SCD that can often start in the first decade of life. Among other functions, kidneys play an important role in regulation of hemoglobin production by secreting erythropoietin (Epo). It has been observed in adults that that patients with sickle cell anemia have Epo levels that correlated with creatinine clearance and inversely with the BUN.
Combination therapy with Epo and Hydroxyurea (HU) has been described in adult patients with SCD. With new developments of oral agents with epo-like properties it could become a valuable treatment approach in pediatrics.
We hypothesized that pediatric patients with SCD will have levels of epo that inversely correlate with kidney disease activity.

Objectives: Evaluation of erythropoietin levels in pediatric patient with SCD and its correlation with markers of kidney function and characteristics of SCD.

Design/Method: Data was collected through retrospective chart review of pediatric patients with SCD followed at Marian Anderson Sickle Cell Center at St. Christopher's Hospital, Philadelphia. Patients were seen in the office between 3/1/21 and 8/15/21. Patients were excluded if they received EPO treatment within 3 months, had underlining kidney disease, or if labs were obtained during a disease exacerbation.

Results: One hundred twenty-three patients were included with an age range of 1-28, mean age of 12, 78 males, and 45 females. Genotypes included were SS (59%), SC (26%), SB+ (10%), and SB0 (5%). Using nonparametric correlations erythropoietin is significantly negatively correlated with cystatin C ($r= -0.373$, $p= <0.001$), Cr ($r= -0.434$, $p= <0.001$), age ($r= -0.275$, $p=0.002$), hemoglobin ($r= -0.683$, $p=< 0.001$) and urine creatine ($r= -0.310$, $p=0.004$). Age is significantly associated with all of these variables. Using partial correlations controlling for age, EPO is significantly negatively correlated with Cystatin C (, $r= -0.525$, $p= <.001$), Cr ($r= -.327$, $p= 0.028$), but not urine creatine ($r= -0.217$, $p= 0.153$).

Conclusion: EPO levels in pediatric patients with SCD indirectly correlate with markers of kidney disease. Similar findings are seen in adults. Further studies with new analysis will be conducted to support the idea of using EPO as a treatment option in pediatric SCD.

Poster # 029

ADVERSE CHILDHOOD EXPERIENCES IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Background: Following the landmark CDC-Kaiser ACE study in 1998 there is a growing body of evidence regarding Adverse Childhood Experiences (ACE) and their potential negative impact on health, especially in adults. The Brief Resilience Scale (BRS) has been developed to assess an individual's ability to recover from stress. The role of ACE and BRS in management and outcome of chronic childhood diseases is less well studied.

Objectives: We aimed to evaluate the relationship between ACE, BRS and sickle cell disease course. It was hypothesized that adult patients or caregivers of pediatric patients with higher ACE scores may have worse disease control and, thus, more frequent Emergency Department visits, hospitalizations, and blood transfusions; and that BRS may mitigate some negative effects of ACE scores.

Design/Method: A retrospective study of subjects sequentially recruited from sickle cell clinic. All patients age ≥ 18y self-completed an ACE questionnaire and a BRS; caregivers completed the scales for children <18y. Chart review was conducted assessing adherence to clinic appointments, number of ED visits, hospitalizations, transfusions and treatment adherence. Correlations were calculated between ACE score and outcomes, then adjusted for BRS score.

Results: 61 subjects were included in the analysis: S-Beta thal (13.1%), SC (36.1%), SS (50.8%). Age ranged from 2 to 20 years (mean 11.2). Respondents completing scales were predominantly caregivers (90.2%) and 9.8% were patients. Insurance was mainly Medicaid (84.5%).

ACE scores ranged from 0 to 10 with mean of 1.6 (SD=2.1) and median of 1 (IQR: 0-2). The BRS score ranged from 1.8 to 5 (mean 3.7±0.8; median 3.7 (IQR: 3.2-4.2)).

A significant positive association was found between ACE scores and number of missed visits (r=0.27; p=.038); after adjusting for BRS scores, the relationship between ACE and missed visits was no longer statistically significant (r=0.22; p=.092).There was no significant correlation between ACE scores and the number of ED visits, hospital admissions or transfusions. Treatment adherence data are still being collected.

Conclusion: There was a significant correlation between ACE scores and missed clinic visits. While this does not directly provide an insight into sickle cell patient disease control, it provides an objective measure highlighting the unique social dynamics facing sickle cell patients. This may indirectly influence patient outcomes as those with higher ACE scores could be less prepared for managing acute events and miss preventative measures that could potentially improve disease outcomes. Further studies should focus on early interventions for at risk families and modifying resilience through education and training.

Poster # 030

SOCIAL ADJUSTMENT IN CHILDREN WITH SICKLE CELL DISEASE, A RETROSPECTIVE STUDY

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Background: Children with sickle cell disease (SCD) are at risk for physical, psychological, cognitive, and social challenges. Research that systematically examines factors related to social health, specifically adjustment, is warranted to improve care delivery.

Objectives: This study aimed to 1) compare social adjustment in children with SCD to published norms for healthy children and other chronic illness populations; and 2) examine the association of disease, and non-disease, related factors with social adjustment in children with SCD prior to transplant.

Design/Method: Data from 32 children with SCD, pre-transplant, (mean age = 10.32, *SD* = 3.27) were retrospectively collected from a neuropsychology clinic at a tertiary care pediatric hospital in Alberta, Canada. The *Behaviour Assessment System for children, Third Edition* (*BASC-3*) parent-proxy, social withdrawal subscale, and the *PedsQL Generic Module* social functioning self- and parent-proxy subscales were used to measure social adjustment. Other standardized measures collected included the *PedsQL Family Impact Module* and *Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2) Parent Form.*

Results: Sixteen percent of patients (n = 5) reported clinically significant social adjustment difficulties on *BASC-3* parent-proxy. However, children with SCD did not experience significantly different social adjustment compared to published norms for healthy and other chronic illness populations except for parent-proxy reports, which were significantly better than children with other chronic illnesses [$t(25) = 2.76$, $p = 0.011$]. Multiple linear regression found better family functioning [$B = 0.48$, $t = 2.65$, $p = 0.016$], and higher executive functioning [$B = -0.43$, $t = -2.39$, $p = 0.028$] were related to higher scores on parent-proxy ratings of social adjustment in youth with SCD [$F(4,18) = 5.88$, $p = 0.003$]. Identifying as male [$B = 0.54$, $t = 3.08$, $p = 0.005$], and living in Canada for a greater number of years [$B = 0.55$, $t = 2.81$, $p = 0.009$], were related to higher *PedsQL* self-reported social adjustment [$F(4,23) = 3.75$, $p = 0.017$]. No significant predictor variables for the *BASC-3* social adjustment were identified [$F(4,16) = 1.63$, $p = 0.22$].

Conclusion: Children with better family functioning, longer residence in Canada, and stronger executive functioning skills evidenced higher levels of social adjustment. Children with SCD experience unique disease complications and sociocultural factors that may be associated with their social adjustment. Understanding and measuring social adjustment in children with SCD warrants future research.

Poster # 031

ASSESSING AN INTERVENTION TO ADDRESS UNMET BASIC NEEDS OF CHILDREN WITH SICKLE CELL DISEASE

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Background: Individuals living with sickle cell disease (SCD) disproportionately experience unmet basic needs, likely due to inequitable social systems rooted in structural racism. The relationship between unmet basic needs, structural racism, and physical health complications may negatively impact patients with SCD's quality of life.

Objectives: This study assesses the implementation of an intervention for identifying and addressing unmet basic needs (WE CARE) for families of children with SCD.

Design/Method: Two pediatric hematology clinics in the northeastern United States implemented WE CARE. Clinical team members regularly reported rates of completion of screening and referral. They also participated in post-implementation qualitative interviews (N=11) related to addressing their patients' unmet basic needs. The integrated Promoting Action on Research Implementation in Health Services (iPARIHS) framework informed the semi-structured interview guide.

Results: Patients received a WE CARE screener at 75% of eligible visits and 66% of requests for help had a corresponding referral documented in the EHR. Rates varied over time and by site in response to key contextual factors. In qualitative findings, we identified five environmental themes within the iPARIHS constructs of context, facilitation, innovation, and recipient. Within the construct of "context", the theme of advocacy arose related to experiencing stigma and bias within and outside the healthcare system. Clinic healthcare providers stated they effectively advocate on behalf of patients and families with SCD by actively centering and listening to patients' experiences and needs. Regarding "facilitation," two themes emerged: 1) research teams and clinical teams were interdependent in ensuring routine implementation of WE CARE, and 2) clinical teams expressed desire and capacity to sustain WE CARE and expand implementation to all hematology patients. With respect to "innovation," respondents described WE CARE as an effective supplement to teams' existing processes for identifying and addressing unmet basic needs. Respondents cited WE CARE as a formal and more advantageous process for doing what was already done informally. Within the construct of "recipient," the theme of trust was bidirectional between staff and families; the value staff placed on fostering rapport with families intersected with families' motivation to communicate their unmet needs due to the comfort and rapport of the built relationships.

Conclusion: These findings suggest that pediatric hematology clinics are an appropriate setting to screen and refer for unmet basic needs, given the trust that families have in their clinicians. When implemented with fidelity, universal screening may enhance equity by offering resources to all families, enabling hematology clinics to provide comprehensive quality care.

Poster # 032

EDUCATION LIAISON IMPROVES IMPLEMENTATION OF SCHOOL ACCOMMODATIONS FOR STUDENTS WITH SCD

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Background: Children with Sickle Cell Disease (SCD) are at risk for cognitive impairment and lower academic attainment. The American Society of Hematology recommends cognitive screening and, when indicated, neuropsychological testing (NPT) and school accommodations. Under federal laws, educational accommodations are available when appropriate to children with certain diagnoses as Individualized Education Plans (IEPs) and 504 plans (504s). Many children with SCD do not receive indicated testing or accommodations.

Objectives: We hypothesize that access to a SCD-specific education liaison (EL) increases the number of children with SCD who receive NPT and educational accommodations.

Design/Method: This is a retrospective study of children aged 5-20 years with SCD who attended at least one SCD center visit from 2017 through 2020. We collected demographics, disease burden, contact with EL, NPT, learning disorders, and educational accommodations with institutional review board approval. Univariate and multivariate analyses were conducted.

Results: The population included 319 children with SCD, of whom 54.9% had HbSS disease, 33.9% had HbSC disease, and 11.2% had other genotypes. 52.4% were male. At baseline, 24.1% of patients had an IEP, 37.6% had a 504, and 52.4% had either accommodation.

The EL had contact with 38.6% of the cohort. Children with contact with EL and those without were similar ages (13.77 vs 13.02 y). EL interaction was associated with prior NPT (OR 3.642, 95CI 1.631-8.132 p=.002), IEP (OR 3.742, 95CI 1.640-8.357 p=.002), and 504 (OR 2.514, 95CI 1.494-4.231, p<.001) by multivariate analysis. Children residing in zip codes with higher poverty levels were more likely to interact with liaison (Pearson R .137, p=.014). Children with overt or silent stroke (OR 1.967), acute chest syndrome episodes (OR 2.183), asthma diagnosis (OR 2.317), hospitalizations since age five (OR 3.334), and pain requiring hospitalization (OR 2.301) were more likely to interact with the EL by univariate analysis (p<.05 for all) and those with hospitalizations since age 5 were more likely by multivariate analysis (OR 2.218, 95CI 1.070-4.597, p=.032).

Children with EL contact were more likely to undergo NPT (OR 5.385), have IEP (OR 4.58), and have 504 (OR 2.038) (p<.001 for all). At the end of the study period, 33.2% had an IEP in place, 53.9% had a 504, and 63.6% which increased from baseline (p<.001 for all).

Conclusion: EL interaction improves the likelihood that children with SCD undergo NPT and receive appropriate educational accommodations. SCD centers should incorporate ELs in their comprehensive care teams to improve academic outcomes for children with SCD.

Poster # 033

SICKLE CELL STORY CLUB: IMPLEMENTATION OF A DIVERSE BOOK GIVEAWAY PROGRAM

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Background: Sickle Cell Disease (SCD) is an inherited blood disorder characterized by crescent-shaped red blood cells that are prone to obstructing blood flow, resulting in significant pain and organ damage. Disease sequelae include chronic anemia, frequent hospitalizations, as well as silent or overt strokes. The psychosocial challenges faced by youth with SCD include lower health-related quality of life, school absenteeism, anxious/depressive symptoms, as well as learning differences in attention, memory, and academic functioning including reading. Book giveaway programs (BGP) in pediatric primary care are designed to enhance the home literacy environment by supplying free children's books at annual well-child appointments. BGPs have demonstrated efficacy for promoting language development, reading skills, parent-child relationships, as well as improved clinic attendance. The appreciation of reading through book ownership may bolster academic success. Children who have a 20-book home library remain in school 3 years longer compared to peers. Literacy promotion is imperative for addressing reading difficulties faced by children with SCD by introducing stories that are salient to their lived experiences. Accessing books with representative characters enhances relatability for readers, though only 12.6% of children's books depict Black characters.

Objectives: This project aims to detail the implementation of a BGP comprised solely of books that promote social-emotional learning and feature Black protagonists as part of a Comprehensive SCD Clinic.

Design/Method: Youth aged 0-21 years (M=8.2) attending a multidisciplinary SCD clinic were given a book at every visit. Families reported on their home literacy environment upon receiving their first book and provided programmatic feedback at subsequent appointments.

Results: Four hundred and fifty-two books in 6 languages were distributed over the first 9 months with youth receiving between 1-5 books. Most books were given to families by the Psychologist (46.2%) or Social Worker (44.7%), allowing for an introduction of psychosocial roles at the time of book distribution. Quantities of books in home libraries ranged from 0-5 (33.2%), 6-10 (15.4%), 11-20 (17.8%), 21-50 (16.2%), or 50+ (17.4%). The average cost per book was $6.47. The patient and family voice will be included through sharing quotes from the time they received their book.

Conclusion: To promote home literacy, a BGP focused on social-emotional learning featuring Black characters was implemented within a multidisciplinary SCD Clinic and was well-accepted by families. The provision of books by embedded psychosocial team members may destigmatize access to mental health care by increasing visibility at medical appointments.

Poster # 034

THE USE OF TELEMEDICINE TO IMPROVE TRANSITION OF CARE FOR PATIENTS WITH SICKLE CELL DISEASE

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Background: Approximately 60% of children with Sickle Cell Disease (SCD) have at least one vaso-occlusive pain episode (VOE) per year. VOE can sometimes require hospitalization, but often needs continued patient-specific management at home following discharge. Despite the recognized utility of personalized treatment plans for patients with SCD, use and communication regarding these pain plans can vary.

The COVID-19 pandemic saw widespread use of telemedicine to improve healthcare access for patients needing medical care. Little is known about its potential usability to improve post-hospitalization pain management in SCD.

Objectives: The objective of this study was to determine if hospital follow-up telemedicine visits allowed for improved caregiver-provider communication regarding home pain management, improved scheduling of outpatient sickle cell follow-up, and decreased readmissions.

Design/Method: Data for telemedicine visits conducted between August 2021 through December 2021 are presented here. All patients with SCD admitted to the hematology/oncology unit at Riley Hospital for Children were eligible for a telemedicine visit within 48 to 72 hours of discharge. Visits were requested by the inpatient nurse navigator and included in the patient's discharge education handout.
Telemedicine visits were performed by Hematology/Oncology Advanced Practice Providers (APPs). During the visits, all patients/caregivers were asked: 1) If they had any difficulty obtaining their medications after discharge, 2) If their home pain plan was reviewed with them prior to discharge, 3) If they had any questions about their regimen, 4) If their pain control was adequate, and 5) If they had a follow-up scheduled with the SCD clinic.

Results: Forty-seven patients with SCD were hospitalized during this timeframe. Average age was 12.75 years (+/-5.82). Most (70%) had Hemoglobin SS, and most were hospitalized for pain (83%). Eight patients were readmitted within 30 days.
Of those hospitalized, 4 did not attend their telemedicine visit (1 due to wrong number, 1 refused the visit, and 2 readmitted prior to scheduled visit). Only 48% of patients were given a copy of their home pain plan. Eighteen patients/caregivers had questions about their home pain plan and dosing, needed augmentation of their plan, and/or had difficulty in obtaining their prescriptions after discharge. Five patients did not have a follow-up appointment with the sickle cell clinic scheduled by the time of their telemedicine visit.

Conclusion: Hospital follow-up telemedicine visits allowed for improved communication regarding home management and scheduling of follow-up. The findings from this work demonstrate the usability of telemedicine to improve transition of care from the inpatient to the outpatient setting.

Poster # 035

EFFECT OF CHELATION ON CARDIAC IRON OVERLOAD IN PATIENTS WITH TRANSFUSION-DEPENDENT THALASSEMIA

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Background: Patients with thalassemia develop iron overload from transfusions and increased intestinal iron absorption. Regularly scheduled red cell transfusions are necessary to suppress ineffective erythropoiesis and maintain normal organ function.
Iron accumulates in the liver, heart and endocrine organs leading to significant morbidity and mortality. Heart failure is the leading cause of death in these individuals. Regular iron chelation is necessary for prevention and treatment of iron overload. Until 2005, the most common chelation treatment in America involved prolonged daily subcutaneous infusions of deferoxamine. Deferasirox and deferiprone are longer-acting oral chelating agents approved in 2005 and 2011 respectively.

Objectives: This single-center retrospective study assessed how the prevalence and severity of cardiac iron overload in patients with transfusion-dependent thalassemia has changed over time since the introduction of long-acting oral iron chelation therapies.

Design/Method: We performed a single-center retrospective longitudinal review of cardiac iron in patients with transfusion-dependent thalassemia. Data was collected from patients who consented to our thalassemia registry. Data collected included demographics, timing of the start of regular transfusions, chelation history, and T2* cardiac iron measurements by MRI. Overall rates and severity of cardiac iron overload were analyzed and compared over time and correlated with chelation history.

Results: 124 patients with transfusion-dependent thalassemia on chelation therapy in our registry had at least one cardiac MRI for iron measurements. Of these, 84 patients were transfusion-dependent for ten or more years before an oral iron chelator was started. Rates of normal iron measurements (T2* > 20ms), moderate iron overload (T2* 10-20ms) and severe iron overload (T2* < 10ms) changed from 46%, 21% and 33% respectively during the 2006-2010 period to 81%, 14% and 5% respectively during the 2016-2020 period. Of 63 patients with sequential MRIs, 35% had a decrease in severity of iron overload while 5% had an increase in severity of iron overload. 60 patients had MRIs prior to or shortly after starting oral chelation as well as subsequent measurements. Initial cardiac iron measurements were normal, moderate-elevated and severely-elevated in 48%, 25%, and 27% respectively, while most recent imaging showed normal, moderately-elevated and severely-elevated cardiac iron measurements in 78%, 12%, and 10% respectively.

Conclusion: Cardiac iron overload has improved over time with the advent of long-acting oral iron chelation regimens, likely from increased compliance and continuous chelator coverage. Correlation with cardiac function and iron overload related morbidity in other tissues will provide a more comprehensive picture of the true benefits of oral chelation.

Poster # 036

ALTERATIONS IN HOMEOSTASIS OF THE HUMORAL IMMUNE SYSTEM IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Sickle Cell Disease (SCD) is a red blood cell disorder associated with hemolysis and inflammation impacting homeostasis of the immune system. Chronic hemolysis significantly affects humoral immunity, specifically impacting B cell function and differentiation in adult patients with SCD. The effects of hemolysis on B cell maturation in pediatric SCD, are however, unclear.

Objectives: To assess the frequency of B cell and plasmablast populations in the peripheral blood (PB) of pediatric and adult patients with SCD in comparison to age-, sex- and race-matched controls.

Design/Method: Adult control PB was obtained from Rhode Island Blood Center. Pediatric control and pediatric and adult SCD PB were obtained from Rhode Island Hospital Hematology and Primary Care clinics. PB samples were stained for B cell and plasmablast cell surface makers. Flow cytometry was performed on BD^{TM} LSRII cell analyzer with Diva software v8.0 (BD Bioscience, San Jose, CA). The software data were processed using FloJo software v10.2. Demographics, clinical, and laboratory data obtained from chart review.

Results: We enrolled 15 pediatric (ages 1-16, mean 7.6 years) and 16 adult (ages 18-53, mean 33.8 years) patients with SCD. A majority of enrolled patients had confirmed HbSS genotype (n=12, pediatric and n=9, adult) and were taking disease modifying therapy with hydroxyurea (n=13, pediatric and n=12, adult). Five pediatric controls (ages 10-16, mean 12.8 years) and nine adult controls (ages 19-53, mean 30.8 years) were also enrolled.
Laboratory results indicated elevated hemolysis in both adult and pediatric patients with an Absolute Reticulocyte Count of 203±87 in pediatric and 214 ± 155 in adult SCD. Flow cytometry data revealed 3.3-fold increase in frequency of naïve B cells (CD19+CD27-, p=0.01) and 3.9-fold increase in memory B cells (CD19+CD27+, p=0.02) in pediatric SCD versus controls. No statistically significant changes in frequencies of transitional B cells (CD19+CD24+Cd38+, p= 0.92) and plasmablast (CD19+CD24-CD38+, p= 0.87,) were noted. There was a trend towards increased naïve B cells in pediatric versus adult SCD (p=0.06). No statistically significant differences in naïve B, memory B, transitional B, or plasmablast populations were noted in adult SCD versus controls.

Conclusion: In our cohort, pediatric patients with SCD had increased frequency of naïve and memory B cells compared to pediatric controls, however no increase in frequency of plasmablasts, suggestive of inhibition of B cells differentiation at this stage. Our findings suggest the effect of SCD associated hemolysis on the humoral immune system in children and warrant further investigation.

(Pal et al., Blood, 2021).

Poster # 037

ETAVOPIVAT ONCE DAILY FOR UP TO 12 WKS IS WELL TOLERATED AND IMPROVES ANEMIA IN PATIENTS WITH SCD

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Background: Etavopivat, an investigational, once-daily (QD), selective, erythrocyte pyruvate kinase (PKR) activator, increased PKR activity, resulting in decreased 2,3-DPG and increased ATP in red blood cells (RBCs) of healthy volunteers (HV) and patients with sickle cell disease (SCD).[1,2] In HV, etavopivat 400mg QD demonstrated maximal pharmacodynamic activity. In randomized multiple-ascending dose studies in adolescent and adult patients with SCD (NCT03815695), etavopivat (300mg, then 600mg) or placebo QD for 2wks was well-tolerated and improved hematologic and hemolytic parameters.

Objectives: Report 12-wk open-label (OL) extension-study results to characterize safety and clinical activity of etavopivat 400mg QD in patients with SCD.

Design/Method: In an OL cohort, ≤20 patients aged 12-65 years will receive etavopivat 400mg QD for 12wks. Assessments: safety, pharmacokinetics, pharmacodynamics, and RBC health.

Results: At the time of analysis,11 patients (HbSS/SC, n=10/1) of median age 27 (17-55) years had been treated in the OL cohort: median (range) treatment duration 12 (1-12) wks; 6 patients completed 12wks. Adverse events (AEs) were reported in 7/11(64%) patients receiving etavopivat for ≥1wk. AEs reported in >1 patient were headache and vaso-occlusive crisis (VOC) (n=2[18%] each). Most AEs were grade (Gr)1/2; 1 patient had Gr4 transient blood creatine phosphokinase increase (unrelated). Serious AEs were Gr3 acute chest syndrome and VOC (unrelated; n=1) and Gr3 deep vein thrombosis (possibly related; n=1).

Sustained improvements in hematologic and hemolytic parameters were observed in patients with SCD treated with 400mg etavopivat QD for up to 12wks. Of 6 patients completing 12wks of etavopivat, 5(83%) achieved a >1g/dL hemoglobin (Hb) increase over baseline (mean 1.39g/dL). Of 9 patients treated for ≥4wks, an increase in Hb >1g/dL was reported for 8(89%); the highest mean Hb increase was 1.81g/dL during treatment. Significant reductions from baseline in absolute reticulocyte count and indirect bilirubin were observed at end of treatment. Etavopivat-treated RBCs from the initial OL patients demonstrated improved functional health, point of sickling, and deformability. Additional patient data will be presented.

Conclusion: Etavopivat 400mg QD for up to 12wks was well-tolerated, with a safety profile consistent with underlying SCD. Etavopivat increased Hb levels and reduced reticulocyte counts and hemolysis markers, supporting increased sickle RBC lifespan and improved anemia. Further,

etavopivat improved RBC health, including point of sickling and deformability. These results support ongoing evaluation of etavopivat in adults and adolescents with SCD in the Phase 2/3 Hibiscus Study (NCT04624659) and will inform the design of a pediatric study.
[1]Kalfa et al, Blood 2019.
[2]Brown et al, Blood 2020.

Sponsor: FormaTherapeutics

Poster # 038

LONG-TERM DEFERIPRONE SAFETY IN PEDIATRIC PATIENTS WITH SCD: ~10 YEARS OF DATA FROM THE US REGISTRY

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Background: Deferiprone is an oral iron chelator initially approved by the FDA in 2011 to treat transfusional iron overload in patients with thalassemia. Clinicians prescribed deferiprone off-label to pediatric and adult patients with sickle cell disease (SCD) before FDA-approval for this indication in 2021. Consequently, there are limited real-world safety data available for deferiprone in pediatric patients with SCD. The deferiprone US safety registry program, started in 2011 as an FDA post-marketing commitment, can help characterize deferiprone's long-term safety in pediatric patients with SCD from off-label prescriptions.

Objectives: To evaluate deferiprone's safety profile in pediatric patients with SCD from a US patient registry.

Design/Method: Data were obtained from the Ferriprox Total Care Registry for all US patients receiving deferiprone between December 5, 2011, and August 31, 2020. In this active drug-surveillance program, the central pharmacy queried for safety information monthly, including adverse events (AEs) irrespective of relationship to deferiprone.

Results: The registry contained 130 pediatric (≤17 years of age at referral) patients with SCD (58% female; mean age 13.1 [SD 3.3] years [range 4–17]) receiving deferiprone for a mean of 2.3 years (SD 1.9; range 0.1–8.5) totaling 301.4 patient-years. At the cutoff date, 46 patients (35%) were still receiving deferiprone, 79 patients (61%) had discontinued treatment or the registry, and drug was on-hold for 5 patients (4%) (eg, at physician's discretion or due to noncompliance). Only 8 patients (6%) discontinued due to AEs; most commonly pyrexia (n=2; 2%) and abdominal discomfort (n=2; 2%); 1 patient discontinued due to increased hepatic enzymes. Overall, 71 patients (55%) reported 250 AEs; the most-common AEs were increased liver enzymes (22 events), sickle cell anemia with crisis (n=13; 10%; 20 events), pyrexia (n=12; 9%; 18 events), and nausea (n=8; 6%; 8 events). Two patients (2%) reported 3 events of arthralgia. Forty-three patients (33%) reported 121 serious AEs (SAEs); the most common SAEs were sickle cell anemia with crisis (n=13; 10%; 20 events) and pyrexia (n=6; 5%; 9 events). No patients reported any agranulocytosis events (the most serious potential SAE associated with deferiprone); 1 patient reported 1 event of (less severe than

agranulocytosis) neutropenia. Two deaths were reported; neither was considered deferiprone related.

Conclusion: Based on ~10 years of data from the US registry of patients receiving deferiprone, deferiprone's real-world safety profile in pediatric patients with SCD was tolerable. Importantly, no new safety concerns were identified for pediatric patients with SCD—providing results consistent with observations in adult populations.

Poster # 039

EXPERIENCE FROM THE U.S. VOXELOTOR EXPANDED ACCESS PROGRAM FOR CHILDREN WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a life-threatening disorder characterized by sickle hemoglobin (HbS) polymerization and red blood cell (RBC) sickling that causes complications such as hemolytic anemia, episodic vaso-occlusion, and multisystem end-organ damage. A substantial unmet need for novel therapies remains. Early interventions that target the underlying pathology of HbS polymerization can potentially prevent hemolysis and downstream complications.

Voxelotor was approved by the US Food and Drug Administration for treatment of adults and pediatric patients (aged ≥12 years) with SCD in 2019, and the indication was expanded in December 2021 to include children as young as 4 years of age. Voxelotor is a HbS polymerization inhibitor that prevents sickling and improves key measures of RBC health.

Objectives: The Expanded Access Program (EAP) is an open-label compassionate-use program providing early access to voxelotor for children with SCD aged 4 to 11 years, hemoglobin ≤ 10.5 g/dL, and no alternative treatment options to improve hemoglobin other than standard treatment.

Design/Method: Patients receive a pediatric-friendly formulation of voxelotor as oral dispersible tablets or powder for oral suspension, dosed daily according to their body weight. Clinical assessments of laboratory parameters and health status measures (Patient Global Impression of Change [PGI-C] and Clinician Global Impression of Change [CGI-C]) are performed every 12 weeks. Safety and clinical response with voxelotor are also monitored.

Results: Between January 6 and November 15, 2021, 66 patients from 13 sites were enrolled. Thirty-nine patients have completed the 12-week follow-up visit. Fifty-nine patients are currently still receiving treatment. The mean (SD) age at entry was 7.9 (2.20) years, and median (range) weight was 26.2 (13-51) kg; 85% of patients received concomitant hydroxyurea. Median (range) treatment exposure was 21.9 (1.4-44.9) weeks. Twelve weeks after starting voxelotor, 72% (28/39) of participants had an improvement in hemoglobin. At 12 weeks, CGI-C scores improved in 59%

(23/39) of patients, and PGI-C scores improved in 55% (21/38) of patients. A positive association between reported medication adherence and clinical improvement was observed.

The safety profile of voxelotor among these patients was consistent with previous reports. Three (4.5%) patients discontinued voxelotor due to treatment-related adverse events.

Conclusion: The preliminary findings of the EAP show that voxelotor treatment was associated with increased hemoglobin levels and reported health improvements in pediatric patients aged 4 to 11 years. Higher reported drug adherence was associated with better clinical outcomes. Further evaluation is needed, with additional data and longer follow-up.

Poster # 040

HOSPITALIZATIONS AND EMERGENCY VISITS FOR SICKLE CELL DISEASE PAIN THROUGH THE COVID-19 PANDEMIC

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Background: The Coronavirus (COVID19) pandemic altered all aspects of life, including healthcare. During the pandemic, social distancing led to decreased transmission of typical viral illnesses, leading to a decrease in these pediatric admissions. However, reviews of hospitalizations indicate that hospitalizations in general decreased during the pandemic, which may have led to some unmet healthcare needs and delays in treatment. Sickle cell pain can be triggered by illness, but often has no clear trigger. Little is known about the effect of the pandemic on emergency room visits and hospitalizations for sickle cell pain.

Objectives: We aimed to compare the emergency room visits and hospitalizations for pediatric patients with sickle cell pain during 2020 (the year of the pandemic) compared with the two years prior.

Design/Method: Retrospective review of data across 12 hospitals of our healthcare system was included. ICD 10 codes for sickle cell crisis were utilized to obtain patient encounters. Pediatric patients 21 years of age and younger with the diagnosis of sickle cell pain crisis who were hospitalized or seen in the emergency room and discharged home were included. The number of patient encounters were compared between years (2018, 2019 and 2020). Also, average length of stay was compared between years.

Results: 396 patient encounters were included over the course of 3 years. Emergency rooms visits/year decreased significantly in 2020 from the 2 years prior ($p<0.0001$): 91 visits in 2020, 162 visits in 2019, and 143 visits in 2018. Hospitalizations also decreased in 2020 compared to the two years prior ($p<0.0001$); 198 hospitalizations in 2020, compared with 289 in 2018 and 298 in 2019. There was a statistically significant increase in the mean length of stay in 2020 compared to years prior ($p=0.0016$): 4.61 (+/- 3.81) days in 2020 compared to 3.92 days (+/- 3.74) days in 2018 and 3.86 (+/- 2.7) days in 2019. 3 patient encounters during 2020 were noted to have a

concomitant diagnosis of COVID, and these patients were not included in the analysis.

Conclusion: Emergency room encounters and hospitalizations decreased during the pandemic. However, admitted patients had a longer mean length of stay. It is possible that the pandemic led to more patients managing their pain in the outpatient setting, but for some patients, this may have meant a delay in care, which may lead to a longer length of hospitalization. Further analysis is needed evaluate trends for this population in the pandemic state across larger groups.

Poster # 041

CLINICAL FEATURES OF SEVERE ACUTE CHEST SYNDROME IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Acute chest syndrome (ACS) is a common complication of sickle cell disease (SCD). Despite advances in care, ACS remains a leading cause of morbidity and mortality in children with SCD. There is an ongoing need to establish clinical parameters associated with severe ACS (sACS) in the pediatric population, to develop early intervention strategies for high-risk patients.

Objectives: The purpose of this study is to determine the relationship between hematologic and radiologic clinical findings and sACS in children with SCD.

Design/Method: We conducted a single-institution retrospective chart review of 120 pediatric patients with HbSS or HbSβ thalassemia and at least one documented episode of ACS. Data was collected from the most severe lifetime ACS episode. We extracted laboratory and radiologic data to compare clinical findings. Continuous variables were analyzed using Welch's t-test; categorical variables were analyzed using Fisher's exact test.

Results: Eighty patients in the moderate ACS group were excluded. Twenty patients (median age 5.6 years, SD 4.20) had mild ACS (no supplemental oxygen requirement, only 1 segmental or lobar infiltrate on chest radiography, transfusion of less than 3 units [or 15 cc/kg] of red blood cells). Twenty patients (median age 7.6 years, SD 4.01) had sACS (acute respiratory failure requiring mechanical ventilation and/or exchange transfusion). Median length of stay (LOS) in the sACS cohort was significantly longer than in the mild cohort (median: 8 days vs 2 days, $p<0.001$). The median absolute neutrophil count (ANC) was significantly higher in the sACS cohort (19.8 x 10 μL vs. 9.4 x 10 μL, $p = 0.004$). The median platelet count nadir was significantly lower in the sACS cohort compared to the mild cohort (165 x 10 μL vs. 309 x 10 μL, $p <0.001$). The median number of lobes affected in the sACS cohort were 3, compared to 1 lobe in the mild cohort ($p <0.001$). Approximately 65% of patients with mild ACS had left-sided disease ($p = 0.18$), while 85% of patients with sACS had bilateral disease ($p = 0.002$). The risk of pleural effusions was significantly increased with sACS [OR 76.00 (95% CI 9.235-825.6), $p <0.001$].

Conclusion: Severe ACS in children is a clinically distinct phenotype associated with longer LOS, higher ANC and lower platelet counts during active ACS, involvement of 3 or more lung lobes, and presence of pleural effusions. Future prospective studies investigating the utility of these specific laboratory and radiographic data as components of an ACS severity prediction score are warranted.

Poster # 042

UTILIZING WEARABLE DEVICES AND A MOBILE APP TO COLLECT PATIENT DATA FOR PAIN SCORE PREDICTION

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Background: Sickle cell disease (SCD) is a genetic blood disorder associated with severe complications including recurrent pain, stroke, acute chest syndrome and early death. Pain is unpredictable, difficult to treat, and the leading cause of hospitalization and morbidity. Recent studies have leveraged mobile health technology (mHealth) and biometric data from wearables, which is easily accessible and can be remotely collected, with minimal inconvenience to the patient. Previous efforts have focused on using machine learning on these larger data sets to develop prediction algorithms. The use of mHealth and machine learning for those living with SCD could provide a better understanding of pain as it relates to biometric values, benefiting patients and providers.

Objectives: We aimed to build algorithms to predict pain in people living with SCD. A consumer wearable (Apple Watch) and mobile app collected data from patients which was then compared with vital signs and pain scores collected from EMR.

Design/Method: Following IRB approval, patients entering the SCD Day Hospital at Duke University were approached, consented, and provided with an iOS Apple smartphone and Apple Watch for the duration of their visit. Data collected included heart rate, sleep quality, heart rate variability, activity, mobility data, and self-reported pain scores. Data was then analyzed using R, four models were fitted and pain score predictors were processed.

Results: We enrolled 20 patients with SCD with a median age of 35.5 (25-59). The prediction models created using heart rate (HR), calories burned, and basal energy burned (BEB) were able to predict participant pain scores correctly with approximately 60% accuracy. HR was found to be the most significant predictor of pain scores. The model with the lowest AIC (Akaike Information Criterion), an estimator of the prediction error classically used for model selection, and thus the most applicable was a heart rate and BEB model. These showed the strongest potential of serving as pain predictors with a correct classification rate of 63%

Conclusion: Overall, mHealth technology conveniently collects clinically relevant data that can predict pain in people living with SCD. Patients found the tool easy to use and effective in providing information to their care team. Furthermore, the data collected was found to be useful to

healthcare providers. Additionally, mHealth tools provide a method of data collection that addresses the needs of people living with SCD, and aids in giving a voice to their disease experience.

Poster # 043

ASSESSMENT OF APPROPRIATENESS AND THOROUGHNESS OF HEMATOLOGY REFERRALS FOR IRON DEFICIENCY ANEMIA

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Background: Iron deficiency anemia (IDA) is a common pediatric concern with neurocognitive and behavioral ramifications if untreated. However, unneeded referrals to subspecialists can be costly financially and emotionally for families. Understanding the role of appropriateness and thoroughness of pediatric hematology referrals would improve the quality of necessary referral to subspecialty clinics and improve initial management by pediatricians.

Objectives: The goal is to assess the appropriateness and thoroughness of pediatric hematology referrals in children referred to the Pediatric Hematology Clinic for concerns of anemia.

Design/Method: A retrospective chart review was conducted of 76 patients seen in the Pediatric Hematology Clinic between December 31, 2014 and December 31, 2019, for chief complaint of anemia. Thoroughness was based on inclusion of laboratory values including hemoglobin (Hb), hematocrit (Hct), red blood cell count (RBC), serum iron level, ferritin, and total iron binding capacity (TIBC). We expected less than 40% of referrals would include at least four of these six elements. Appropriateness was based on evaluation of hemoglobin values, dietary history, and history of prior iron therapy. We expected less than 50% of referrals would include three or more of these criteria.

Results: Of the 76 patients included, 17 (22%) met all criteria for appropriateness, and 11 (14%) were missing only one component, for a total of 28 records (37%) with three or more criteria. Thirty-four (45%) records met four or more of the thoroughness criteria, and only 14 (18%) included all six criteria. When Pearson-Chi test applied to evaluate for any statistical significance in appropriateness between patients 0-4 years of age and those older than 4, no statistical significance was found ($p=0.68$).

Conclusion: Less than 50% of referrals met appropriateness criteria, with only 37% including three out of the four listed elements. Regarding thoroughness, 45% of records included four of the six criteria, surpassing the 45% initially hypothesized. The most omitted elements included ferritin (missing from 64% of referrals) and TIBC (missing from 63% of referrals). Dietary history was missing from 58% of referrals. These would be possible areas of intervention to improve referral quality and may help reduce unnecessary referrals by improving the initial evaluation by general pediatricians.

Poster # 044

IMPROVING COMPLIANCE WITH IRON SUPPLEMENTATION GUIDELINES IN BREASTFED INFANTS

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Background: Infants born at term, who are exclusively or primary breastfed, have sufficient iron reserves to last until four to six months of age. Literature has shown that a substantial proportion of infants over the age of six months, particularly breastfed infants, appear to have low absorbed iron and are at risk for iron deficiency. Iron deficiency is a common cause of anemia in children, however iron deficiency alone, has been linked to neurocognitive and behavioral deficiencies, some of which may be irreversible. It is for these reasons that the American Academy of Pediatrics (AAP) recommends supplementation of all exclusively breastfed or primarily breastfed infants starting at four months of age until they are well established on iron rich foods.

Objectives: To increase documentation of iron intake and supplementation requirements in exclusively and primarily breastfed infants as per the AAP guidelines.

Design/Method: Interim analysis of a prospective quality improvement study. The study compared all four and six month well child checks (WCC) of otherwise healthy, term infants who were primarily or exclusively breastfed. Data were collected before and after an educational intervention in our academic pediatric resident continuity clinic. The study compared documentation of and compliance with existing AAP iron guidelines before and after the intervention.

Results: Interim analysis included 164 records of exclusively or primarily breastfed infants at their four or six month WCC. There were 146 pre-intervention visits and 18 post-intervention visits. Prior to the intervention iron supplementation was reported in 4.2% of the four-month WCC, whereas post-intervention it was reported in 16.7% ($p = 0.089$). At the six month WCC 9.8% documented iron supplementation pre-intervention, whereas post-intervention documentation was 16.7% ($p=0.598$).

Conclusion: Interim analysis shows that our educational intervention seems to have increased compliance with the AAP iron supplementation guidelines at the four and six month WCCs in exclusively and primarily breastfed infants, although statistical significance has not been met. The post-intervention sample was small but follow up data collection and analysis are underway at our institution. Educational interventions may increase compliance with AAP iron guidelines.

Poster # 045

DE NOVO DHX38 VARIANT ASSOCIATED WITH CONGENITAL DYSERYTHROPOIETIC ANEMIA WITH RING SIDEROBLASTS

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Background: CDAR (ClinicalTrials.gov Identifier: NCT02964494), a registry for patients with Congenital Dyserythropoietic Anemia (CDA) in North America, has been created with the goal to provide a longitudinal database and associated biorepository to facilitate natural history studies and research on the pathogenetic mechanisms involved in the CDAs. Here we present a case of a child with transfusion-dependent anemia since birth, growth delay, and dyserythropoiesis on bone marrow evaluation who was enrolled in CDAR. Ring sideroblasts (RS) were noted resembling acquired myelodysplastic syndrome (MDS) with the characteristics of Refractory Anemia with RS (RARS). Whole-exome sequencing revealed a de novo, germline *DHX38* missense variant (c.3310A>C, p.Thr1104Pro) in the proband. DHX38 is a splicing factor highly expressed during terminal erythropoiesis similarly to SF3B1, the gene most frequently mutated in MDS-RARS.

Objectives: The aim of the study is to investigate this de novo *DHX38* variant as a candidate gene causing CDA with RS due to abnormal alternative splicing in various transcripts including ones involved in iron metabolism.

Design/Method: RNA-seq data of CD71+ reticulocytes from the proband were analyzed and compared to normal controls. Erythropoiesis cultures from patient-derived iPSCs were utilized to reproduce the disease in vitro, while extra-hematopoietic abnormalities of the nucleus and mitotic defects were explored in fibroblasts generated from patient's skin biopsy.

Results: RNA-seq analysis indicated approximately 7,000 differentially expressed genes, including upregulated expression of genes involved in iron-related pathways, and also evidence of splicing defects. An aberrantly spliced isoform of *SLC25A39*, a mitochondrial carrier participating in iron trafficking, was significantly increased (FC=99.11, $p<0.05$) with downregulation of the main protein-coding isoform (FC=-11.63, $p<0.05$) which was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR). In erythropoiesis cultures of patient-derived iPSCs, cytospins indicated dyserythropoiesis which was quantified by imaging flow cytometry as an increased frequency of binucleation in the erythroblasts produced from patient iPSCs. Grape-shaped nuclei were detected in cultures of patient's fibroblasts indicating improper mitotic exit due to aberrant chromosome segregation.

Conclusion: *DHX38* p.Thr1104Pro is a probable causative mutation for this case of CDA with RARS. Loss of DHX38 splicing activity likely leads to ineffective erythropoiesis, transfusion-dependent anemia, and iron overload via alternative splicing and intron retention and defects in chromosome segregation and cell division.

Poster # 046

CLINICAL PRESENTATION AND OUTCOMES OF PEDIATRICS AUTOIMMUNE HEMOLYTIC ANEMIA: RETROSPECTIVE ANALYSIS

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Background: Autoimmune Hemolytic Anemia (AIHA) is a rare disease in childhood characterized by the presence of autoantibodies against erythrocyte membrane leading to excessive or uncompensated red cell destruction. The clinical presentation of AIHA varies widely from mild anemia to severe life-threatening anemia. Primary AIHA occurs with no clear disease association whereas secondary AIHA is directly associated with a systemic illness. Evans syndrome (ES) is defined as autoimmune destruction of at least two hematologic cell types. Some patients present with isolated AIHA and may develop ES over months to years.

Objectives: To improve our knowledge of the disease manifestation and treatment outcomes.

Design/Method: A chart review was performed in 21 patients diagnosed with AIHA at CHMC (2009-2020). The patients were grouped by demographics, clinical features, subdivided into primary or secondary AIHA, and treatment with single or combined therapy. The treatments consisted of glucocorticoid, IVIG, Rituximab, combination of other immunosuppressors, transfusion, and splenectomy. The rate of cure and time until hemoglobin normalization was determined.

Results: The mean age at diagnosis was 7.42 years (0.25 to 17 years). Patient population included 52% male and 48% female. The clinical features were fever, jaundice, sclera icterus, hepatomegaly, splenomegaly and 29% had 2 or more of these features. The mean hemoglobin at presentation was 6.17 g/dl (2.6 to 9.9 g/dl). Thirty eight percent of the patients had combined AIHA/ES. Direct antiglobulin test (DAT) was negative in less than 1% of the patients. Majority (62%) had secondary AIHA, infections being the most common cause followed by autoimmune diseases.
RBC transfusion occurred in 76% of the patients (mean Hgb at transfusion 5.65 g/dl, range 2.7 to 9.4 g/dl). All patients diagnosed with primary AIHA received a combination therapy (steroids plus any other treatment modalities) compared to 62% in secondary AIHA.
Patients in primary AIHA took an average of 19 days compared to 43 days in the secondary AIHA to normalize their hemoglobin levels. All patients with primary AIHA were cured compared to 30% in secondary AIHA.

Conclusion: Secondary AIHA patients are more likely to present to the hospital and have a prolonged time to recovery compared to patients with primary AIHA who all are cured. These findings highlight the importance of appropriate investigation and proper management of AIHA. Further investigation of comparison of length of follow up between the primary and secondary AIHA groups may help understand the long-term effects on patients requiring long term therapy.

Poster # 101

NEUROFIBROMATOSIS TYPE 1 PATIENTS WITH PLEXIFORM NEUROFIBROMAS TREATED WITH SELUMETINIB

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Background: Neurofibromatosis-1 (NF-1), is an autosomal dominant multiple congenital neurocutaneous anomaly syndrome characterized by malignant and non-malignant tumor growths. PNs have been elusive to surgical interventions due to inoperable sites of growth and substantial complications. The pathogenesis of NF-1 associated tumorous growth stems from a mutation in Neurofibromin leading to unregulated transduction of mitogenic signaling. Recently, the oral agent Selumetinib, an inhibitor of the downstream protein MEK-1/2 of the RAS-MAK pathway, was approved for pediatric NF-1 patients with inoperable PN. The approval was based on Phase 2 clinical trials with a small number of patients.

Objectives: Retrospectively review our early access data of NF-1 patients with PN who were treated with Selumetinib, pertaining to patient response to treatment, tumor shrinkage, symptom improvement and associated drug side effects.

Design/Method: IRB approved, retrospective chart review was conducted on pediatric NF-1 patients with inoperable PN being treated with Selumetinib between 2016-2021. Sixty patients with NF1 PN were identified and 10 were treated with Selumetinib, some through the early access program before FDA approval. Data pertaining to patient demographics, burden of disease, and treatment response were obtained. Adverse effects were graded based on CTCAE version 5.

Results: Ten patients, aged 3-17 years at the start of treatment, were identified. Median age was 9.5 years. The most common anatomical locations of PNs were the face, neck and spine. The most common comorbidity was optic pathway glioma (5 patients). Resolution of pain and improved functionality was reported in 7 and 5 patients within the first year of treatment. Two-dimensional MRI demonstrated 4 patients had regression of PNs within the first 8 months. The most common adverse event was rash (5 patients), occurring within 3 months of starting treatment. Decrease in ejection fraction occurred in 2 patients after 6-11 months of treatment, though one was deemed to be due to variation in measurement from a different operator. Neurocognitive and psychological changes were also observed in some patients.

Conclusion: This retrospective study demonstrates that a majority of patients reported improvement of their PN-related symptoms within a year of treatment, some with parallel radiographic evidence of tumor regression from two-dimensional MRI. All adverse reactions were noted to be mild and self-limited, requiring minimal intervention. Inter-operator variation accounted for the reduction in cardiac EF in one of the patients who had decreased EF after Selumetinib. Selumetinib was well-tolerated in a majority of the patients, though the number is limited.

Poster # 102

PREVALENCE OF MALIGNANCY AND ROLE OF ONCOLOGIC SURVEILLANCE IN OLLIER DISEASE AND MAFFUCCI SYNDROME

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Background: Ollier disease (OD) is rare and characterized by multiple benign cartilaginous tumors known as enchondromas. When multiple enchondromatosis is associated with spindle cell hemangiomas it is known as Maffucci syndrome (MS). Somatic IDH1 and IDH2 mutations are identified in up to 80% of individuals. Patients are at increased risk for chondrosarcoma and other malignancies. There are no universal or consensus oncologic screening guidelines. Presently, there is no approved medical treatment for enchondromatosis.

Objectives: To describe the prevalence of cancer in pediatric patients with OD and MS at a single institution.

Design/Method: A retrospective chart review of patients diagnosed with OD or MS at Boston Children's Hospital was conducted. Patient demographics, clinical information, and oncologic surveillance plans were recorded.

Results: Forty-five patients (22 males [45%], 23 females [51%]) were identified; 36 with OD, 8 with MS, 1 with multiple spindle cell hemangiomas. Median age at diagnosis was 5 years (range 2 months to 14 years). Patients presented with pathologic fracture (20%) or discovery of a "lump" (33%). Functional limitation (48%) and pain (60%) were common. Six patients (5 with MS [83%], 1 with OS [17%]) developed malignancy between 10 and 29 years of age (mean 22.8 years); five are alive with an average follow-up of 6 years (range 1-24 years) after cancer diagnosis. One patient died from metastatic chondrosarcoma. Oncologic diagnoses included grade I/II chondrosarcoma (n=6), acute myelogenous leukemia (n=1), grade III anaplastic astrocytoma (n=1), and paraganglioma (n=1). Sequencing of tumor in 3 patients revealed IDH1 (p.R132C) mutations. One patient with OD developed parathyroid hyperplasia and an IDH1 (p.R132C) was identified from affected tissue. Tissue from a patient with multiple spindle-cell hemangiomas revealed an IDH2 (p.R172T) mutation.

Conclusion: Current literature suggests that patients with OD and MS are at highest risk for malignancy in their second and third decades of life. In our cohort, five patients (4 with MS, 1 with OD) developed malignancy prior to age 25. The true prevalence of malignancy in pediatric patients with OD and MS is unknown. At our institution, patients are now followed by the Vascular Anomalies Center and Pediatric Cancer Genetic Risk Program and receive annual whole-body MRI with surveillance of known neoplasms or concerning lesions. Larger, prospective studies are needed to assess the role of surveillance with whole-body MRI in pediatric OD/MS patients.

Poster # 103

INCIDENTAL FINDINGS? IDENTIFYING 'ADULT' PREDISPOSITION SYNDROMES IN PEDIATRIC ONCOLOGY PATIENTS

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Background: Recent estimates indicate that up to one-quarter of pediatric oncology patients have an underlying cancer predisposition syndrome (CPS); 2-5 fold higher than estimates for adult patients. The use of germline Next-Generation Sequencing (NGS) has increased since multi-gene panels emerged more than a decade ago. A variety of germline NGS panels are utilized by genetic counselors, but gene content is variable and typically curated for adults with cancer. The Cancer Predisposition Program at the UPMC Children's Hospital of Pittsburgh offers patients comprehensive germline genetic testing, which has identified unexpected yet clinically relevant pathogenic variants (PVs).

Objectives: We present a group of pediatric patients identified to have germline PVs atypical for their cancer phenotype.

Design/Method: Patients were evaluated by a pediatric oncologist and genetic counselor during a clinic visit. Pre- and post-test genetic counselling was performed. Retrospective chart and literature review were completed.

Results: We found that 97% of families (335/346) evaluated in the cancer predisposition program opted for germline genetic testing, suggesting that most are motivated to pursue genetic testing despite the possibility of an incidental or uncertain result.

We identified 12 children with 14 germline PVs atypical for their cancer phenotype (leukemia, neuroblastoma, Wilms, ovarian, pineoblastoma, sarcomas). This result occurred in almost 10% of cases (12/122) that underwent panel testing in the clinic.

Three patients with leukemia had heterozygous PV's in Lynch Syndrome associated genes. Leukemia is an expected phenotype with constitutional mismatch repair deficiency, but not typically of Lynch Syndrome. Three patients with sarcomas had PV's in genes not established to cause their tumor type.
The identification of 14 PV's led to cascade testing of 18 first-degree family members. High-risk screening and management protocols were implemented in all 10/10 PV positive relatives, who were diagnosed only after the identification of the PV in the child.

Conclusion: Our findings add to other reports describing novel cases of adult CPS in the pediatric oncology population. In our cohort, significant PVs were identified in patients with both solid and liquid tumors.

The identification of adult CPS in children provides anticipatory knowledge for the child's future cancer risks and management. Four out of twelve children with incidental findings began screening protocols immediately (SDHA, PTEN, APC), and all 12 children had results identified which altered the patient's medical management once the patient reached adulthood.

Our work highlights the value of utilizing comprehensive germline testing in the pediatric oncology population to identify clinically relevant pathogenic variants (PVs).

Poster # 104

ALPELISIB FOR THE TREATMENT OF PROS: RESPONSE RATE BY IMPUTATION IN EPIK-P1

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Background: *PIK3CA*-related overgrowth spectrum (PROS) is a group of rare disorders driven by gain-of-function mutations in *PIK3CA*. No pharmacological therapy addressing PROS etiology is approved. Alpelisib, a PI3Kα inhibitor, directly targets the effects of *PIK3CA* mutations. EPIK-P1 demonstrated the efficacy and safety of alpelisib in PROS. Primary analysis of the primary objective found, among complete cases, 37.5% (12/32; 95% CI, 21.1%-56.3%) of patients had ≥20% lesion volume reduction at week 24 via independent radiological assessment. 74.2% of patients with imaging (23/31) reported any reduction in target lesion volume. Mean reduction was 13.7%.

Objectives: Due to the real-world nature of EPIK-P1, 5 patients with ≥1 target lesion identified at index had a missing response status at week 24. Supportive sensitivity analyses looked to confirm the robustness of the primary analysis by imputing missing volumetric measurements.

Design/Method: EPIK-P1 was a retrospective non-interventional medical chart review of patients (≥2 years, N=57) with severe/life-threatening PROS conditions treated with ≥1 alpelisib dose initiated ≥24 weeks before data cutoff. The efficacy population (n=37) included patients with ≥1 target lesion identified at index date. Patients in the efficacy population missing a response status at week 24 were not included in the primary analysis (complete case). Sensitivity analyses calculated response rate by imputing missing values 3 different ways. *Multiple imputation:* Percentage change in the sum of target lesion volume at week 24 was imputed by a systematic random sampling method (Markov chain Monte Carlo) using sum of target lesions at baseline, age, and percentage change from index date in the sum of target lesion volume at weeks 24, 36, and 52 as covariates. Response status was determined for each patient. Response proportion was calculated for each imputed data set (n=100). Individual response rates were combined into an overall estimate using Rubin's rules (Little and Rubin 2002). *Best-case scenario:* Patients with missing responses at week 24 were considered responders. *Worst-case scenario:* Patients with missing responses at week 24 were considered non-responders.

Results: Response rate was 36.7% (95% CI, 20.6%-52.9%), 45.9% (17/37; 95% CI, 29.5%-63.1%) and 32.4% (12/37; 95% CI, 18.0%-49.8%) for multiple imputation, best-case scenario, and worst-case scenario, respectively.

Conclusion: Sensitivity analyses demonstrate the robustness of the EPIK-P1 primary analysis, as response rates are highly supportive of those previously reported. When considered with the ~74% of patients who observed any reduction in lesion volume, these data strongly speak to the meaningful clinical benefit alpelisib may provide patients with PROS. Supported by Novartis Pharmaceuticals Corporation.

Poster # 105

ALPELISIB FOR THE TREATMENT OF PROS: EPIK-P1 SECONDARY ANALYSES ON PAIN

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Background: *PIK3CA*-related overgrowth spectrum (PROS), a group of rare overgrowth disorders and vascular anomalies driven by gain-of-function mutations in *PIK3CA*, has no approved pharmacological treatment. Pain, a common presentation and/or complication of PROS, is complex to manage and impacts quality of life. Treatment with alpelisib, a PI3Kα inhibitor, was effective, including in reducing pain, in a small number of patients with PROS (Venot et al. *Nature.* 2018;558:540-6). EPIK-P1 evaluated alpelisib in a larger population (N=57), demonstrating efficacy after 24 weeks or 6 months of treatment (Canaud et al. ESMO 2021. LBA23).

Objectives: As treating the underlying cause of PROS may improve pain, we assessed changes in pain severity over time as a secondary objective in EPIK-P1.

Design/Method: EPIK-P1 was a retrospective non-interventional medical chart review of patients ≥2 years with PROS treated with alpelisib. Eligible patients had severe and/or life-threatening conditions, confirmed *PIK3CA* mutation, and received ≥1 dose of alpelisib ≥24 weeks before data cutoff. Pain severity scores from questionnaires were planned to be reported over time to evaluate pain as a secondary objective; however, due to the study's retrospective nature, such data were not consistently collected across patients. Therefore, pain and its management were evaluated using a composite endpoint. Pain reduction was reported in patients at week 24 if scores improved from pain severity questionnaire (ie, Wong-Baker, FLACC, and numerical scale rating), the number of concomitant opioid and/or non-opioid medications decreased, and the number and/or severity of pain-related medical conditions decreased.

Results: Pain severity questionnaire data were available for only 6 patients at both the index date (date of treatment initiation) and at week 24. Based on the composite pain endpoint, 42 of 57 patients (73.7%) reported pain at index date. Of these 42 patients, 31 (73.8%) had pain reduction at week 24: grade 3 pain-related medical conditions were reported in 36 (85.7%) patients at index date and in 5 (11.9%) patients at week 24; opioid and non-opioid concomitant pain medication use was reported by 16 (38.1%) and 12 (28.6%) patients, respectively, at index date and 12 (28.6%) and 9 (21.4%) patients, respectively, at week 24.

Conclusion: The use of a composite indicator for pain reduction limits the extent of missing information and efficiently estimates the incidence of pain in a real-world setting; further validation may be necessary. In EPIK-P1, most patients experienced pain reduction at week 24, driven primarily by a marked decrease in pain-related medical conditions. Funding provided by Novartis Pharmaceuticals Corporation.

Poster # 106

A NOVEL MOBILE APP TO FACILITATE SURVEILLANCE PROTOCOL ADHERENCE IN CANCER PREDISPOSITION PATIENTS

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Background: Evaluation for hereditary cancer is becoming increasingly integrated into the practice of oncology. There are over 60 cancer predisposition syndromes attributable to germline pathogenic variants in 100+ genes. Strategies to reduce cancer risk for these patients are necessary, often orchestrated through multimodal surveillance protocols comprised of imaging studies, procedures, and bloodwork. Protocols differ based on syndrome, age, gender, medical history and are periodically updated. While intensive surveillance has shown improvement in patient quality of life, even overall survival, it can be cumbersome to manage. Technology via a mobile application can greatly reduce the burden of adherence to clinical surveillance protocols by providing set reminders and schedules. Further, a mobile application can offer a data repository for personal and family medical histories, syndrome-specific patient education, and care coordination resources. This type of mobile application can help streamline complex multidisciplinary care for patients, families, and their providers.

Objectives: The objective of our study is to ascertain usability and feasibility data regarding a novel smartphone app designed to improve education about and adherence to recommended cancer surveillance protocols for patients and families with cancer predisposition syndromes

Design/Method: HomeTown was developed by The AppHatchery, a Georgia Clinical & Translational Science Alliance initiative focused on developing innovative, translational medical apps. The app allows users to build a "hometown" network, inputting specific personal and family history, health care providers, and health care facilities. The app provides built-in recommended age-, gender-, and syndrome-specific surveillance guidelines, though allows users to customize based on individual needs and provider recommendations. Surveillance protocols are centralized into one location and integrated into the in-app calendar with push notification reminders to schedule and/or attend appointments. An education section links directly to syndrome-specific websites, allowing users to view information about key cancer predisposition syndromes. Finally, usability and feasibility surveys help determine whether the app meets the needs of patients, touching upon usefulness, expectations, satisfaction, and learning curves.

Results: To date, 16 patients have enrolled in the HomeTown study. Additionally, semi-structured interviews were conducted with 7 of these patients to provide feedback on app features they liked, found confusing, and areas for improvement.

Conclusion: Strategies to reduce cancer risk for patients with predisposition syndromes are necessary, though recommended surveillance protocols can be cumbersome. HomeTown is a novel smartphone app providing users with built-in age-, gender-, and syndrome-specific surveillance

guidelines, customization options, and push notification reminders to schedule and/or attend clinical visits. Usability and feasibility data gathering is underway.

Poster # 107

GERMLINE FINDINGS IN PEDIATRIC MELANOMA

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Background: Approximately 10% of adults with melanoma harbor a pathogenic or likely pathogenic germline variant in a cancer predisposing gene. It remains unclear whether the same holds true for children and young adults with melanoma.

Objectives: The goal of this study was to determine the prevalence and spectrum of germline variants in children and young adults with melanoma who underwent genetic testing in the Cancer Predisposition Clinic (GPC) at St. Jude Children's Research Hospital.

Design/Method: The charts of children and young adults with melanoma who were referred to the GPC between June 2014 and September 2021 and underwent germline testing were retrospectively evaluated. Demographic, clinical, and family history data were gathered, as well as information surrounding the results of germline genetic testing.

Results: Thirty-eight patients were included in this study (21 males, 17 females) with an average age at melanoma diagnosis of 11.2 years (range: 1–32). The majority were white (n= 36, 95%). Diagnoses included malignant melanoma (n=19; 50%), spitzoid melanoma (n=14; 37%), and uveal melanoma (n=5; 13%). Thirty-two patients had primary melanoma, while 6 developed melanoma as a subsequent malignant neoplasm. Eight patients (21%) had a positive family history of melanoma. Thirteen (34%) underwent comprehensive testing of 63–115 genes, and the remainder underwent testing with smaller gene panels. Overall, five patients (13%) harbored germline pathogenic variants: one with bi-allelic *PMS2* variants (p.Ile611AsnfsTer2; p.Pro246Cysfs, consistent with (c/w) known diagnosis of constitutional mismatch repair deficiency [CMMRD]); and one each with heterozygous *TP53* (p.Arg213Gln, c/w Li-Fraumeni syndrome); 17q21.31 deletion (c/w Koolen-de Vries syndrome); *BRIP1* (p.Gln685Ter), and *ATM* (p.Lys750Lys; silent change with skipping of exon 14) variants. Cascade testing revealed *de novo* status for the *TP53* and 17q21.31 deletion variants and maternal inheritance for the *ATM*, *BRIP1,* and *PMS2* p.Ile611AsnfsTer2 variants (the father has not been tested). Of the five patients with positive germline results, four had spitzoid melanoma. The patient with CMMRD had a positive family history of melanoma. All germline variant-positive individuals were counseled regarding syndrome-specific cancer risks and recommended surveillance.

Conclusion: In this convenience cohort, 13% of children and young adults with melanoma who underwent germline testing through the GPC harbored an underlying mutation in a cancer predisposition gene with several of these genes not currently associated with melanoma formation.

Efforts are underway to evaluate tumor genomic data for loss of heterozygosity and/or mutational signatures to further elucidate the role of these germline variants in melanoma tumorigenesis.

Poster # 108

INCIDENCE OF PEDIATRIC, ADOLESCENT, AND YOUNG ADULT CANCERS IN UNITED STATES MILITARY HEALTH SYSTEM

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Background: There is limited research on cancer incidence in pediatric and adolescent/young adult (AYA) patients using healthcare claims data. The Military Health System (MHS) is a complex global healthcare system that provides universal health coverage to 2.3 million pediatric and AYA beneficiaries. The Military Health System Data Repository (MDR) is a comprehensive billing data repository that offers a novel opportunity to assess cancer incidence.

Objectives: This study aims to establish an algorithm to estimate cancer incidence rates within the MHS pediatric and AYA populations and validate it using the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program.

Design/Method: This study aimed to determine the number and type of pediatric and AYA (0-28 years) cancer diagnoses from 2013-2017 in the MHS. The MDR was queried for relevant International Classification of Diseases (ICD) codes. Incident cases were defined using a 3-year lookback period for all age groups and a 1-2 year lookback period for those under 3. Our method restricted incident cases to individuals who had ≥3 diagnoses of that type within 90 days. Cases underwent a verification stage utilizing provider taxonomy codes, ensuring that the relevant ICD codes were placed in the medical record by clinicians and surgeons directly involved in the identification and initial management of these diagnoses. Age-specific incidence rates within the MHS were compared to the SEER database using standardized incidence ratios organized by cancer subtype.

Results: This algorithm effectively validated this method to predict cancer incidence rates in the MHS for the most common pediatric and AYA cancer diagnoses. The standardized incidence ratio (95% confidence interval) between the MHS and SEER were comparable for each of the following diagnoses: acute lymphoblastic leukemia 0.89 (0.77-1.01), acute myeloid leukemia 1.07 (0.85-1.3), central nervous system tumors 0.95 (0.82-1.09), Hodgkin's Lymphoma 0.95 (0.82-1.09) and bone tumors 1.01 (0.83-1.21).

Conclusion: This study is the first to report pediatric and AYA cancer incidence rates using the MDR database and represents a new method of describing cancer incidence. Currently, the method is best suited for common pediatric and AYA cancer diagnoses. Future aims include evaluating alternative criteria for the algorithm to capture additional rare cancers. Using this data, we can accurately define and capture the burden of pediatric and AYA cancer within the MHS. Accurate identification of cases within the MDR serves as an invaluable research tool for cancer

epidemiology and can inform future study of geographic patterns of care, clinical trial enrollment, and patient outcomes.

Poster # 109

IMPLEMENTATION OF ALGORITHM TO DECREASE INAPPROPRIATE USE OF RASBURICASE

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Background: Tumor lysis syndrome (TLS) is an oncologic emergency categorized as the rapid breakdown of malignant cells that result in hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Allopurinol and rasburicase are medications used to reduce uric acid levels in the blood, thereby decreasing the risk of tumor lysis syndrome. When to use one agent versus the other can be tricky, as there are currently no guidelines published to aid in this decision-making.

Objectives: At Oklahoma Children's Hospital, a medication use evaluation was completed to assess the use of rasburicase over a one-year period. It was determined that rasburicase was prescribed inappropriately due to lack of guidance, thereby resulting in unnecessary costs of care.

Design/Method: A multi-disciplinary quality improvement team used the Plan, Do, Study, Act methodology aimed at decreasing the use of rasburicase. In the Plan phase, the team developed an algorithm to aid prescribers in decision making when ordering either allopurinol or rasburicase. The algorithm was implemented at Oklahoma Children's Hospital in January 2021 as part of the Do phase. A follow-up medication use evaluation was conducted ten months after implementation of the algorithm in order to assess prescribing patterns of allopurinol and rasburicase during the Study phase. The team analyzed the data and found a substantial decrease in the use of rasburicase leading to a significant cost savings for the hospital. As part of the Act phase, the team updated the hospital's rasburicase policy to include the treatment algorithm and prescribing interventions identified.

Results: During the initial one-year period, 40 doses of rasburicase were administered to 21 patients, accounting for a total cost of $101,884. After implementation of the algorithm, 17 doses of rasburicase were administered to 10 patients during the 10-month follow-up period, for a total cost of $37,891. The algorithm is projected to decrease use of rasburicase by 50% for an anticipated yearly cost savings of over $51,000 when scaled to a one-year follow-up period.

Conclusion: Using the Plan, Do, Study, Act methodology, a multidisciplinary quality improvement team was able to decrease the overall use of rasburicase at Oklahoma Children's Hospital by implementing an algorithm to aid in prescribining allopurinol and rasburicase for prevention of tumor lysis syndrome.

Poster # 110

CHG FOAM IMPROVES ADHERENCE AND PATIENT SATISFACTION COMPARED TO WIPES FOR CLABSI PREVENTION

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Background: Central line associated blood stream infections (CLABSIs) are a significant source of morbidity and mortality for pediatric hematology/oncology patients. Nurses at our institution use a daily hygiene bundle as a part of our CLABSI preventative practices. This bundle has included daily bathing with soap and water followed by using 2% chlorhexidine gluconate (CHG) cloths to wipe down the skin. CHG is a broad-spectrum antiseptic that disrupts bacterial cell walls and consistent use decreases CLABSI rates; however, adherence was suboptimal. A new 4% CHG foam soap presented a potentially more convenient option, as it could be applied directly while bathing.

Objectives: We hypothesize that this new CHG foam would increase adherence while maintaining excellent primary CLABSI prevention.

Design/Method: We initially selected high-risk patients admitted to the Hematology-Oncology and Bone Marrow Transplant (BMT) units to trial the 4% CHG foam instead of the wipes. Patients selected had tunneled external central venous lines (CVLs), prolonged immunosuppression, and a history of poor-adherence with CHG wipes. Patients and parents completed surveys to describe their experiences with the CHG foam. After this initial trial cohort, CHG foam was implemented as an option for the entire Hematology-Oncology and BMT inpatient units. CHG adherence rates were measured by random audits by nursing administration, and CLABSI incidence was measured by retrospective chart review. Results were analyzed using run charts and u-charts, respectively.

Results: Twenty-two of 24 surveyed patients and families preferred the CHG foam over wipes, reporting that they were more likely to bathe using the foam, and that the foam made the required daily bathing easier. The Hematology-Oncology unit reported high rates of adherence (>90%), with no downward trends or median shifts demonstrated by run chart analysis. BMT unit monthly adherence rates demonstrated an upward run during the intervention period, suggesting an increase in the median compliance from 55% (range 36-75%) at baseline to 81.6% (range 58-96%). Primary CLABSIs remained rare events, as average monthly rates remained the same for both units (<1/1000 CVL days) and no values were above the upper control limit on u-charts.

Conclusion: Four percent CHG foam was a favorable option for patients to maintain daily hygiene, and daily adherence improved over time. CLABSIs remained rare events during our study period. CHG foam offers an easy and efficient method to aid in daily hygiene maintenance.

Poster # 111

"NOT JUST A BATH": A MULTI-DISCIPLINARY QI PROJECT TO INCREASE COMPLIANCE OF DAILY CHG TREATMENTS

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Background: Many children with cancer and blood disorders are at risk for central line associated bloodstream infections (CLABSI). Daily bathing with chlorhexidine gluconate (CHG) is a strategy to reduce CLABSI, and standards of care at our institution require daily baths followed by a CHG treatment in all patients. Compliance with daily CHG treatments was identified as the component of our unit CLABSI bundle with the lowest compliance over a 12-month period, therefore a multi-disciplinary quality improvement (QI) project was developed to improve compliance with daily CHG treatments.

Objectives: SMART aim: Increase compliance with daily CHG treatments for patients admitted to the hematology/oncology unit with central venous catheters from a baseline of 83% to greater than or equal to 90% from February to August, 2021.

Design/Method: We used mixed-methods to assess barriers and facilitators to the current CHG treatment process and to inform QI tools (Ishikawa and Key Driver diagrams). We conducted 18 semi-structured interviews with nurses, physicians, advance practice providers, and parents as well as surveys administered to a convenience sample of 30 nurses and 30 parents. Plan-Do-Study-Act (PDSA) cycles included PDSA#1 (Feb-April): Implementation of unit bath board, re-education on electronic medical record (EMR) documentation requirements, daily documentation reminder texts, documentation audits with direct feedback by QI team, stocking bath supplies in patient rooms, updated signage on CHG treatments in patient restrooms, EMR order for daily CHG treatments, and implementation of an escalation protocol to address patient/parent refusal of CHG treatments. PDSA#2 (May-June): Additional documentation education, discussing CHG treatments at new diagnosis education, and follow up with unit staff and parents to obtain feedback on initial interventions. PDSA#3 (July-Aug): Additional documentation education. Monthly infection control data on CHG compliance served as the primary outcome measure.

Results: Following PDSA Cycle 1, unit compliance with CHG treatments improved to 91%. Compliance was sustained following PDSA cycle 2 at 90% and improved to 93% by the end of PDSA Cycle 3. Regular education with nursing staff about EMR documentation decreased incomplete documentation from baseline of 21% to 11% by the end of PDSA Cycle 3. Stocking bathing supplies in the room was identified by nurses and parents as a key intervention to improve compliance with CHG treatments.

Conclusion: Over a six-month period our multi-disciplinary QI team exceeded the SMART aim goal. Input from key stakeholders identified key drivers and informed our initial and subsequent interventions. Next steps include additional interventions to address patient/parent refusal of CHG treatments.

Poster # 112

IMPLEMENTATION OF AN UV-C LIGHT DISINFECTION DEVICE IN AN ONCOLOGY UNIT: A QUALITY IMPROVEMENT STUDY

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Background: Mobile phones have been recognized as fomites and contributors to healthcare-associated infections (HAIs). There is a growing need for the use of renewable and efficient disinfection devices within healthcare settings especially with the ongoing pandemic. We previously reported a 98.2% reduction in pathogenic bacteria on phones after one 30 second cycle of an ultraviolet-c light (UVC) disinfection device.

Objectives: To study the impact of implementing UVC devices in an oncology unit and assess healthcare workers' (HCW) utilization of the devices.

Design/Method: A prospective study of HAIs in a closed inpatient pediatric oncology unit between Oct, 2020-Oct, 2021 after implementation of UVC devices, and an optional survey for HCWs using the device.

Results: Within the oncology unit with UVC devices (ONC+UVC), there were no cases of CAUTI observed before vs after UVC device implementation. There was no difference in the amount of CLABSI before vs after UVC device (23 vs 20; p=0.120), no difference in the amount of C. Diff infections before vs after UVC device (8 vs 5; p=0.718), and no difference in the amount of MRSA infection before vs after UVC device (1 vs 0; p=0.487).

Between oncology units without UVC device (ONC-UVC) vs ONC+UVC, there were no differences in the amount of CAUTI infections (1 vs. 0; p=0.328) and C. Diff infections (1 vs 5; p=0.134). There were no cases of MRSA between both units. However, there was significant difference in the amount of CLABSI infections between ONC-UVC vs ONC+UVC (4 vs 20; p=0.014).

Of 58 surveys completed, 38 (65.5%) were RN, 7 (12.1%) were MD, 3 (5.2%) were PT, 10 (17.2%) were others. Approximately 47% used the UVC device once per shift, and majority (n=50; 89%) reported that the UVC device is easy to use. More than half (n=39; 68.5%) thought the device is effective in reducing viruses and bacteria on mobile phones, and majority (n=47; 82%) thought it can prevent infection in the hospital. Most (n=48; 84%) of the HCWs felt safer with UVC devices during patient care, and 50 HCWs (87.7%) had increased frequency of disinfecting mobile phones.

Conclusion: HCWs reported increased mobile phone disinfection with implementation of a UVC device. Although there was a decrease in rates of HAIs upon implementation of the UVC device, it was not statistically significant. However, there was an overwhelmingly support amongst the HCWs in utilizing the device and its contribution to infection prevention. Evaluation of hospital acquired viral infections are ongoing.

Poster # 113

ATRAUMATIC NEEDLES FOR LUMBAR PUNCTURES WITH INTRATHECAL CHEMOTHERAPY:ASSESSMENT FOR PRACTICE CHANGE

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Background: Intrathecal (IT) chemotherapy is a critical component of pediatric acute lymphoblastic leukemia treatment. Post-dural puncture headaches are reported at a frequency of 2-15% with the use of conventional lumbar puncture (LP) needles. The use of atraumatic LP needles has recently been endorsed by the Children's Oncology Group; however the feasibility of the change to these needles has not been assessed. There are hypothesized concerns around the success and safety of using atraumatic needles, including longer sedation times, more LP attempts, and increase in traumatic taps.

Objectives: Assess the feasibility and safety of using atraumatic needles to deliver IT chemotherapy in comparison to conventional needles

Design/Method: PDSA cycle #1 compared conventional 22-gauge needles and atraumatic 25-gauge needles by measuring number of LP attempts, traumatic taps, and procedure times. Increased number of attempts were noted with the atraumatic needles, and providers found that the 25-gauge needles were very flexible. This led to PDSA cycle #2, which compared 24-gauge and 25-gauge atraumatic needles.

Diagnostic LPs were excluded. We suggested a switch to conventional needles after two failed atraumatic LP attempts, though providers could switch earlier. Data analysis excluded procedures with ≥4 attempts or durations ≥20 minutes.

Results: No serious safety events were associated with the use of atraumatic LP needles. There were 240 procedures attempted with conventional needles and 356 with atraumatic needles. For conventional needles, 88.8% and 97.1% were successful at the first and second attempt respectively. For atraumatic needles, 76.7% and 87% were successful at the first and second attempt. When comparing successful procedures (240 conventional, 313 atraumatic), traumatic taps occurred with 17.5% and 19.2% of conventional and atraumatic LPs. Procedure times were longer for atraumatic LPs with an average of 5 minutes 56 seconds, compared to 3 minutes 21 seconds for conventional LPs.

For PDSA cycle #2, there were 18 procedures with 24-gauge atraumatic needles and 187 procedures with 25-gauge atraumatic needles. Number of attempts were similar (1.1 versus 1.12) and the average duration was similar (4 minutes 57 seconds versus 5 minutes 14 seconds). Traumatic taps were slightly lower with 24-gauge needles at 16.7%, versus 19.8% with 25-gauge needles.

Conclusion: Procedure and sedation times are increased with atraumatic needles. We will assess the impact of using concentrated volumes of IT chemotherapy with PDSA cycle #3.

Success with atraumatic needles will likely improve with increased provider experience. We will also perform another PDSA cycle to evaluate 22-gauge atraumatic needles once they are available.

Poster # 114

A QUALITATIVE ASSESSMENT OF PERCEIVED BARRIERS TO USE OF A CONTINUOUS TEMPERATURE MONITORING DEVICE

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Background: We recently reported that use of high frequency temperature monitoring (HFTM) wearable devices (WD) leads to early detection of fever events in cancer patients (Flora et al, *Cancer Cell*, 2021), which could greatly improve patient outcomes. Prior studies have shown that HFTM WD are feasible and generally acceptable by patients. However, to enable maximal uptake of this approach, it is important to explore barriers to use of HFTM WD that are perceived by patients and family caregivers.

Objectives: To explore perceived barriers to use of HFTM WD among pediatric patients with cancer.

Design/Method: We conducted a retrospective analysis of qualitative data from a single-center, observational IRB-approved study of an FDA-approved HFTM WD (TempTraq®; BlueSpark Technologies, Inc.) among pediatric families. Eligible pediatric cancer participants consented to the application of the WD, which is a Bluetooth®-connected patch applied to the skin using a silicone-based adhesive. Research coordinators performed routine monitoring for WD compliance and entered qualitative data into the study's REDCap database. The present analysis focused specifically on capturing qualitative information on perceived barriers to use of the WD. Two coordinators reviewed the data, identified common themes, and developed a codebook. After independently coding the data, four coordinators convened, resolved discrepancies, and identified major themes.

Results: Between November 2020-December 2021, 55 participants enrolled in this observational research study. The median age was 7 years (range: 3 months-19 years). From the qualitative analysis of participant feedback, four main themes emerged: potential skin issues (e.g., irritation, poking); psychosocial barriers (e.g., too busy, too stressed); clinical barriers (e.g., too ill); and technological barriers (e.g., poor Bluetooth connectivity). The most common barriers were skin irritation and toddlers/young patients removing the patches from perceived discomfort. Nonetheless, participants showed continued interest in using the HFTM WDs.

Conclusion: Our study identified perceived barriers to use of HFTM WD and indicated continued interest in this approach among patients and families for home monitoring. Our findings can inform future study designs to optimize uptake of this approach, which may improve pediatric cancer patient outcomes.

Acknowledgements
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Poster # 115

PATIENT CHARACTERISTICS ASSOCIATED WITH PATIENT-CONTROLLED ANALGESIA PUMP USE DURING CANCER THERAPY

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Background: Pediatric oncology patients commonly report cancer-related pain. This is associated with increased distress and lower health related quality of life. More research is needed to identify patients most at risk for severe pain symptoms so that early interventions may be implemented.

Objectives: To identify pediatric cancer patients at risk for requiring use of an opioid patient-controlled analgesia pump (PCA) during therapy.

Design/Method: A convenience sample of patients diagnosed with cancer (2006- 2021) who received systemic chemotherapy were identified through the electronic medical record. Their pain symptoms and management were abstracted during their active treatment and were censored at completion of therapy, time of death, allogeneic stem cell transplant, first admission for anti-GD2 monoclonal antibody therapy, or when lost to follow-up. Nominal variables were compared using Pearson's Chi-square/Fisher's exact test and multivariable Cox Proportional Hazard model was performed.

Results: Two hundred one patients were followed for a median of 218 days. Diagnoses included 52.7% hematologic malignancies and 12.4% metastatic solid tumors. The most frequently reported pain symptoms were neuropathy (33.8%), musculoskeletal pain (32.3%), mucositis (26.9%), and headache (24.4%) with 92.5% of patients requiring at least oral opioid medications.

A hospital admission requiring a PCA for pain control occurred in 17.4% (N=35) of patients. There was no difference in PCA use based on gender, race/ethnicity or household structure. Factors associated with PCA use included metastatic solid tumor diagnosis (22.9% vs. 10.2%, P=0.050) and any alkylating agent exposure (82.9% vs. 62.7%, P=0.022). Patients requiring a PCA were older with median age 10 vs. 6 years (P=0.011). The only reported pain type directly associated with need for a PCA was chest pain (8.6% vs. 1.2%, P=0.038), however, the most common indications for PCA use were mucositis (43.2%), abdominal pain (21.6%), and neuropathic pain (18.9%). In multivariable analysis, each year of age increased the hazard of needing a PCA during a hospital admission by 71% (95% confidence interval [CI] 1.015-1.30, P=0.12) and was a trend that having a metastatic solid tumor resulted in a 2.1 fold increased hazard (CI 0.96-4.8, P=0.064). The median duration of PCA use was 7 days (interquartile range 3-12). Of the 35 patients requiring a PCA during an admission, 20% had a subsequent admission requiring a PCA.

Conclusion: Use of PCA is common in pediatric oncology, particularly in older patients with metastatic solid tumors. Additional research is needed to determine if earlier supportive interventions can decrease the need for hospital admission requiring PCA pain control.

Poster # 116

"KEEP MOVING FORWARD": COPING MECHANISMS AND ADVICE FROM ADOLESCENTS AND YOUNG ADULTS WITH CANCER

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Background: It is well established that a cancer diagnosis disrupts patients' lives. This is especially true among adolescent and young adult (AYA) cancer patients who are concurrently undergoing key developmental educational, vocational, and social milestones. Previous work has established that these disruptions are distressing, and various interventions have been implemented to provide support, with variable success. Less well understood are the strategies AYA cancer patients use independently that enable them to successfully cope with their cancer experience.

Objectives: The aim of this investigation is to 1) Describe stressors encountered by AYA oncology patients, 2) Identify independently- adopted strategies AYAs use to cope with their cancer experience, and 3) Report advice imparted by AYAs to their peers diagnosed with cancer.

Design/Method: This single-institution concurrent mixed methods study collected demographic data; survey data examining knowledge, values, concerns, and needs; and conducted semi-structured interviews. Eligible patients were 12 to 25 years old, had been diagnosed with cancer within the past 2 to 12 months and received treatment at the institution's adult cancer center or pediatric hospital.

Results: Twenty-seven eligible participants were identified. Most were male (63%), at least 18 years old (67%) and within 6 months of their cancer diagnosis (85%). About half (55%) were treated at the pediatric hospital. We identified 5 themes related to stress and disruption: 1) Uncertainty surrounding diagnosis and treatment; 2) Impact on goals; 3) Loss of independence; 4) Limitations of support network; and 5) Side effects. Importantly, four broad domains of coping emerged, which were applied in varying degrees to the above stressors: A) **Self-advocacy** encompassed actively engaging with the medical team and independently seeking information; B) **Access support network** included appreciating being cared for and accepting help; C) **Action items** covered concrete "to do's" including focusing on what one can control, participating in activities and hobbies as able, staying occupied during hospitalizations and outpatient treatments, and volunteering time and experience; D) **Attitude framing** included more complex strategies such as taking advantage of life disruptions by using the time to carefully examine goals, welcoming new perspectives imparted by diagnosis and treatment, working to accept new reality, and recognizing that goals may need modification but are still achievable.

Conclusion: AYAs are experts of their cancer experience. Their collective wisdom and reflective advice provides lived experience guidance for the development of impactful psychosocial

interventions for future oncology patients.

Poster # 117

REVISITING FUO FROM A PEDIATRIC ONCOLOGY STANDPOINT: A SINGLE INSTITUTION EXPERIENCE

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Background: Fever of unknown origin (FUO) is a common presentation in children with an extensive differential diagnosis that encompasses multiple specialties. From an oncologic standpoint, the differential includes marrow infiltrative disorder, such as acute leukemia, neuroblastoma, and other malignancies, and hyperinflammatory syndrome, such as hemophagocytic lymphohistiocytosis (HLH), among others. Due to the rarity of HLH and nonspecific symptoms at initial presentation, specialists are often consulted later in the disease progression, which complicates disease evaluation further. Cook Children's Medical Center (CCMC) has recently developed a multidisciplinary histiocytic disorder group that is often consulted on cases presenting with FUO in order to increase awareness and potentially not miss new HLH cases.

Objectives: In this study, we examine the clinical presentation, workup, and treatment of patients consulted on by this histiocytic disorder group and describe the clinical course of the patients diagnosed with HLH.

Design/Method: This is a retrospective, observational study evaluating patients aged ≤21 years, who were admitted to CCMC for FUO and consulted on by the histiocytic disorder group between May 2020 and November 2021. Patients who were not referred to the histiocytic disorder program or did not initially present with FUO were excluded.

Results: A total of 13 patients were included in the study. One (8%) patient remained undiagnosed, and 12 (92%) patients had a definitive diagnosis involving rheumatology (31%), oncology (38%), infectious disease (15%), and other (8%). More specifically, 2 (15%) of patients consulted on by the histiocytic disorder program were diagnosed with HLH. A ferritin level was collected in 12 (92%) patients and elevated in all 12 patients. Five (38%) patients demonstrated a ferritin > 10,000 microg/L with diagnostic variability among oncology, rheumatology, and infectious disease specialties. Soluble IL-2 receptor was collected in 10 (77%) of patients. The value was elevated in all 10 patients; however, only 2 of these patients were diagnosed with HLH.

Conclusion: The differential diagnosis of FUO is extensive, even within the field of oncology. A total of 13 patients consulted by the histiocytic disorder program at a single institution were investigated. One case of neuroblastoma and 2 cases of HLH were discussed in particular. A review of the current diagnostic criteria for HLH may be warranted given recent findings of markers such as soluble IL2 receptor and ferritin as inherently nonspecific.

Poster # 118

A REPORT FROM THE UNIVERSITY OF CALIFORNIA CHILDREN, ADOLESCENT AND YOUNG ADULT CANCER CONSORTIUM

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Background: Over the past decade, the care of adolescent and young adult (AYA) patients has advanced to address complex medical and psychosocial issues and disparities in outcomes when compared to pediatric or older adult cancer patients. In June 2019, representatives from all University of California (UC) pediatric oncology programs met in Sacramento to discuss approaches to collaborative work. The result was the UC Children, Adolescents and Young Adults Cancer Consortium (UCCAYACC), formed to facilitate the development and implementation of research and promote harmonization of clinical pathways and best practices. For this study, the AYA subcommittee partnered with the national non-profit leader in AYA Care, Teen Cancer America (TCA), to assess the facilities and services for AYA cancer patients across the UCCAYACC.

Objectives:
1. Describe qualitatively and quantitatively the different programmatic efforts occurring within the AYA programs across the UCCAYACC.
2. Use the data to strengthen the AYA programs by:
    a. Assessing best practices at the different UC sites from which standard operating procedures can be developed to improve AYA care within the UC health system.
    b. Improve opportunities for collaborative research.

Design/Method: Surveys describing the AYA programs across the UCCAYACC were sent electronically, including both fixed response and open-ended questions. The TCA survey included questions about the number of AYA patients, AYA program referrals, resources for onco-fertility preservation, and affiliations with AYA-specific research.

Results:
- Quantitative findings: Five of seven of the AYA programs were in developmental stages at the time of this initial survey. Two programs were described as established. Four programs (57%) indicated adult oncology collaborations. Five hospitals offered male fertility preservation at diagnosis regardless of risk, while two sites offered upon request and to high-risk patients only. Three hospitals offered female fertility preservation only to high-risk patients and upon request; two hospitals reported offering at diagnosis regardless of risk; and one hospital reported that it is rarely offered.
- Qualitative findings: Major themes included interest in improving the onco-fertility program and patient and staff education on AYA care. Programmatic strengths to be implemented across the UCCAYACC included networking opportunities through an annual retreat or social media accounts to encourage peer-to-peer mentoring and leadership.

Conclusion: Surveys across the UCCAYACC highlighted the need to enhance AYA clinical trial enrollment, build standardized guidelines, increase access to resources, reinforce collaboration with adult oncology, and improve referrals to onco-fertility and psychological support. Future directions to establish AYA programs across the UCCAYACC include development of standard operating procedures, services, and clinical trial pathways.

Poster # 119

CONNECTING CHAMPIONS: MENTORSHIP FOR KIDS & YOUNG ADULTS WITH CANCER

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Background: Patients with a pediatric oncology diagnosis often experience significant psychosocial side effects following intense treatment and hospitalization. These side effects include, but are not limited to, a reduction in social activities and a decrease in self-confidence. Previous research suggests peer support and personalized social interaction as promising interventions for the negative outcomes associated with this population. One intervention that may be beneficial for psychosocial development is mentoring, which is associated with positive behaviors, relationships, and career preparedness in at-risk youth. Providing mentors to patients with a pediatric oncology diagnosis may help mitigate the psychosocial effects of treatment. Connecting Champions (CC) is a non-profit organization that works towards combating the negative outcomes associated with pediatric cancer through mentorship and companionship.

Objectives: This study is being conducted in two phases and this abstract covers phase 1. The first phase examines the relationship between patients with an oncology diagnosis and their appointed mentor. The second phase will examine how their relationship is related to psychosocial outcomes.

Design/Method: Data was collected via survey administration to participants who were previously in or are currently a part of CC. The survey was administered to 33 participants (51.52% male), ages 10-22 (M=17.03, SD=3.28), and included basic demographic information along with the Mentoring Process Scale (MPS). This measure consists of 26 items with a 7-point likert scale where 1=Not at all true and 7=Very true.

Results: A two-sample t-test analysis was performed to examine if the current and past participants differed in their responses to the MPS. Findings indicated participants did not differ in their responses to the survey ($t=0.63$, $p>0.05$). Overall, both previous and current participants rated their mentors highly (M=5.74, SD=0.60), suggesting they have a positive relationship with their mentor. MPS scores were positively correlated with minutes spent with their mentor ($r=0.65$, $p<0.05$) suggesting more time spent with a mentor increases the quality of the relationship.

Conclusion: These findings begin to contribute to the literature on mentoring in vulnerable youth. Next steps of this research will look at psychosocial outcomes that may be associated with mentoring in this group. Patients with a pediatric oncology diagnosis have been considered at-risk

in regard to their educational motivation and career-readiness. We will examine how mentoring influences the behaviors, relationships, and career preparedness in patients with a pediatric oncology diagnosis, contributing to the previous research with at-risk youth in general. Our next steps will examine if mentoring may mitigate these negative outcomes.

Poster # 120

ESTABLISHING METRICS TO ASSESS PERSPECTIVES OF VIRTUAL LEARNING IN ADOLESCENTS WITH CANCER

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Background: School absenteeism is one challenge faced by children with cancer and has been associated with declining academic performance and feelings of social isolation. Virtual learning may improve school participation and outcomes in this population. This form of instruction has gained prominence during the COVID-19 pandemic, allowing for real-time remote learning when being present at school poses health-related risks.

Objectives: 1. To develop two internally reliable metrics that evaluate adolescent experiences with virtual learning. 2. To determine if adolescents with cancer have an affinity for virtual learning and if they find aspects of one learning environment easier than the other. 3. To determine if a cancer diagnosis is associated with perceptions about school.

Design/Method: We conducted a cross-sectional survey of adolescent patients presenting to either the hematology oncology or primary care clinic between June and September of 2021. Exploratory Factor Analysis was used to construct and verify the internal reliability of two metrics: one to assess general affinity for virtual learning (Virtual Learning Affinity Score, or VLAS) and one to compare ease of learning between virtual and in-person school (Scholastic Comparison Score, or SCS). These metrics were compared across cancer status, controlling for demographics. Independence between cancer status and perceptions about school was also explored.

Results: Of a total of 68 respondents, 54% identified as female and 25% as having cancer. The majority (60%) were in high school; grade level ranged from elementary to college. We found no significant difference in VLAS or SCS scores between those with and without cancer. In both groups, VLAS scores indicated a neutral affinity for virtual learning (no significant difference from a neutral score of 24), and SCS scores showed that respondents found in-person learning easier. We found no significant associations between cancer status and feelings of safety in regular school or elective participation in virtual learning.

Conclusion: We developed two internally reliable metrics to measure virtual learning experiences in adolescents. Based on these metrics, we found that individuals with cancer feel the same way about virtual learning as their peers. Both groups neither like nor dislike virtual learning and ultimately find it easier to engage in the regular classroom. Importantly, having a cancer diagnosis may not imply that a child, or their caregiver, feels unsafe about attending school in-person.

Overall, these findings suggest that efforts to improve academic outcomes may be best directed at continuing to make in-person learning inclusive and accessible to those with cancer.

Poster # 121

CANCER AMONG CHILDREN AND ADOLESCENTS TREATED IN A HOSPITAL IN HAITI: SURVIVAL 2010-2014

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Background: Children with cancer managed in developed countries have higher survival rate compared to those managed in developing countries (1).

Objectives: To study the 2-year survival of pediatric cancers managed in Haiti from 2010 to 2014.

Design/Method: Newly diagnosed pediatric cancers at Saint Damien Hospital in Haiti were. To process statistical analysis, we use excel 2016 OS, and RStudio 2021.09.1+372. Log-rank test compared time to death across subgroups. The time to death from any cause in children with cancer was the endpoint of the study. Survival rate was obtained from any cases of death within 24 months from the date of diagnosis. Survival curves and probability of survival at 24 months were estimated using the Kaplan–Meier curves. Three year-survival probabilities, Hazard Ratio (HR) along with 95% confidence intervals (95%CI) are presented

Results: Pediatric cancers were studied according to age, gender, the type of cancer and therapeutic outcome. A total of 14 types of pediatric cancers were diagnosed. The mortality rate was 25.9% and occurred mostly in children that were less than 5 years of age. Death was more likely to occur in children diagnosed of Leukemias compared to those with Wilms tumor (HR= 0.41; 95% CI 0.07 - 2.32); Retinoblastoma (HR =0.69; 95% CI; 0.11; 4.20); and all the other tumors combined (HR= 0.54; 95% CI 0.10 - 2.99). For all diagnoses combined, the 2-year survival was 75%. Survival for the most common pediatric cancers were Leukemias 68%, Wilms tumor 70% and Retinoblastoma 90%. The cases with relapse had the lowest 2-year survival (15%), followed by the cases with complications (58%) and children that are less than 5 years old (64%)

Conclusion: The 2-year survival for Pediatric cancers in our study was lower than what it is reported in developed countries. Late presentation, diagnostic delay, lack of newly effective antineoplastic drugs challenge the management of cancers in Haiti, thus worsens the outcomes.

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Poster # 122

PEDIATRIC ONCOLOGIC MORTALITY WITHOUT ASSOCIATION TO RACE OR SOCIOECONOMIC STATUS

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Background: Multiple investigators describe the presence of racial disparities in outcomes for pediatric cancers utilizing the Surveillance, Epidemiology, and End Results (SEER) database. There is a paucity of data from midwestern and midsized institutions in the SEER database limiting the generalizability of this data.

Objectives: This study analyzed data from Akron Children's Hospital (ACH), which is a medium-sized, midwestern institution. The data was evaluated for association between mortality and race and socioeconomic status (SES).

Design/Method: An institutional database from ACH identified patients of all races and SES, less than 19 years of age at the time of diagnosis during 2009-2013. Three subset analyses were performed, including all patients receiving chemotherapy (n=380), all oncologic patients (n=357), and non-Hispanic white and non-Hispanic black oncologic patients (n=345). A Chi2 Test of Independence evaluated for a dependent relationship between survival and race. Cox Proportional Hazards Models assessed for predictors, confounders, and mediators for survival.

Results: There was a dependent relationship between race and SES, with non-Hispanic black individuals skewed towards the lowest SES quintile. Each subset analysis showed that overall survival was independent from sex, race, cancer subtype, and SES category and dependent on stage of diagnosis. Additionally, race and stage at diagnosis were not associated for all oncologic patients or when comparing non-Hispanic black and non-Hispanic white individuals (p-values = 0.655 and 0.707 respectively).

Conclusion: Pediatric oncologic mortality at ACH is independent of race or SES indicating there are limitations to the generalizability of the national data. Further evaluation is needed to assess racial and SES disparities in relation to pediatric oncologic mortality at the local and regional level where patients receive care.

Poster # 123

MEDICAL TOURISM?: INTERNATIONAL PATIENTS AT ST. JUDE CHILDREN'S RESEARCH HOSPITAL BETWEEN 2009-2019

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Background: A child's country of residence can be a limiting factor in their survival when faced with a cancer diagnosis. Children born in high-income countries have a lower chance of getting cancer but a high chance of survival, whereas children born in low-income countries have a higher

chance of receiving a cancer diagnosis, but often a significantly low cure rate if they do. Due to a lack of local medical care, patients may travel from a low-income country to a high-income country with greater resources, a practice sometimes labeled ‘Medical Tourism.' Furthermore, since the process of acceptance as an international patient can be lengthy, patients may arrive at centers without prior notice and nothing but the hope of receiving care.

Objectives: To analyze the characteristics of international pediatric patients arriving at St. Jude Children’s Research Hospital (SJCRH) for medical treatment from 2009-2019.

Design/Method: We conducted a retrospective chart review to analyze the characteristics of international patients at SJCRH, including demographic information, primary disease, the WHO Region and Economic Region for their country of origin, resource utilization, therapy type, and treatment outcomes.

Results: Of the 415 patients studied, most were white (68.1%) arriving from a high-income (41.7%) or upper-middle-income country (44.4%), while only 1.4% arrived from low-income countries. Most patients were from Latin America and the Caribbean (53.7%) while only 2.2% presented for care from Sub-Saharan Africa. The majority of patients (94.5%) came with prior acceptance as an international patient while 5.5% arrived unannounced. Of patients arriving without prior approval, most (78.3%) were Spanish-speakers. Walk-in patients required a larger number of hospital resources, such as interpreters and ethics consults, than those who were previously accepted.

Conclusion: While patients traveling to SJCRH came from all World Bank Regions, low-income countries were underrepresented, different from the typical definition of Medical (oncology) Tourism, suggesting patients did not travel from a low to a high-income country. The global patients who arrive at SJCRH without prior approval present staff with a unique ethical dilemma, as they have a competing responsibility to treat the child in front of them but also to care for local children with limited resources. To reach children living in low-income countries and bridge the gap in access to lifesaving cancer treatments, it is imperative to improve global outreach and build capacity for the treatment of pediatric malignancies.

Poster # 124

DEATH WITHIN ONE MONTH OF PEDIATRIC CANCER DIAGNOSIS: PATIENT-LEVEL CLINICAL AND PREDICTIVE FACTORS

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Background: 7.5% of pediatric cancer deaths occur in the first month post diagnosis, and this group of patients generally does not survive long enough to benefit from treatment advances. The risk factors for this phenomenon, termed early death (ED), are understudied, especially at the patient level. Previous population-based analyses have identified that ED disproportionately impacts specific groups: patients of Black race or Hispanic ethnicity, patients living in poverty,

infants, late adolescents, and patients with specific diagnoses including AML, hepatoblastoma, intracranial tumors, and metastatic solid tumors. The patient-level socioeconomic and specific clinical characteristics remain poorly understood because childhood cancer ED has never been assessed at the patient level.

Objectives: Determine which potential ED risk factors are assessable and not assessable through medical chart review, and characterize the patient-level clinical characteristics and risk factors for ED at Children's Hospital Colorado (CHCO).

Design/Method: We conducted a retrospective case-control study of 89 oncology patients diagnosed 1995-2016 at CHCO. ED was defined as death within one month of diagnosis (n=45), with controls surviving >31 days chosen randomly from the same cohort (n=44). Records for each patient were manually reviewed for sociodemographic, clinical, and diagnostic course information. Death certificates were reviewed to compare and confirm data. Odds ratios and 95% confidence intervals were estimated for the association between early death and potential risk factors.

Results: Factors correlating significantly with higher risk for ED included White race, CNS tumors, and metastatic disease. Sex, ethnicity, primary language, insurance status, and area of residence did not correlate with risk. Time from first symptoms to first care was longer for ED vs. non-ED cases. Presenting symptoms were significantly different between ED and non-ED cohorts. ED patients were significantly less likely to have started any treatment than non-ED patients, but the majority had begun treatment before death. The most common cause of death was progressive disease/mass effect for CNS tumors but infection for leukemia.

Conclusion: Compared to prior population data, our patient-level findings on pediatric cancer ED at CHCO did not show increased risk based on minority race/ethnicity or evaluable socioeconomic disadvantages, perhaps due to lower power or study/institution-specific factors. Our data validate prior clinical findings and then expand on them, showing potential delays in initial presentation, differing initial symptoms, and cancer type-dependent cause of death. While this patient-level study expands our understanding of ED, further understanding of potential barriers to care and causative socioeconomic factors will only come from a prospective study that includes family interviews.

Poster # 125

BETTER NUTRITION:IMPROVING EARLY MALNUTRITION IDENTIFICATION AND INTERVENTION IN PEDIATRIC ONCOLOGY

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Background: Children with cancer are at increased risk of malnutrition. Per a screening survey, ~30% of our leukemia patients are at risk. Given the cyclic nature of cancer therapy, malnutrition can be missed causing increased risk of morbidity and mortality. Nutrition Best Practice Guidelines (NBPGs) were developed to standardize the diagnostic criteria of malnutrition and

create an algorithm to guide treatment decisions. A formalized process was developed to consult clinical nutrition, document malnutrition status in the medical record, and measure compliance with NBPGs.

Objectives: The purpose of this quality improvement project is to decrease the number of pediatric patients with leukemia experiencing malnutrition. Measured goals include decreasing malnutrition incidence, increasing percentage of newly diagnosed patients with a nutrition consult within 30 days of diagnosis, increasing percentage of accurate provider nutrition status documentation, and increasing percent compliance with NBPGs when malnutrition is diagnosed.

Design/Method: A multidisciplinary team used the Model for Improvement with an aim statement, key driver diagram, and process flow map. Evidence-based NBPGs were created with diagnostic criteria and an algorithm to guide malnutrition treatment decision-making. A standardized dietitian referral process was developed. NBPGs were refined via multiple PDSA cycles. Preliminary NBPGs were presented to the Quality Improvement Committee. Draft NBPGs then went to the Best Practice Committee (BPC) for clarifications. BPC reviewed changes and referred the proposed NBPGs to the provider team for review. The NBPGs were then approved for use by the provider group. Documentation of nutrition status as well as compliance with the NBPGs was measured. Annotated run charts and Shewhart charts evaluated improvement.

Results: Data collection began July 2019 and continues through December 2021. The outcome goal was met, decreasing the incidence of malnutrition by 25%, from 28% to 21%. After special cause variation, data currently shows common cause variation around our revised mean of 16%. Process measures were also met, i.e. increasing percentage of newly diagnosed patients with a nutrition consult within 30 days of diagnosis to 80%, increasing percentage of accurate provider documentation of nutrition status to 80%, and increasing percentage of compliance with NBPGs to 80%.

Conclusion: Care standardization and malnutrition documentation have increased understanding and awareness of this complex topic in pediatric oncology and led to decreased incidence of malnutrition in our active treatment leukemia population.

Poster # 126

IMPROVING VITAMIN D STATUS AMONG CHILDREN WITH CHILDHOOD CANCER

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Background: With improving childhood cancer survival rates, more children are living into adulthood. These patients are at an increased risk of developing chronic health conditions such as decreased Bone Mineral Density (BMD). Poor nutritional status during and after childhood cancer treatment contributes to the development of decreased BMD. Studies have investigated the prevalence of Vitamin D deficiency in patients with childhood cancer and found an increased

prevalence compared to healthy controls.

Objectives: The aim was to evaluate the effectiveness of an educational and an order set intervention on improving the rates of testing and the resultant reduction in Vitamin D deficiency.

Design/Method: An educational intervention was developed which involved creation of a Vitamin D care decision tree that detailed how to interpret testing results and the appropriate medical management and re-testing interval. The oncology dietician also performed staff education sessions and created visual cues that were provided to all oncology providers. Additionally, inclusion of orders for Vitamin D levels was included in all Acute Lymphoblastic Leukemia (ALL) maintenance chemotherapy admission order sets within the Electronic Medical Record. This phase of therapy was when the Vitamin D levels orders were more frequently missed. The educational intervention started in March 2020. A retrospective cohort study was conducted analyzing 1234 patient encounters between March 2020 and August 2021 at one pediatric tertiary care referral center.

Results: The proportion of patients with Vitamin D levels ordered improved from an average of 90% in 2020 to an average of 93% in 2021. The number of patients with abnormal results that received a prescription for vitamin D was 93% in 2020 and 92% in 2021. The SMART goal for this intervention was 20% reduction in Vitamin D deficiency in childhood cancer patients within 18 months of starting the intervention. There was a 17% reduction in Vitamin D deficiency in childhood cancer patients between March 2020-August 2021.

Conclusion: The educational and order set intervention was an effective intervention for improving rates of testing for Vitamin D deficiency. Additionally, after implementation of the intervention, there was a decrease in the number of patients with Vitamin D deficiency. Next steps include expanding these interventions to the other hospitals within the same hospital system.

Poster # 127

USE OF A RAPID HYDRATION PROTOCOL FOR PEDIATRIC ONCOLOGY PATIENTS RECEIVING NEPHROTOXIC CHEMOTHERAPY

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Background: Cyclophosphamide, ifosfamide, and cisplatin are commonly used chemotherapeutic agents in pediatric oncology. Aggressive intravenous hydration is needed to initiate and maintain appropriate urine volume and specific gravity. Prolonged time to achieve hydration parameters delays the onset of chemotherapy and lengthens hospital stay. We hypothesize that implementation of a Rapid Hydration Protocol (RHP) for eligible pediatric oncology patients within our institution will safely decrease time to chemotherapy readiness compared to historical practice.

Objectives: Our global aim was to implement a RHP to reduce time to administration of chemotherapy requiring pre-hydration. Our SMART aim was to decrease time to chemotherapy

readiness, defined as the time from initiation of intravenous fluids to achieving a urine specific gravity less than 1.010, from a historical baseline of 5.1 ± 0.9 hours (mean ± SEM) using our previous hydration protocol to 3.3 hours (a reduction of 2x SEM) within <6 months.

Design/Method: Eligible patients ≥3 years old undergoing chemotherapy pre-hydration received one 20 milliliter/kilogram and up to two 10 milliliter/kilogram normal saline boluses over one hour (maximum 1 liter). Patients transitioned to standard continuous fluid infusion (200 milliliters/m^2/hour) when their urine met parameters at any time during the protocol or after the third bolus regardless of urine specific gravity. Patients with baseline hypertension were excluded. Time to chemotherapy readiness for patients receiving RHP was compared to historical control patients (n=8), who received hydration with one 15 milliliter/kilogram normal saline bolus prior to standard continuous fluid infusion. Balancing measures assessed included rates of fluid overload and hypertension with use of RHP. Likert-scale surveys completed by nurses, physicians, and pharmacists assessed ease of protocol workflow. Data were reviewed to identify action items for RHP improvement for incorporation into subsequent Plan-Do-Study-Act (PDSA) cycles.

Results: The RHP was first implemented in a small cohort to assess feasibility, with no safety concerns identified and ease of workflow highly rated by providers. The protocol was expanded to a broader cohort in PDSA cycle 2 (n=6). Time to chemotherapy readiness using RHP was 3.8 ± 0.7 hours, a decrease from 5.1 ± 0.9 hours (p=0.16).

Conclusion: Evaluation of the RHP after two PDSA cycles demonstrates feasibility and a clinically meaningful reduction in time to chemotherapy readiness for pediatric oncology patients receiving nephrotoxic chemotherapy. Future PDSA cycles will continue to optimize RHP workflow to safely improve efficiency of chemotherapy delivery and will expand RHP to patients receiving high dose methotrexate.

Poster # 128

BUILDING A COMPREHENSIVE PEDIATIRC CARDIO-ONCOLOGY PROGRAM AT UT SOUTHWESTERN IN DALLAS, TEXAS

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Background: Cardiac dysfunction following exposure to cancer therapies is a well-documented chronic health condition among childhood cancer survivors. Early detection and interventions may lead to improvements in cardiovascular health and overall quality of life.

Objectives: To describe the process in the development of a Pediatric Cardio-Oncology Program at UT Southwestern /Children's Health in Dallas, Texas with the goal of early identification, prevention, and treatment of cancer related cardiotoxicity among childhood cancer patients and survivors.

Design/Method: A collaborative team among pediatric oncologists, cardiologist and nurse practitioners was established in January of 2020. Monthly meetings were conducted to determine the clinical needs, available resources and organization of the program. Partnership with the cardiovascular imaging department was established to coordinate standardized cardiac surveillance imaging protocols.

Results: Participants in the Program include pediatric oncologists and cardiologists, nurse practitioners, psychologists, and dieticians. An institutional clinical protocol was developed to guide referral, screening, and monitoring of high-risk patients. The protocol is based upon recommendations from the Children's Oncology Group (*Long-Term Follow-Up Guidelines)* and supplemented with clinical experience and consensus expert opinion. Patient eligibility is determined based on cardiovascular risk profile. Patients evaluated in the Cardio-Oncology program are classified into 3 groups: 1) screening population (patients at high risk due to cardiac and oncologic history but with no evidence of cardiac dysfunction); 2) early intervention (patients with evidence of structural or mild systolic and/or diastolic cardiac dysfunction); 3) heart failure (patients with moderately or severely depressed cardiac function or symptoms of heart failure). Since October 2020, 14 monthly clinic sessions have been held for 49 unique patients: 17 patients (35%) had hematological malignancies, 32 patients (65%) had malignant solid tumors, mean age at the time of evaluation was 15.1 years ±3.4 years, 28 were males (57%). Mean anthracycline equivalent dose was 324 mg/m^2 (SD 170 mg/m^2). Twenty-eight patients (57%) received radiation therapy. Seven patients (14%) had left ventricular (LV) dysfunction defined as a LV Ejection Fraction (EF) of <55% or LV Shortening Fraction (SF) <28%. Nine families completed a satisfaction survey: 88% of respondents were "very satisfied" with the clinic visit and viewed this clinic as high quality and useful.

Conclusion: A multi-disciplinary Pediatric Cardio-Oncology Program for high-risk childhood cancer survivors has been successfully established to address the cardiovascular health needs of this population.

Poster # 129

REDUCING RE-ADMISSIONS RATES IN PATIENTS NEWLY DIAGNOSED WITH ALL: A QUALITY IMPROVEMENT STUDY

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Background: Treatment advancements for childhood Acute Lymphoblastic Leukemia (ALL) have resulted in improvements in survival. Treatment-related morbidity and mortality remain significant, especially during induction therapy. High disease burden, severe immune compromise, and chemotherapy-related side effects may necessitate hospital re-admissions.

Objectives: To identify preventable causes of re-admissions during induction and implement changes to decrease re-admissions by 25%.

Design/Method: An electronic leukemia-specific dashboard was utilized to monitor diagnosis and re-admissions for leukemia patients. Patients were excluded that had relapsed disease, began treatment at another institution or had trisomy 21.

Results: During the initial study period from August 2018 to August 2020, 98 patients were diagnosed with ALL and 47 (48.0%) were re-admitted during induction, for a total of 55 re-admissions. Eighty-seven percent of patients were discharged on or before day 8 of induction, the majority on days 4 or 5. Median day of induction at re-admission was 16. Five re-admissions (9.1%) occurred prior to day 8 of therapy. Of the 55 re-admissions, ten patients required ICU care and 2 died. The most common reasons for re-admission were fever (n=26; 47.3%), constipation (n=13), abdominal pain (n=13), bacteremia (n=11), and diarrhea (n=6). The study team reviewed the etiology of each re-admission and categorized each as preventable, possibly preventable, or not preventable. Sixteen (29.1%) re-admissions were deemed preventable and 8 (14.5%) were considered possibly preventable.

The first PDSA cycle included two interventions, which began in August 2020. All newly diagnosed leukemia patients remained hospitalized until at least 8 of induction. Also, a discharge checklist (Figure 1) was implemented, focusing on education around the preventable re-admission causes. From September 2020 to October 2021 there have been 44 new ALL diagnoses, that met study criteria. There were nineteen re-admissions in 17 patients (38.6%). Thirteen (68.4%) were not preventable, primarily due to fever (57.9% of re-admissions). Additional reasons for re-admission included constipation, poor nutritional status, seizures, and nausea/vomiting. Four patients required ICU admissions and there were zero deaths.

Conclusion: Almost half of the new ALL diagnoses between August 2018-2020 were re-admitted during induction. Although some admissions are not preventable, such as for fever, there were many readmissions that may have been prevented with improved patient education and longer monitoring prior to discharge. Implementation of a discharge checklist and standardized day of discharge has reduced the overall percentage of patients re-admitted. A higher proportion of recent re-admissions were deemed not preventable. There continues to be preventable causes for re-admission, suggesting further interventions are needed.

Poster # 130

UNDERSTANDING PREVALENCE AND CAUSES OF MORAL DISTRESS AMONGST PAEDIATRIC ONCOLOGY HEALTHCARE WORKERS

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Background: Moral distress (MoD) is a phenomenon commonly experienced by healthcare workers (HCWs) caring for patients with life-threatening illnesses and has been tied to burn-out. The specific contributors to MoD in the field of paediatric oncology have not been well-studied.

Objectives: The primary objective was to quantify MoD amongst paediatric oncology HCWs. Secondary objectives were: to identify risk factors for higher levels of MoD, to identify variations in self-reported MoD over 12 weeks, and to establish the Moral Distress Thermometer (MDT) as a useful research tool at our institution.

Design/Method: Paediatric oncology HCWs at the Hospital for Sick Children were invited to complete two tools for measuring MoD at baseline, Measure of Moral Distress-Healthcare Practitioners (MMD-HP) and MDT. Those who completed this baseline survey were invited to complete an additional MDT every 2 weeks over a 12-week period. MMD-HP and MDT scores were analyzed for associations to distinct personal and environmental risk factors and to each other.

Results: One hundred thirty-nine HCWs (41.5%) completed the baseline survey. Participants were mostly female (n=120, 87.6%) and had an average of 10.4 +/- 8.8 years of experience in the field. All participants were found to experience some MoD (MMD-HP scores: 9-288), with a mean score of 123 +/-57. More than half (n=76, 55.5%) of respondents reported having left or having had considered leaving their position due to MoD and those currently considering leaving had higher MMD-HP scores (170 vs. 115, $p<0.001$). Situations involving administration of aggressive treatments that were perceived to be potentially inappropriate ranked as the greatest environmental contributor to MoD. Personal risk factors for higher MoD included female gender vs. male gender (126.8 vs. 85.4, $p=0.01$) and RN role vs. staff physician role (136.3 vs. 85.3, $p=0.02$). Duration of experience was not linked to MMD-HP score ($p=0.54$). Baseline MDT and mean MDT scores over 12 weeks showed strong correlation to MMD-HP scores ($p<0.0001$ and $p=0.0003$, respectively), with mean MDT scores showing no significant fluctuation over the 12-week period.

Conclusion: Moral distress was reported by all HCWs surveyed and higher levels of MoD strongly correlated to consideration of resignation. RN role and female gender were identified as risk factors for greater MoD, as were situations in which patient treatment was perceived to be overly aggressive. MoD for the cohort did not significantly fluctuate over 12 weeks. The MMD-HP and MDT showed excellent correlation.

Poster # 131

RELATIONSHIPS BETWEEN PARENTAL ANXIETY AND CHILD QUALITY OF LIFE IN ADVANCED CHILDHOOD CANCER

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Background: In many chronic childhood illnesses, increased parent psychosocial distress is associated with lower parent-reported child quality of life. Similarly, in childhood cancer, studies have shown that greater parental anxiety is correlated with lower child quality of life, including for children who have completed cancer treatment. Given the higher symptom burden and increased anxiety and uncertainty in the setting of disease relapse, we would expect this relationship to be preserved in families affected by advanced childhood cancer. However, the association between parental anxiety and child health-related quality of life (HRQoL) has not been previously evaluated

in children with relapsed/refractory cancer and their parents.

Objectives: To examine relationships between parental trait anxiety and both parent-reported and child self-reported quality of life for children with advanced cancer.

Design/Method: Children (ages 5-17) with relapsed or refractory cancer and their parents who spoke English and were not cognitively impaired were recruited for this single-institution cross-sectional study. Parents completed a demographic form and measures of their own baseline anxiety (State-Trait Anxiety Inventory – Trait form, STAI-T) and their ill child's quality of life (age-specific PedsQL-Generic and PedsQL-Cancer, parent report). Children also completed measures of quality of life (age-specific PedsQL-Generic and PedsQL-Cancer, child report). Spearman's rho coefficients assessed correlations between total parent STAI-T score and both parent-reported and child-reported quality of life dimensions.

Results: Twenty children (mean age 9.5 years, 50% female) and their 20 parents (90% mothers) were included. Children's diagnoses were 55% extracranial solid tumors, 35% hematologic malignancies, and 15% CNS tumors. The strongest and statistically significant inverse correlations were observed between parental trait anxiety and components of the parent-reported child psychosocial HRQoL (r_s = -0.49[emotional], - 0.45[school], -0.54[global], all $p < 0.05$). Within the cancer-specific dimensions, the stronger correlations were again in the inverse direction. The correlation between parental anxiety and parent report of child pain was statistically significant (r_s= -0.45, $p = 0.048$). Correlations of parental anxiety with all dimensions of child-reported HRQoL were generally smaller ($r_s < 0.40$), positive, and not statistically significant ($p > 0.05$).

Conclusion: Given the inverse correlation between parental anxiety and child psychosocial quality of life, assessment of parent mental health needs and access to interventions to reduce anxiety should be provided as routine care for parents of children with advanced cancer. Further research is needed to better understand if interventions targeting parental anxiety will impact child quality of life.

Poster # 132

IDENTIFYING PREFERENCES FOR CANCER TREATMENT FACTORS IN AYAS USING THE MYPREF TOOL

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Background: As the number of cancer-directed therapies increase, adolescents and young adults (AYAs) with advanced cancer face increasingly complex treatment decisions. Yet, little is known regarding the relative importance of various treatment factors to patients and families facing these decisions. We developed *MyPref,* an adaptive conjoint analysis-based tool, to quantify preferences and augment the AYA voice in the decision-making in advanced cancer.

Objectives: To characterize the importance of various treatment factors to participants using the *MyPref* survey tool, and to examine differences in preferences between AYAs and their

identified trusted person (parent or other) and between younger and older AYAs.

Design/Method: We conducted a pilot study of *MyPref* among 45 AYAs with cancer that had progressed despite initial treatment; 15 identified a trusted person (TP) that completed the tool. *MyPref* quantifies participant preferences for 9 treatment-related factors and generates a summary estimating of the importance of each factor relative to others, where higher percentages indicate stronger preferences. A two-sample t-test was used to determine differences in the mean calculated preference between AYAs and their TPs and between older (>23 years) and younger (15-22 years) AYAs.

Results: Among 45 AYA participants, most identified as male (64%) and white (82%), with an average age of 23 (range 15-30) years. Of the 15 TPs, 13 (87%) were mothers.
The *MyPref* calculated preferences for all participants indicated that 'time until cancer progression' (19.2%, SD=6.9), 'quality of life' (18.6%, SD=5.3), and 'side effects from treatment' (14.6%, SD=5.0) were the most important treatment factors. PTPs' preferences for 'time until cancer progression' and 'quality of life' were significantly greater than AYA preferences for these factors [22.6 (SD 4.9) vs. 18.0 (SD 7.4), p=0.008; 12.5 (SD 5.2) vs. 17.6 (SD 5.1), p=0.018]. Conversely, AYA preferences for 'chance of hospitalization' and 'where treatment is given' were greater than PTP factor preferences [12.6 (SD 5.0) vs. 9.5 (SD 4.7), p=0.036; 8.9 (SD 5.9) vs. 5.9 (SD 3.5), p=0.021]. Among AYAs, the mean calculated preference for 'frequency of clinical visits' was significantly higher for AYAs under 23 years old when compared to older AYAs [10.8 (SD 6.1) vs 8.6 (SD 5.5), p=0.004.]

Conclusion: Preferences for factors related to cancer treatment were highly variable and differed by age and between AYAs and their trusted persons. Both patient and family preferences for factors related to cancer treatment should be routinely assessed and incorporated in advanced cancer treatment decision-making.

Poster # 133

ADVICE TO CLINICIANS ON COMMUNICATION FROM ADOLESCENTS AND YOUNG ADULTS WITH CANCER AND PARENTS

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Background: Effective communication is integral to improving healthcare delivery and outcomes. In pediatric oncology, parental report of high-quality communication is associated with parental self-efficacy, decreased regret, increased hope, and greater trust in the physician. Studies of adolescents and young adults (AYAs) with cancer demonstrate preferences for engagement in decision-making, transparent disclosure of prognosis, and long-term side effects. However, we know little about how the communication needs of AYAs and parents compare. By asking for communication advice from AYAs and parents, we can identify salient guidance for how clinicians can better communicate. Furthermore, comparing advice from AYAs and parents allows us to

identify unique or differing priorities.

Objectives: To elicit and compare communication advice to clinicians from the perspectives of AYAs with cancer and parents.

Design/Method: Thematic analysis of semi-structured interviews from 2 qualitative communication studies. In one study, we interviewed 80 parents of children with cancer at 3 hospitals during treatment, survivorship, or bereavement. In the second study, we interviewed AYAs with cancer at 2 hospitals during treatment or survivorship. We asked AYAs and parents to provide communication advice for oncology clinicians. Using thematic analysis, we identified and compared themes between AYAs and parents.

Results: In a preliminary analysis of 20 AYA and 45 parental transcripts (analysis is ongoing), we identified categories of advice related to three overarching themes: interpersonal relations, informational preferences, and care delivery. Within relational advice, both parents and AYAs described empowering patients and families, maintaining hopefulness and optimism, and demonstrating empathy and caring. AYAs placed special emphasis on clinicians minimizing their prognostic apprehensions by demonstrating optimism, maintaining a calm demeanor and building strong and lasting interpersonal connections. AYAs advised clinicians to acknowledge parental roles and appropriately incorporate their parents in communication. Parents uniquely emphasized the importance of the clinician listening actively to their input. Within care delivery advice, AYAs and parents advised clinicians to demonstrate competence and provide resources for self-management. Within informational preferences, AYAs and parents advised clinicians to support understanding of information by appropriately pacing delivery of information, using understandable language, and preparing families for the future.

Conclusion: AYAs with cancer and parents provided overlapping themes of communication advice. AYAs emphasized the importance of being calm and developing strong relationships. Parents emphasized that clinicians should listen actively to their input. By following this advice, clinicians can better meet the communication needs of AYAs with cancer and parents.

Poster # 134

PARTNERING TO IMPROVE OUTCOMES FOR ADOLESCENTS AND YOUNG ADULTS WITH CANCER: A PILOT STUDY

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Background: Adolescent and young adult (AYA) oncology patients, defined by the National Cancer Institute as those between the ages of 15-29, have unique psychosocial needs that impact their treatment and survival. To better serve this vulnerable patient population, we established an AYA Oncology Program in August 2020. To assess program efficacy and stakeholder acceptability, we conducted a pilot study over the first 18 months of program implementation.

Objectives: The study objectives included: 1) Assess baseline AYA-centered practices, 2) Identify priority areas for improvement, 3) Implement change.

Design/Method: This pilot study was designed similarly to quality improvement methodology; baseline planning and investigation, enacting initiatives, examining outcomes and modifying accordingly. This was conducted in partnership with the Adolescent Health Initiative (AHI), an organization with expertise in delivering optimal adolescent healthcare. Adolescent champions were identified among providers, nursing, clinic staff and social work. Baseline satisfaction surveys were sent to AYA patients, and baseline surveys assessing competency and efficacy of caring for adolescent patients were sent to providers and staff. AHI worked with the AYA program to develop indicators in 12 broad domains specific to adolescent oncology care and were assessed by program staff and champions at three timepoints (baseline, mid-year, year-end): access to care, environment, confidentiality, best practices, reproductive and sexual health, behavioral health, nutritional health, cultural responsiveness, respectful treatment, adolescent involvement, caregiver engagement and community engagement.

Results: We report the results of our mid-year assessment. Survey participants included 16 providers/staff and 28 AYA patients. Multiple improvement opportunities were identified. AYAs reported communication, privacy, confidentiality, adolescent involvement, and access needs. Providers and staff identified confidentiality, sexual health, behavioral health and adolescent involvement needs. Initiatives to meet the identified needs include consistently referring AYAs to adolescent medicine to improve risk taking behavior screening and sexual education, consistently referring AYAs to reproductive endocrinology for fertility preservation, staff and provider trainings on AYA relevant issues, improved AYA educational material, and AYA inclusive signage and decor in clinic spaces. Next steps include working to expand clinic and infusion hours to include evenings and weekends, developing and implementing best practices for AYA clinic visits, implementing depression and anxiety screening and developing a database to track AYAs to identify gaps in care.

Conclusion: The AYA Oncology Program benefitted from a formal evaluation supervised by experts in adolescent health. A dedicated, iterative process involving key stakeholders was essential to successfully address the unmet needs of a complex and diverse patient population.

Poster # 135

MEDICAL MARIJUANA AND CANNABINOID PRODUCTS IN PEDIATRIC HEMATOLOGY ONCOLOGY: PROVIDER PERCEPTIONS

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Background: As a growing number of states have legalized medical marijuana (MM), there has been a concurrent increase in patients and parents inquiring about the potential role of medical marijuana and cannabinoid (CBD) products in the treatment of pediatric hematology/oncology (PHO) patients. However, literature on the safety and efficacy of these treatments in this population is sparse, thus placing a greater reliance on the individual provider's perceptions and

knowledge to form recommendations.

Objectives: To evaluate PHO providers' knowledge, perceptions, barriers and current practices for the use of medical marijuana and cannabidiol products in pediatric hematology and oncology patients.

Design/Method: An anonymous electronic 34 question survey was developed and piloted by PHO faculty. The survey information was sent to PHO providers in August 2021 with email reminders through December 2021.

Results: 362 providers have responded to the survey so far. Of those, 344 responders completed question block 1 (ability to prescribe MM/CBD and initiating conversations), 326 completed block 2 (recommending MM/CBD), 276 completed block 3 (resources used to form recommendations) and 271 completed the final block (confidence in knowledge). 71.8% (251/344) of respondents practice where medical marijuana is legal but only 7% (27/344) have a license to prescribe. While 88% (304/344) discuss MM and CBD with patients, 64% (220/344) of conversations are initiated by families/patient. Providers are most comfortable prescribing MM and CBD for management of chronic symptoms in collaboration with palliative care to alleviate nausea, vomiting, anxiety, pain, and stimulate appetite. Despite the frequency of conversations, only 15.6% (51/326) of providers recommended MM or CBD to more than 10% of their patients, with the primary reasons being lack of evidence in regards to efficacy and side effects. While 68% (189/276) used peer reviewed data to make decisions, providers also reported using information from non-peer reviewed sources (17.8%, 49/276), patients and families (22.1%, 61/276) and dispensaries (6.5%, 18/276). Almost half (48%, 130/271) expressed having insufficient knowledge to make recommendations regarding MM or CBD.

Conclusion: Most providers do not feel comfortable recommending either MM or CBD products, due to a lack of clinical trials and empiric evidence in the field of pediatric hematology and oncology. This highlights the need for clinical trials, education, and policy development in this rapidly growing field to best provide supportive care for our pediatric hematology and oncology patients.

Poster # 136

GRIEF CHALLENGES FOR PARENTS PARTICIPATING IN A MENTORSHIP PROGRAM AFTER A CHILD DIED OF CANCER

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Background: The death of a child is an extremely difficult experience for parents and results in profound life-long grief. Grief after the death of a child is associated with increased psychical and psychosocial morbidity in surviving parents as compared to non-bereaved parents. Research demonstrates that parents desire opportunities to connect and interact with other bereaved parents after the death of a child. These experiences allow bereaved parents to identify

shared experiences, normalize their grief reactions, and feel less lonely and isolated. To address this need, our institution established a peer-to-peer mentorship program for bereaved parents, where trained bereaved parent mentors offer support to newly bereaved parents.

Objectives: This study aims to describe the characteristics of the Bereaved Parent Mentor Program's participants and qualitatively analyze the content of their documented encounters related to challenges and triggers associated with grief discussed between the mentor-mentee dyads.

Design/Method: We used a retrospective cohort design and content analysis for this study. Mentors documented each interaction with their mentees using a secure web platform, including what was discussed, and any concerns or needs identified necessitating professional psychosocial support. Descriptive statistics were used to characterize mentors and mentees. Inductive codebook development was performed followed by code application to the encounters with subsequent reconciliation, and synthesis of findings to identify themes.

Results: A total of 1,359 encounters occurred between 39 mentors and 150 mentees from January 1, 2014, through February 29, 2020. Most mentors and mentees were mothers (66% and 80%, respectively). Several themes emerged including discussions around the challenges of grief and specific grief triggers. Challenges included interactions with others, specifically variation in grief expression between partners, the grief of surviving siblings, and exchanges with others in the community. Specific triggers for more intense grief reactions, such as holidays, birthdays, or important dates in the medical experience were highlighted. Parents described various emotions associated with these grief challenges and triggers including guilt or regret over decisions, sadness and depression, and/or anger. Finally, many dyads described the loneliness or lack of purpose felt after the death of a child.

Conclusion: This structured bereaved parent mentor support program promoted thoughtful discussions in which parents shared challenges faced after the death of a child. Future research should evaluate the overall impact the program has on bereaved parent's psychosocial and physical well-being. Additionally, it is important to identify opportunities to support and provide anticipatory guidance for bereaved parents experiencing these specific challenges and triggers.

Poster # 137

MULTI-INSTITUTIONAL EXPERIENCE OF FENTANYL FOR BROWN FAT MITIGATION IN PET/CT IN PEDIATRIC ONCOLOGY

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Background: Brown fat is a metabolically active tissue which can take up the ^{18}FDG tracer used in PET/CT scans, potentially leading to diagnostic uncertainty. Metabolically active brown fat is more prevalent in children than adults with recent studies demonstrating an incidence of brown fat

uptake in 34-40% of children with cancer. The resultant diagnostic uncertainty can impact clinicians' ability to interpret scans in pediatric oncology patients and has the potential to result in unnecessary invasive procedures, upstaged risk stratification, or additional therapy. A lack of clinical consensus remains regarding the safest and most effective method for suppressing brown fat uptake of ^{18}FDG.

Objectives: We report the first multi-institutional analysis of the use of fentanyl to mitigate brown fat uptake of ^{18}FDG in patients receiving PET/CT scans with a focus on safety in pediatric oncology patients.

Design/Method: This is a multi-institutional, retrospective review of pediatric (aged >1 year to <25 years) oncology patients undergoing ^{18}FDG-PET/CT scans following pretreatment with fentanyl from April to December of 2021. Scans were conducted per institutional treatment regimens. Patients received a weight based dose of fentanyl 10 minutes prior to tracer injection. Vital signs, clinical outcomes, and presence of brown fat was recorded. Similar data was recorded on patients who underwent PET/CT scans without fentanyl premedication during this same time period to serve as the control group.

Results: Thirty-nine scans were completed with fentanyl pre-treatment. Patients were evenly split by sex (n=20, 51%male) with median age of 15 (range 6y-18y). Controls (n=78) not pretreated with fentanyl demonstrated brown fat tracer uptake in 19.2% (n=15) of scans, compared to the fentanyl pretreated cohort, who demonstrated brown fat tracer uptake in 15.4% (n=6) of scans. Brown fat uptake was most common in cervical (n=5, 83%) supraclavicular (n=5, 83%), intercostal (n=1, 17%) and pararenal (n=2, 33%) areas. There were no adverse events including zero incidents of bradycardia, hypoxia, or hypotension in the pretreated fentanyl cohort.

Conclusion: Fentanyl, used for brown fat mitigation in pediatric oncology patients, was well tolerated without any adverse safety events. The observed incidence of brown fat tracer uptake in patients receiving fentanyl pre-medication was higher than previously reported in the literature (15.4% vs 6.7%) and was slightly lower than in the control group (15.4% vs. 19.2%). Larger, prospective, multi-institutional clinical trials are warranted to further explore the safety and efficacy of fentanyl for brown fat mitigation pediatric oncology patients.

Poster # 138

HOW TO REDUCE TRAUMATIC DIAGNOSTIC LUMBAR PUNTCUTRES – IS IT ALL ABOUT THE PLATELET COUNT?

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Background: Lumbar punctures are routinely used in the diagnosis and risk stratification of acute lymphoblastic leukaemia in children. Blood-contaminated (traumatic) lumbar punctures can result in diagnostic uncertainty and can necessitate additional intrathecal chemotherapy. This increases the risk of both acute toxicity and neuro-cognitive late effects. We sought to identify factors, both modifiable and non-modifiable, that are associated with traumatic lumbar punctures, with the

overall aim of reducing their incidence.

Objectives: Our unit uses a platelet transfusion threshold of 20 $x10^9$/l for all lumbar punctures, and our primary objective was to determine if lower platelet counts (20-49 $x10^9$/l) correlate with traumatic lumbar punctures. Our additional objective was to identify other patient and clinician associated factors which correlate with traumatic lumbar punctures.

Design/Method: Retrospective analysis of all pediatric patients (aged 1-15) diagnosed with acute lymphoblastic leukaemia at a principal treatment centre in the United Kingdom between 2018 and 2020. Data were collected at three time-points during the induction phase of treatment, Days 1, 8 and 29 from commencement of treatment. Statistical correlation of lumbar puncture blood staining (>500 red blood cells/mm^3) with patients' platelet count, age, induction regime (NCI standard versus high risk), day of induction, and grade of performing clinician was assessed using the Chi^2 test.

Results: A total of 74 patients were included in the analysis, 50% male and 50% female. The age at diagnosis ranged from 1 to 14 years (median 5 years, mean 6.2 years). A total of 219 lumbar punctures were analysed. Interestingly, a lower platelet count (20-49 $x10^9$/l) did not significantly increase the probability of a blood-stained lumbar puncture (p=0.5); nor did transfusion of platelets to those patients with a platelet count between 20-49 x10^9/l (p=0.68). A lumbar puncture performed by a senior clinician (Consultant)) rather than a trainee was significantly less likely to result in a traumatic lumbar puncture (p=0.0001). Additionally, children aged 11-14 years were significantly more likely to have a traumatic lumbar puncture than those aged 1-5 or 6-10 (p=0.022).

Conclusion: In the cohort analysed, a transfusion threshold of 20 $x10^9$/l platelets did not impact upon the likelihood of a traumatic lumbar puncture. However, we found that traumatic lumbar punctures occur more frequently in older children and when performed by more junior clinical staff. We would therefore recommend that the diagnostic lumbar puncture be performed by an experienced clinician, whilst supporting junior staff in developing competency in the procedure at less critical time-points.

Poster # 139

SIGNIFICANT BURDEN OF ADVERSE EVENTS DURING THERAPY FOR T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

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Background: Despite excellent cure rates, morbidity in T-cell lymphoblastic leukemia and lymphoma (ALL, LLy) remains high. Limited data exist regarding adverse event (AE) rates during induction and consolidation therapy in pediatric ALL/LLy, and the literature does not discriminate between B-ALL and T-ALL/LLy patients. We recently described differences in AEs for ALL

patients treated with 3-drug vs 4-drug induction and showed that treatment with 4-drug induction was associated with higher risk of AEs.

Objectives: To describe rates of clinically relevant AEs during induction and consolidation for patients with T-ALL/LLy and to compare rates for patients with B-ALL and T-ALL/LLy.

Design/Method: Patients treated for ALL/LLy at Children's Healthcare of Atlanta from 2010-2019 were included. Demographic and AE data were manually abstracted. AEs were graded according to NCI Common Terminology Criteria for Adverse Events v5.0 definitions. Abstraction captured grades 3-5 acute respiratory distress syndrome, anaphylaxis, constipation, hepatotoxicity, hypertension, hyponatremia, hypotension, hypoxia, ileus, neuropathy, pancreatitis, seizure, sepsis, and stroke and grades 2-5 fever, hyperglycemia, infection, and thromboembolic events. Descriptive statistics were tabulated. Categorical data utilized Chi-square or Fisher's exact test when expected counts were <5.

Results: The cohort included 290 patients (88 T-ALL, 32 T-LLy, 170 B-ALL treated with 4-drug induction); 9 T-ALL/LLy patients were excluded from consolidation analysis for incomplete data. Overall, 85 T-ALL/LLy patients (70.8%) experienced at least one induction AE; common AEs were infection (26/120; 21.7%), hypertension (24/120; 20%), and hypoxia (22/120; 18.3%). Eighty-nine T-ALL/LLy patients (74.2%) experienced at least one consolidation AE; fever (39/111; 32.5%), infection (35/111; 31.5%), and ALT elevation (36/111; 30%) were most common. Fever was significantly more common in T-ALL patients in induction as compared to T-LLy patients (11 [12.5%] vs 0 [0%]; p=0.04). In consolidation, hyponatremia was more common in T-LLy patients as compared to T-ALL patients (12 [40%] vs 15 [18.5%]; p=0.03). B-ALL patients treated with a 4-drug induction were significantly more likely than T-ALL/LLy patients to experience fever (50 [29.4%] vs 11 [9.2%]; p<0.0001), infection (65 [38.2%] vs 26 [21.7%]; p=0.003), or sepsis (23 [13.5%] vs 7 [5.8%]; p=0.03) during induction.

Conclusion: Patients with T-ALL/LLy experience high rates of AEs in both induction and consolidation. Infection was common in both courses. Unexpectedly, B-ALL patients treated with a 4-drug Induction regimen had higher rates of fever, infection, and sepsis. This study describes the AE profile of T-ALL/LLy patients during induction and consolidation and can guide patients and families regarding AE risks during these chemotherapy courses.

Poster # 140

SERIAL PROCALCITONIN AIDS IN IDENTIFYING SEVERE EVENTS IN LOW-RISK FEBRILE NEUTROPENIA EPISODES

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Background: A current focus of febrile neutropenia (FN) research is on effective risk stratification of episodes at low-risk for severe adverse events; a scenario where de-escalated therapy may be appropriate. Risk stratification of FN based on single clinical decision rules (CDR) tool is not optimal and leads to misclassification up to 5% of low-risk FN episodes who experience severe

events. Few international groups have incorporated inflammatory biomarkers into CDR with improved results, but no such tool has been validated in a North American patient cohort.

Objectives: To evaluate the outcomes of outpatient FN episodes using a CDR combined with serial procalcitonin.

Design/Method: A single center, prospective cohort study was performed over 12 months. Febrile neutropenia was defined per Infectious Disease Society of America guidelines. Clinical risk stratification was performed at presentation using a slightly more restrictive, modified CDR tool published by Alexander, et al., recommended by the Children's Oncology Group. Serum procalcitonin was obtained at presentation and first morning of admission; median time of draw after fever onset was 2 and 16 hours, respectively. The study low-risk (SLR) group met clinical low-risk criteria and had serial procalcitonin <0.4 ng/mL. The study high-risk (SHR) group met either clinical high-risk criteria or low-risk criteria with an elevated procalcitonin ≥0.4 ng/mL. Severe events were blood stream infections (BSI) or intensive care unit (ICU) admission or death. Differences between the groups were calculated with a Wilcoxon Rank Sum test and chi-squared test of association for continuous and categorical variables.

Results: Of the 148 FN episodes recorded, 112 (76%) episodes had an initial outpatient fever. The analytic group was further restricted to 94 (84%) outpatient episodes with available serial procalcitonin values. There were 66 (70%) episodes in the SHR group, and severe events were diagnosed in 20% (3/15) of patients included only due to elevated procalcitonin. The SHR group saw all 11 BSI events [17% (11/66) vs. 0% (0/28); *P*= 0.03] and majority ICU admissions [8% (5/66) vs 4% (1/28); *P*=0.67]. The SLR group had a single patient with serial low procalcitonin diagnosed with *Pneumocystis jirovecii* pneumonia on day 7 of admission after transfer to the ICU.

Conclusion: Serial procalcitonin may improve the performance of the CDR, but analysis was limited due to the small sample size. We propose future investigations should formally evaluate the utility of adding serial procalcitonin to a CDR in capturing severe events in low-risk FN episodes.

Poster # 141

USING RISK STRATIFICATION TO SHORTEN HOSPITAL STAYS SAFELY IN CHILDREN WITH FEBRILE NEUTROPENIA

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Background: While week-long admissions have generally been the standard of care for pediatric oncology patients with neutropenic fever (F&N), hospitals have begun reducing inpatient time for patients with low-risk F&N, or F&N identified as low risk for serious infection. In July 2018, Johns Hopkins Pediatric Oncology instated the Early Discharge Policy, which allows for pediatric patients with low-risk F&N to be discharged after 48 hours if they meet certain criteria.

Objectives: We aimed to compare the characteristics and clinical outcomes of patients before and after institution of this policy. This study investigated whether, as a result of the Early Discharge

Policy, low risk F&N pediatric oncology patients have a reduced length of stay compared to prior to this intervention, without changes in patient safety, such as increased readmissions or infectious complications.

Design/Method: In this retrospective review at Johns Hopkins Children's Center, Baltimore, Maryland, we included all patients between 2 and 28 years of age (mean age, 11.7 years). To determine how the new policy has affected patients, 18 months of patient chart review prior to the change of policy (January 17, 2017- July 17, 2018) were analyzed and compared to 18 months of prospective chart review data collected after the change in policy (July 17, 2018 – January 17, 2020). Average length of stay and rates of unplanned readmission, PICU admission, bacteremia, mortality, and *C. difficile* and nosocomial infections were measured.

Results: In low-risk F&N patients eligible for early discharge, the average duration of stay for F&N was 2.33 days longer for patients prior to institution of the policy (n=47, LOS: 4.53 ± 4.27 days), compared to patients admitted post-policy (n=44, 2.20 ± 0.51 days; P=0.0001 Kruskall Wallis test). There was no significant difference in the incidence of readmission after discharge, PICU admission, serious infection, or death within 30 days in the two cohorts.

Conclusion: The Early Discharge Policy is associated with significantly reduced hospital stays with no change in infectious complications or patient safety, demonstrating the importance of continuing and improving its use at Hopkins and other hospitals. Reducing time spent inpatient in low-risk F&N pediatric oncology patients would greatly improve family quality of life, decrease nosocomial infections, and cut costs for both families and healthcare systems.

Poster # 142

A NORTH AMERICAN SURVEY OF THE MANAGEMENT PRACTICE OF PROLONGED PEDIATRIC FEBRILE NEUTROPENIA

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Background: Febrile neutropenia (FN) is a common result of chemotherapy leading to life-threatening illness. The International Pediatric Fever and Neutropenia Guideline Panel issued guidelines in 2012 (updated in 2017) on the management of FN in children with cancer or recipients of hematopoietic stem cell transplants (HSCT) to provide guidance for management of prolonged FN. These guidelines recommend obtaining peripheral cultures at presentation (weak recommendation), initiating antipseudomonal monotherapy without modification except for changes in clinical status (strong recommendation), avoiding the use of empiric antifungal therapy except for patients with high risk of invasive fungal disease (strong recommendation), and not using galactomannan and β-D-glucan to evaluate for invasive fungal disease (weak recommendation and strong recommendation, respectively). The need for obtaining repeat blood cultures beyond 72 hours is unclear in pediatric FN, but recommended against in adult FN.

Objectives: Determine physician management of FN on days 1, 4, 5, and 7 with fever in the setting

of negative blood cultures, in patients with ALL (acute lymphoblastic leukemia), neuroblastoma (NB), and acute myeloid leukemia (AML) or HSCT.

Design/Method: An electronic survey consisting of practice-pattern questions was sent to 1,631 pediatric hematologist/oncologists in the US and Canada. 162 complete responses were recorded for questions relating to ALL and neuroblastoma, 115 for AML, and 37 for HSCT.

Results: 99.7% of respondents obtain ≥1 central venous catheter blood culture at presentation with 31% also obtaining peripheral blood cultures. Blood cultures on subsequent days of fever are obtained more frequently in the HSCT subgroup (96%) compared to the other groups (ALL (85%), p=0.03; NB (87%), p=0.022; and AML (89%), p=0.044) and overall, more frequently in the AML/HSCT subgroup compared to ALL/NB (93% vs 86%; p=0.03). 92% of respondents initiate empirical antipseudomonal monotherapy for ALL/NB patients compared to 43% for AML/HSCT patients (p=0.002). The AML/HSCT subgroup is more likely to be treated with vancomycin compared to the ALL/NB subgroup both on presentation (54% vs 4%; p=0.025) and overall (61% vs 28%; p=0.004). Aminoglycoside use is less frequent, and used similarly in AML/HSCT patients as compared to ALL/NB patients (10% vs 7%; p=0.12). For FN lasting ≥96 hours, 81% of physicians test for fungal disease, sending fungal cultures (56%), serum galactomannan (72%), and/or β-D-glucan (52%), and 76% initiating antifungal therapy.

Conclusion: Physician practice deviates from pediatric specific guidelines for the management of FN. Further research is needed to understand the basis for these practice pattern differences.

Poster # 143

A NOBLE PURSUIT IN QI: CODE NEON (NEW EVALUATION OF FEVER IN NON-ONCOLOGIC NEUTROPENIA)

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Background: Evidence-based guidelines for evaluation of fever in non-oncologic patients with neutropenia are lacking, potentially due to the heterogeneity of diagnoses that cause chronic neutropenia in the pediatric population. Prior to the implementation of recent risk stratification, patients at our institution with a broad range of etiologies for chronic neutropenia were treated similarly to the high-risk oncology population, often receiving blood cultures and broad-spectrum antibiotics despite clear differences in etiology of neutropenia and associated risk of bacterial infection. This approach led to increased health care resource utilization despite relatively low risk of serious bacterial infection in many patients.

Objectives: By July 1, 2022, 75% of patients seen in pediatric hematology clinic each month with a known diagnosis of persistent neutropenia will have an evaluation and management plan for fever documented in their electronic health record.

Design/Method: To develop appropriate fever plans, our team reviewed the literature to create three risk groups (low, moderate, high) for serious bacterial infection based on the individual's diagnosis, history of infections, co-morbidities, and additional risk factors such as a central line, past neutrophil response with fever/infection, and clinical condition at the onset of fever. Based on these risk groups, we created standards of care varying from low-risk evaluation by primary care physician to high-risk immediate evaluation with administration of empiric antibiotics. Using the Model for Improvement and Plan-Do-Study-Act (PDSA) cycles, we created a process for documentation of the fever plan by the primary hematologist in the patient chart based on the patient's risk group. Data were generated and reviewed by an electronic health record report and chart review. Our process measure was tracked on a statistical process control chart. Balancing measures of serious infections, emergency department visits, and hospitalizations were also tracked.

Results: Our baseline from May 2021 was 0% as the process had not yet been defined or implemented. From June to December 2021, we increased to a centerline of 40% with special cause variation showing a trend up toward our goal line after PDSA cycles including definition of risk groups, standardization of documentation in the medical record, and promotion among the provider teams. We have not seen significant changes in our balancing measures.

Conclusion: Creating risk stratifications for febrile non-oncologic patients with neutropenia has helped define a specific management plan for each individual patient, and quality improvement methodology will continue to guide our next steps of implementation and improvement.

Poster # 144

ACUPRESSURE IN HOSPITALIZED PEDIATRIC ONCOLOGY PATIENTS WITH FEBRILE NEUTROPENIA - A PILOT STUDY

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Background: Chemotherapy-induced neutropenia is an expected side effect during cancer therapy. Prolonged neutropenia can lead to treatment delays and chemotherapy dose reduction. Patients with neutropenia are at increased risk for life-threatening infections, and when febrile they require hospitalization and broad-spectrum IV antibiotics. Acupuncture and related techniques have received increased interest in several clinical trials in adult oncology, where their use has resulted in improved blood cell counts. Little is known regarding the impact of needleless acupressure intervention in pediatric oncology patients.

Objectives: The purpose of this pilot study was to evaluate the effects of daily treatment using predetermined acupressure points on hospitalized pediatric oncology patients with febrile neutropenia. Our primary objective was to determine if this protocol decreased the time to blood cell count recovery, a requirement for hospital discharge. The metric used for count recovery was absolute phagocyte count (APC), which is ANC (absolute neutrophil count) + AMC (absolute monocyte count). The endpoint for count recovery was APC $\geq 500/\mu L$.

Design/Method: In this pilot study, pediatric oncology patients admitted to the University of Minnesota Masonic Children's Hospital who had febrile neutropenia (ANC < 500/μL and temperature > 100.3F) were offered enrollment. Enrolled subjects received daily acupressure treatments until APC recovery. Cases were disease-matched to historical controls by treatment protocol as closely as possible. Time variables, including time to APC recovery and length of stay (LOS), were analyzed using the non-parametric Wilcoxon rank sum test.

Results: Twelve cases (enrolled October 2020-September 2021) were group-matched to thirty-four historical controls (pulled from the medical records database, January 2015-October 2019). APC recovery in days was the same in both groups, with a median of 3.0 days, p=0.352. The LOS in days was also similar: cases 4.94 vs. controls 3.43 days, p=0.431. No enrolled patients experienced treatment-related adverse events. One patient was removed from the study early due to contracting COVID-19 when there was a limited supply of personal protective equipment.

Conclusion: Acupressure presents a unique non-pharmacologic method to potentially support count recovery. Although we were unable to demonstrate a significant impact of acupressure on APC recovery in our pediatric population, we note limited sample size. Only 12 of the goal 35 patients (per initial power analysis) were enrolled. This was due, in part, to impacts of the COVID-19 pandemic, including necessary restrictions on elective research protocols during the study window. Further studies are needed to explore the role of acupressure in pediatric oncology.

Poster # 145

IMPLEMENTING RISK STRATIFICATION FOR FEBRILE NEUTROPENIA ADMISSIONS IN CHILDREN WITH CANCER

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Background: Febrile neutropenia (FN) is a common side effect of chemotherapy and one of the most common reasons for unplanned hospitalizations. At Rady Children's Hospital- San Diego, current practice requires that children with cancer who present with FN are admitted for broad-spectrum IV antibiotics until they are afebrile and show evidence of neutrophil recovery. Growing evidence supports outpatient management of patients with low-risk FN, and guidelines recommend adopting a risk stratification strategy for patients with FN and incorporating it into routine clinical management.

Objectives: SMART Aim: To increase the percentage of accurate FN risk stratification documentation in children with cancer and FN admitted from an outpatient setting from 0% to 50% over 11 months using quality improvement (QI) methodology.

Design/Method: A multi-disciplinary QI team used QI tools and designed interventions to improve the utilization and documentation of a newly developed FN risk stratification algorithm. QI tools included process mapping and key driver and Ishikawa diagrams to identify barriers and facilitators

to implementation. Interventions were evaluated using Plan-Do-Study-Act (PDSA) cycles. PDSA Cycle 1 (August-September 2020) included development of a new FN risk stratification algorithm which was physically available in clinical working areas and electronically available via our secure shared division folder, creation of electronic medical record smart phrases to easily add FN risk stratification documentation to patients' notes, and provider education and training at division meetings on the evidence-based clinical algorithm and FN documentation process. PDSA Cycle 2 (October-December 2020) included additional education and training and targeted e-mail reminders to attendings when covering the inpatient service. PDSA Cycle 3 (January-June 2021) included additional education and training, provider surveys to obtain feedback on barriers to documentation, and fellow involvement with targeted e-mail reminders to document for any overnight FN admissions.

Results: From August 1, 2020 to June 30, 2021, there were a total of 111 FN admissions. Following PDSA Cycle 1, 26.7% (4/15) had FN risk stratification documented. After PDSA Cycle 2, documentation improved to 52% (13/25) and was maintained after PDSA Cycle 3 at 50.7% (36/71).

Conclusion: We successfully improved the utilization and documentation of the FN risk stratification algorithm by using QI methodology. Targeted e-mail reminders and involvement of fellows who were invested and "clinical champions" for the project were key contributions to our success. A new QI project is underway to use the newly developed risk stratification algorithm for clinical management to decrease the length of hospitalization for patients with low-risk FN.

Poster # 146

COMPLICATIONS BY CENTRAL LINE TYPE DURING INDUCTION CHEMOTHERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Central venous lines (CVL) are essential for delivery of therapy for patients with pediatric acute lymphoblastic leukemia (ALL). However, CVLs are associated with an increased risk of bloodstream infections (BSIs) and thromboembolic events (TE), and can lead to significant cause of morbidity. Prior studies have shown conflicting data regarding the impact of CVL type on the extent of these risks.

Objectives: To describe rates of CVL-associated BSIs and TEs in ALL patients receiving induction therapy and compare differences by type of line.

Design/Method: Patients aged 1-21 years diagnosed with ALL between January 1, 2010 to May 15, 2018 at Children's Healthcare of Atlanta (CHOA) who had a port or peripherally inserted central catheter (PICC) were included. Manual and automated chart abstraction collected demographics, clinical, disease, and CVL data. Descriptive statistics were calculated for all study

variables; chi-square and Mann-Whitney U tests were performed to analyze factors associated with the type of CVL including differences in BSI and TE. Analyses were completed using SAS 9.4 (Cary, NC).

Results: There were 489 patients included. Ports were more commonly placed (n=402, 82%). Patients with a port were significantly more likely to be younger (Median: 5.4 years, IQR=3.4, 9.8), while older patients were more likely to have a PICC (Median: 10.7 years, IQR=4.4, 14.9) ($p<0.01$). There were no significant differences in the type of CVL received by sex, race, or ethnicity. There were 23 (4.7%) patients with a TE; TEs were significantly more likely in patients with a PICC (12.6%) compared to a port (3.0%) ($p<0.01$). Patients with a port had a longer median time from CVL placement to TE (Median: 23.5 days, IQR=16, 30) compared to those with a PICC (Median: 15.0 days, IQR=2, 27), though this difference was not significant ($p=0.14$). Overall, 54 (11%) patients had a BSI and there were no differences in BSI rates by CVL type (port: 11.2%, PICC: 10.3%, $p=0.82$). Patients with a PICC had half the time from PICC to BSI (Median: 7 days, IQR=6, 16) compared to those with a port (Median: 14 days, IQR=8, 17) ($p=0.05$).

Conclusion: BSIs and TEs are uncommon during ALL induction, however CVL type does affect risk. Patients with a PICC were more likely to have a TE and to develop TE closer to placement. Contrary to prior studies, there were no differences in BSI rates by CVL type. Work is ongoing to evaluate if antibacterial prophylaxis varied by CVL type and impacted these results.

Poster # 147

ADHERENCE TO STANDARDIZED GUIDELINES IMPROVES CONTROL OF VOMITING IN PEDIATRIC PATIENTS WITH CANCER

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Background: Chemotherapy is crucial for successful pediatric cancer treatment. Vomiting is a common and distressing acute side effect of chemotherapy, which negatively impacts quality of life, nutritional status and the ability of patients to tolerate further treatment. In fact, chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing treatment-related symptoms. Standardized guidelines, based on evidence, have been developed for anti-emetic therapy regimens to improve control of nausea and vomiting. It is unknown whether adherence to existing clinical practice guidelines (CPG) improves clinical outcomes.

Objectives: To determine the benefit of adherence to CPGs on complete control of vomiting during chemotherapy in newly diagnosed pediatric patients with cancer and to evaluate potential factors that may contribute to achieving complete control in these chemotherapy-naïve patients.

Design/Method: An electronic dashboard of pediatric patients newly diagnosed with cancer at Phoenix Children's Hospital between January and August 2020 and receiving their first cycle of chemotherapy was utilized to monitor diagnosis, chemotherapy regimen, anti-emetic medications utilized, and episodes of vomiting. Chemotherapy blocks were classified as guideline-consistent if the appropriate prophylaxis medications, as per current Children's Oncology Group (COG)

recommendations, were administered prior to and during the chemotherapy block, guideline-consistent PLUS if they received additional anti-emetic medications in addition to guideline recommendations, and guideline inconsistent if they did not receive the appropriate prophylactic medications. Retrospective review was completed to determine which patients had complete control of vomiting, defined as no vomiting during the block and not requiring additional anti-emetic medications.

Results: Data from 136 patients were included. There was no statistical difference in in age, gender, race, or ethnicity between patients who achieved complete control (47.8%) and those who did not (52.2%), but emetogenicity classification was associated significantly with achievement of complete control ($p=0.0064$). Age was the only demographic associated with a significant difference in guideline adherence, with younger patients being more likely to be guideline inconsistent ($p<0.0001$). Patients who received anti-emetic medications classified as guideline consistent PLUS were significantly more likely to achieve complete control than all other patients (OR=3.69, 95% CI: 1.22-11.15). Multivariate analysis (controlling for age, gender and emetogenicity) showed that patients receiving guideline-adherent medications were more likely to have complete control (OR 2.90, $p=0.026$).

Conclusion: Our results suggest that adherence to CPGs improves complete control of CINV. The inclusion of additional prophylactic antiemetic medications (our guideline-consistent PLUS category) to those that were guideline consistent improved complete control, suggesting that modification of existing CPGs might improve CINV control.

Poster # 148

ADDRESSING ADHERENCE TO GUIDELINES ON PREVENTION OF ACUTE CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

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Background: Chemotherapy induced nausea and vomiting (CINV) is a common adverse effect in children receiving cancer treatment, with impact on quality of life in both patients and caregivers. Without antiemetic prophylaxis, the incidence of CINV in children is 30-90% within the first 24hr of initiating moderately emetogenic chemotherapy (MEC) and > 90% with highly emetogenic chemotherapy (HEC). The Pediatric Oncology Group of Ontario published clinical practice guidelines on chemotherapy emetogenicity and prevention of acute CINV based on the most current pediatric evidence. Despite recommendations on evidence-based strategies, adherence to these guidelines has shown to be low and there continues to be a paucity of literature regarding the barriers to adherence.

Objectives: Our smart aim was to improve adherence to guidelines on prevention of acute CINV in hospitalized patients to >70% by June 30, 2021. Secondary objectives included assessing guideline adherence based on chemotherapy emetogenicity (MEC vs HEC).

Design/Method: Baseline data was collected for 6 months prior to the intervention. Using process

mapping and a staff survey, the identified barriers to CINV guideline adherence included: 1) insufficient guideline knowledge, 2) access to guideline when prescribing chemotherapy, 3) formulary access to newer anti-emetics (palonosetron, aprepitant). These barriers were addressed with several interventions, and data was collected for 6 months following their implementation. Interventions included: 1) educational session on guideline, 2) development of a tool for prescribing anti-emetics based on chemotherapy emetogenicity, 3) addition of newer anti-emetics to inpatient formulary.

Results: A total of 270 inpatient chemotherapy administrations (MEC, HEC) were analyzed over a one-year period (N=131 pre-intervention, N=139 post-intervention). Initial rates of CINV guideline adherence were 25% which improved to 72% post-intervention ($p<0.001$). In subgroup analysis, guideline adherence in the MEC group improved from 13% to 34% ($p=0.016$), and in the HEC group from 32% to 93% ($p<0.001$). The most common reason for non-adherence in the MEC group was lack of another prophylactic anti-emetic in addition to ondansetron, either dexamethasone or aprepitant (where dexamethasone was contraindicated).

Conclusion: Given the distress CINV has on patients, our aim was to improve adherence rates to evidence-based guidelines for prevention of acute CINV in our pediatric oncology center. After identifying barriers and implementing a series of interventions, we were able to successfully improve the overall rates of guideline adherence, particularly in the HEC subgroup. For the MEC subgroup, guideline adherence remained poor. Our next steps will involve exploring factors for lack of prophylactic anti-emetics and improve guideline adherence in this population.

Poster # 149

DOUBLE BLIND, PLACEBO CONTROLLED TRIAL OF APREPITANT WITH CROSSOVER DESIGN: NO EVIDENCE OF BENEFIT

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Background: Aprepitant is a NK1 receptor antagonist recommended as an adjunct to 5HT3 inhibitors and steroids in the prevention of chemotherapy-induced nausea and vomiting (CINV) with highly emetogenic chemotherapy (HEC). Its use was approved in children based on the phase 3 trial published by Kang et al, which included patients receiving ondansetron, but did not specify dose or the use or dose of dexamethasone, resulting in heterogeneity between the two arms. Due to the expense and potential toxicity of aprepitant, we felt further study necessary.

Objectives: Determine if aprepitant is beneficial in reducing CINV when used in combination with standardized doses of antiemetics in pediatric patients receiving HEC.

Design/Method: We performed a randomized, double blind, crossover study. Each patient received two identical cycles of HEC, one with standard antiemetic treatment (**ST**) of ondansetron 0.15 mg/kg (max 16 mg) q8 hours and dexamethasone 0.2 mg/kg (max 10 mg) daily for 3-5 days + placebo and the investigational arm (**AP**) with ondansetron, dexamethasone decreased 50%, and

aprepitant, given at a dose of 3 mg/kg (max 125 mg) PO on day 1 and 2 mg/kg (max 80 mg) PO on days 2 and 3. The investigational pharmacy dispensed both dexamethasone and aprepitant or placebo. We randomized which regimen was given first, stratified by age group (<6, 6-9.99, and ≥ 10 years of age) and diagnosis (CNS vs. other solid tumors).

We measured efficacy by using the Baxter Animated Retching Faces (BARF) scale daily during chemotherapy and the Modified Functional Living Index-Emesis (FLIE) questionnaire, reporting the effect of CINV on quality of life the previous 5 days, on day 6 of each cycle.

Results: We enrolled 18 subjects and 16 received 2 cycles of therapy and were assessable for the primary outcomes. We looked at the differences between the day 6 FLIE question 1 response when receiving AP and their response when receiving ST, whether given first or second. The differences were assessed by Student's paired t-test, or the sign test, as appropriate, and showed the scores did not differ significantly, averaging -0.1369 points difference on a 7 point Likert scale (p-value 0.8936). Likewise, the day 2 BARF scores did not differ significantly between the two treatments (mean +0.18 points on 5 point scale [p-value 0.375]).

Conclusion: Our study showed no evidence to suggest a benefit from aprepitant use when given as recommended with ondansetron and dexamethasone for preventing CINV during HEC.

Poster # 150

TUMOR LYSIS SYNDROME RISK FACTORS, INCIDENCE AND MANAGEMENT IN ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS

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Background: Pediatric acute lymphoblastic leukemia (ALL) patients are at risk for tumor lysis syndrome (TLS) at diagnosis and with therapy initiation due to lymphoblast lysis, which can adversely affect organ function. The optimal management is not well-standardized.

Objectives: To examine the incidence and timing of tumor lysis complications in pediatric ALL patients to determine optimal management.

Design/Method: All patients diagnosed from 2007-2021 with ALL were identified and tumor lysis related lab values and complications were collected from time of presentation through day 7 of induction therapy. Wilcoxon Rank-Sum test and Pearson's Chi-squared test were used for continuous and categorical variables respectively.

Results: Of 357 ALL subjects, 4.84% (17) required immediate dialysis (ID) at cancer presentation and had higher median presenting lactate dehydrogenase (LDH) 2153, white blood cell count (WBC) 312.9, and uric acid (UA) 10.9 than in non-ID patients, whose median values were LDH 483, WBC 10.2, and UA 4.9, all P <0.001. Patients receiving ID were numerically but not significantly older (median 10.4 vs. 5.4 years, P=0.175) and more commonly had T-cell versus B-

cell ALL (52.9% vs. 11.2%, P=<0.001). Of the 340 patients not requiring ID, 1.8% eventually underwent dialysis (pre-induction [1], Day 1 of induction [1], Day 2 [1] and Day 3 [3]). All had T-cell ALL, were older (median 14.0 vs. 5.3 years, P<0.001) and had higher presenting median values LDH 1415, WBC 66.3, UA 10.8, potassium 5.3, and creatinine 1.07, than non-dialysis patients, LDH 474, WBC 10.0, UA 4.8, potassium 4.3 and creatinine 0.53 (P values 0.012, 0.006, <0.001, 0.023, and <0.001 respectively). Only 4.1% (14/340) needed intervention for hyperkalemia and no primary intervention was needed after induction Day 2. Rasburicase was required in 10% (N=34) but only in 2 subjects after induction day 2 (both on Day 5). Allopurinol was started on 69.1% of subjects at presentation and 98.8% by induction start. Phosphate binders were used in 25.6%. The median intravenous fluid rate used was 1.5x maintenance from presentation until induction Day 3, then maintenance on Day 4-5 and 0.5x maintenance by Day 6. Despite no dialysis needed beyond Day 3, on induction Day 4, 43.6% of patients remained on ≥1.5x maintenance with 25.6% still receiving this on Day 5. Despite rasburicase never used beyond Day 5, 40.6% remained on allopurinol on Day 6.

Conclusion: TLS is a source of morbidity in ALL requiring prompt identification and ideally prevention. Risk stratification can lead to safe, earlier de-escalation of management.

Poster # 151

PALIFERMIN AS SECONDARY PROPHYLAXIS FOR CHEMOTHERAPY INDUCED MUCOSITIS: A RETROSPECTIVE EXPERIENCE

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Background: Chemotherapy induced mucositis is common among patients treated with certain chemotherapy protocols. Furthermore, admissions for severe mucositis represent a burden for both patients and the healthcare utilization. Palifermin is a human keratinocyte growth factor originally FDA approved in 2004 with an update with pediatric dosing in 2013. Palifermin is, however, an expensive medication so we should be thoughtful in its use and be able to make informed decisions for whom we should provide this prophylaxis.

Objectives: To review the impact of palifermin prophylaxis against chemotherapy induced mucositis in pediatric patients

Design/Method: We retrospectively reviewed the charts of 13 patients, 7 of whom received palifermin (Group A) and 6 of whom never received palifermin (Group B). Inclusion criteria included patients treated for osteosarcoma (n=3) or non-Hodgkin lymphoma (n=10). Severe mucositis was defined as an admission requiring a Patient Controlled Analgesia (PCA) for mucositis pain and/or Total Parenteral Nutrition (TPN) due to inability to tolerate oral intake. IRB approval was obtained for this retrospective dataset.

Results: Among group A, five of the seven patients had a preceding episode of mucositis where 2 of these 5 had >/= 2 severe mucositis episodes, and palifermin was used as secondary prophylaxis. Four of these five had no further admissions for mucositis. In group B, three of the six individuals

had two or more severe mucositis episodes. Episodes of severe mucositis were particularly common in our dataset following administration of COPADM1 (Cyclophosphamide, Vincristine, Prednisone, Doxorubicin, Methotrexate) chemotherapy (7 instances) and COPADM2 chemotherapy (3 instances). All 3 cases following COPADM2 chemotherapy occurred in the group B. Median admission length was 7 days (range 3-41 days).

Conclusion: Palifermin was effective in reducing the future occurrence of severe chemotherapy induced mucositis with only one individual experiencing severe mucositis following administration of palifermin. In addition, group B had a high rate of severe mucositis (50%) following COPADM2. Two patients received palifermin prior to COPADM2, and neither had severe mucositis after this chemotherapy, suggesting some efficacy in preventing severe mucositis for this subset of patients. Palifermin's healthcare costs are not insignificant, costing about $10000 for 3.35 mg or about $30000 for a dose. This, however, is balanced against the costs of hospital admission (about $3700 per night), staffing, PCA use, TPN use, and the psychosocial burden of prolonged admissions.

Poster # 152

AUTOMATED ELECTRONIC HEALTH RECORD ASCERTAINMENT OF TYPHLITIS: A CHILDREN'S ONCOLOGY GROUP REPORT

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Background: Typhlitis is a rare but potentially serious adverse event (AE) during pediatric leukemia therapy. Currently on Children's Oncology Group (COG) trials, clinical research associates (CRAs) manually ascertain AEs according to Common Terminology Criteria for Adverse Events (CTCAE) definitions. However, despite this significant effort, we previously reported that COG AE typhlitis reports had a sensitivity of only 37%.

Objectives: To develop and test an automated typhlitis identification algorithm using electronic health record (EHR) data.

Design/Method: This study used EHR data from patients in the Leukemia Electronic Abstraction of Records Network (LEARN) treated at Children's Hospital of Philadelphia from 2011 through 2019. The study cohort was divided into a derivation cohort (patients not enrolled on a trial) and a validation cohort (patients enrolled on a trial). A trained medical student reviewed patient charts in the validation cohort to establish a gold standard dataset of typhlitis AEs. An automated algorithm to identify the presence of typhlitis was created *a priori* based on the CTCAE v5 definition and included the following criteria being met in an overlapping timeframe: receipt of antibiotics, neutropenia (ANC<1000/mm^3), and non-negated mention of typhlitis or neutropenic colitis in a clinician note. Relevant data were automatically extracted from the EHR for all patients. We iteratively refined a rules-based natural language processing algorithm using the derivation cohort to identify non-negated mentions in notes accounting for word misspellings. Once completed, the

algorithm was applied to the validation cohort. AE report data from trial AAML1031 were received from COG. Performance was determined for algorithm-based and COG-based typhlitis identification using chart abstraction as the gold standard.

Results: The derivation cohort included 346 patients. The validation cohort included 270 patients (961 courses). Gold standard chart abstraction identified 16 courses with typhlitis; 3 patients had more than one chemotherapy course with typhlitis. The automated algorithm identified 37 courses with typhlitis, of which 13 were true positives (sensitivity 81.3%, PPV 35.1%). COG AE reports correctly identified 4 courses with typhlitis (sensitivity 44.4%, PPV 100.0%).

Conclusion: The automated algorithm can successfully identify true cases of typhlitis with higher sensitivity than manual COG reports. The algorithm found false positives, but reduced the number of courses a CRA would need to review from 961 to 37 by detecting those with potential typhlitis. This automated algorithm could provide a useful screening tool to reduce manual effort required for low incidence complex AE reporting. Testing at a second institution is ongoing to demonstrate generalizability.

Poster # 153

DIAGNOSIS AND MANAGEMENT OF TYPHLITIS IN PEDIATRIC LEUKEMIA PATIENTS

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Background: Typhlitis is a rare, but important, adverse event (AE) that children with acute leukemia may develop during anti-cancer therapy. Most patients with typhlitis can be managed conservatively with nil per os (NPO) status, antibiotic therapy, and observation, but approaches to both diagnosis and treatment are varied.

Objectives: This study sought to describe rates of typhlitis in pediatric patients with leukemia and approaches to diagnosis and treatment as a first step towards providing evidence-based consensus on management.

Design/Method: This study used manually abstracted electronic health record data from patients in the Leukemia Electronic Abstraction of Records Network (LEARN) treated at the Children's Hospital of Philadelphia from 2011 through 2019 and Children's Healthcare of Atlanta from 2010 through 2018. Following a predefined chart abstraction guide, trained abstractors identified chemotherapy course dates and the presence of each of the following data elements: receipt of antibiotics, neutropenia (ANC<1000/mm^3), true mentions of typhlitis or neutropenic colitis in clinician note, and radiology testing. Granular data were collected from imaging reports on type, mentions of typhlitis, and related descriptors. Descriptive statistics were performed using SAS.

Results: Of the 592 patients (2893 courses) in the cohort, 23 (3.9%) patients had a typhlitis event in at least one course. Overall, 26 (0.9%) courses had typhlitis. Imaging was performed in all

typhlitis events, but typhlitis was only mentioned in imaging findings for 17 (65.4%) events. Of the radiology reports mentioning typhlitis, 14 (82.4%) confirmed a true case of typhlitis. Computerized tomography (CT) scan (n=19, 73.1%) and x-ray (n=20, 76.9%) were the most common imaging types used; ultrasound was only performed in 12 (46.2%) typhlitis events. More patients who had CT scans (n=10, 52.6%) had true cases identified on imaging than any other imaging type (x-ray: n=1, 5.0%; ultrasound: n=4, 33.3%). Evaluating management, the patient was made NPO in 20 (76.9%) typhlitis events and was treated with antibiotics in 22 (84.6%) events.

Conclusion: There are a range of diagnostic and management strategies for typhlitis, including in use and type of imaging. While imaging was widely used in patients with concern for typhlitis, radiology reports only definitively described typhlitis in 60% of typhlitis events. Work is ongoing to determine the utility of obtaining imaging in the diagnosis of typhlitis given this low rate of definitive mentions and of the impact of different management strategies on duration and morbidity of typhlitis.

Poster # 154

CONSTIPATION IN ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS RECEIVING HIGH DOSE METHOTREXATE

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Background: Pediatric cancer patients suffer from a wide variety of chemotherapy induced side effects, including constipation. Psychological factors, chemotherapeutic medications, and lifestyle changes play a role in the multifactorial development of constipation. Methotrexate is a common chemotherapy agent administered for leukemia treatment and is primarily eliminated by the kidneys and liver. Failure to clear methotrexate from the body results in toxicities including mouth sores, mucositis, and organ dysfunction. To date, no studies have examined the correlative relationship between constipation and delayed methotrexate clearance.

Objectives: This study aims to examine the characteristics of chemotherapy induced constipation management, and the relationship between methotrexate delays and constipation.

Design/Method: This single institution, retrospective study, analyzed data from Riley Hospital for Children, included patients aged 0-26 years of age that were diagnosed with acute lymphoblastic leukemia from January 2010-September 2021. Constipation was defined as no documented stool for 48 hours.

Results: We investigated 37 unique pediatric oncology patients with acute lymphoblastic leukemia with an average age of 7.9 (range 0-26) years. Majority were male (76%), and Caucasian (89%). We captured 100 unique encounters of patients receiving methotrexate with an average admission of 5 days. Over one third (n= 39, 39%) of patients during inpatient admission met our definition of constipation, without a stool for 48 hours, with only 8% of patients having documentation of constipation in a progress note. Of patients with documented constipation, 87.2% (n=34) experienced some delay in methotrexate clearance and 20.5% (n=8) experienced a methotrexate

toxicity during their admission. Only 8% of patients had a scheduled constipation medication prescribed. As needed constipation medications were prescribed to 41.0% (n=16) of constipated patients, while only administered 13% (n=2) of the time. Miralax was the most common scheduled and as needed medication (88%). Additionally, 39% of patients had an as needed opioid prescribed that was utilized during admission, and majority of patients received at least one dose of vincristine. Prior to admission, 41% of constipated patients had historical constipation during previous admissions, and 92% of patients did not have a last stool documented prior to chemotherapy administration.

Conclusion: Patients admitted for methotrexate clearance suffered from constipation without appropriate bowel regimens. In addition to their prolonged hospitalizations, they received opioids and vincristine, both well known to worsen constipation. Future prospective studies should focus on appropriate bowel regimens and secondary effects of constipation on drug clearance in pediatric oncology patients.

Poster # 155

PERIPHERAL NEUROPATHY IN PATIENTS RECEIVING VINCRISTINE & LEVOFLOXACIN COMPARED TO VINCRISTINE ALONE

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Background: Vincristine (V) is a central chemotherapy agent for leukemia, lymphoma, and solid tumors. Levofloxacin (L) is a first line antibiotic used to treat infection and as prophylaxis against febrile neutropenia. Both drugs cause peripheral neuropathy (PN), but the cumulative effect of both drugs on PN is unknown.

Objectives: To evaluate the incidence and extent of PN in patients receiving vincristine and levofloxacin (VL) compared to vincristine alone (VA).

Design/Method: This retrospective cohort study reviewed all patients with oncologic diagnoses likely to require V therapy from 2015-2020. Patients were excluded if they did not receive V, did not receive treatment at our institution, or had CNS tumors. Data extracted via chart review included age at diagnosis, gender, race, oncologic diagnosis, PN symptoms, and treatments for PN. PN symptoms were further categorized as sensory (S), motor (M), or autonomic (A). Management of PN, including need for medications, physical therapy, and/or braces, was noted. Drug exposure was calculated in cumulative dosage and number of doses.

Results: 182 patients were screened with an eligible diagnosis. 49 patients were excluded due to not having received V (35), unavailable information (10), or therapy prior to 2015 (4). 133 patients were included in the study. 53 (40%) patients were female. Mean age at diagnosis was 8.28 years (range 4 months – 30 years). 52 (39%) patients had no exposure to L (VA group) and 81 (61%) patients had exposure to L (VL group). 115 patients (86%) reported 1 or more symptoms of PN: constipation (91%), leg pain (72%), extremity weakness (57%), difficulty walking (57%), foot drop (53%), numbness/tingling of fingers/toes (40%), loss of deep tendon reflexes (25%), and jaw pain

(22%). The incidence of PN was higher in the VL group (73/81, 90%) compared to the VA group (42/52, 80%) (p-value 0.20). The VL group reported increased number of neuropathy symptoms (p-value 0.03). More patients in the VL group reported PN symptoms spanning more than 1 category (p-value 0.002). The VL group was more likely to require management of PN (p-value 0.02). Patients are 46% more likely to have an increased number of neuropathy symptoms in the VL group compared to the VA group ($\beta = 0.375$, p-value < 0.001). Total cumulative dose of both V and L were independent predictors of having increased neuropathy symptoms (p-value < 0.05).

Conclusion: Exposure to levofloxacin in patients receiving vincristine significantly increases the burden of peripheral neuropathy.

Poster # 156

AN INITIATIVE TO INCREASE ACTIVITY AND SURVEILLANCE FOR NEUROPATHY IN CHILDREN WITH ALL

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Background: During therapy for acute lymphoblastic leukemia (ALL), pediatric patients often experience prolonged hospital stays and chemotherapy toxicity from medications, such as steroids and vincristine (VCR). As a result, patients may experience a decrease in physical activity, acceleration of muscle mass loss, and peripheral neuropathy, ultimately decreasing their quality of life.

Objectives: To decrease these comorbidities by promoting patient-driven activity during hospitalization and early detection and management of VCR-induced neuropathy.

Design/Method: We utilized the Institute for Healthcare Improvement Model of Improvement as our quality improvement (QI) framework to implement a quality improvement initiative called Exercise is Medicine (EiM). The key components of the EiM initiative for patients with ALL include (1) educating stakeholders to increase awareness of the importance of patient ambulation during hospitalization, (2) incorporating a daily patient/caregiver driven mobility program called Miles in Motion (MiM) to increase patients' activity, and (3) expanding physical therapy (PT) and orthotics consults for early detection and management of neuropathy. Data was collected between July 2020 and October 2020 for 115 patients ≤21 years of age. Data included prevalence and frequency of PT consults, PT session completion rates, prevalence of neuropathy screenings, and 1-minute sit-to-stand test (STST) scores from admission and discharge.

Results: After implementation of our initiative, PT consults for oncology patients increased from 31.4% to 41.9%. and frequency of debilitated patients (defined as requiring PT sessions 4 or more times per week) decreased from 23.2% to 17.5%. Additionally, successful completion of PT sessions rose from 84.6% to 90% post-intervention. By discharge, 77% of patients improved or maintained baseline of their 1-minute sit-to-stand test (STST) scores, thus indicating improvement or preservation of pre-admission endurance. Screening for early detection of VCR-induced peripheral neuropathy increased by 57.5% and orthotic consults for early management of VCR

induced neuropathy increased from 29% to 61.5%.

Conclusion: EiM initiative in children with ALL maintained or prevented significant functional muscular weakness due in part to early ambulation as well as early detection and management of VCR-induced peripheral neuropathy. As such, to improve physical outcomes, we recommend implementation of the EiM initiative for children with ALL who are admitted to the hospital.

Poster # 157

BLINATUMOMAB ASSOCIATED SEIZURE RISK IN PATIENTS WITH DOWN SYNDROME AND B-LYMPHOBLASTIC LEUKEMIA

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Background: Children with Down Syndrome (DS) and B-lymphoblastic leukemia (B-ALL) are at increased risk of both relapse and treatment-related mortality, compared to those without DS. On COG study AALL1731 for *de novo* B-ALL, patients with DS and higher risk features (DS-High) are treated with a regimen replacing intensive elements of conventional chemotherapy with three 28-day cycles of blinatumomab. The DS-High group includes all NCI high risk (HR) patients; NCI standard risk (SR) patients with end-induction minimal residual disease positivity, unfavorable cytogenetics, CNS3 status, steroid pre-treatment, neutral cytogenetics with CNS2 status, or testicular disease. Neurotoxicity is a known risk of blinatumomab, with an incidence of 4% among non-DS pediatric patients with relapsed ALL (Brown et al, JAMA 2021). However, the specific risk in patients with DS has not yet been described.

Objectives: To describe an early interim report of increased seizure incidence associated with blinatumomab in older DS-High patients enrolled on AALL1731 to date.

Design/Method: We reviewed seizure incidence among patients with DS enrolled on AALL1731 from June 2019 to June 2021 who received blinatumomab. Blinatumomab 15 mcg/m^2/day was administered, with dexamethasone pre-medication in cycle 1. Infusions were interrupted for seizures, with resumption at 5 mcg/m^2/day permitted following full resolution for grade 1-3 seizures.

Results: Among DS NCI HR patients, 8 of 47 (17%) had a seizure during blinatumomab infusion. All 8 seizures occurred in patients over 10 years old. Six of the 8 seizures occurred in cycle 1, and most in the first 3 days. Four had concomitant fever or cytokine release syndrome. Seizures were grade 2 (n=2) or grade 3 (n=6), and all resolved with full neurologic recovery. Of the 8 patients, 5 received further blinatumomab,with no further seizures reported. There was no indication of increased seizure risk among NCI SR DS-High patients, or among DS or non-DS patients receiving blinatumomab on other study strata.

Conclusion: The incidence of seizures associated with blinatumomab in DS-ALL patients older

than 10 years appears higher than previously reported in children without DS. The majority of seizures occurred within the first 3 days. All patients fully resolved without sequelae, and no patient who resumed blinatumomab at the lower infusion rate experienced further seizures. Seizure prophylaxis may be advisable in DS patients while receiving blinatumomab, particularly those ≥10 years of age. Further follow-up and a larger sample size are needed to confirm incidence and identify risk factors predisposing DS patients to neurotoxicity.

Poster # 158

HYPONATREMIA ASSOCIATED WITH INDUCTION CHEMOTHERAPY REGIMENS FOR LYMPHOBLASTIC LEUKEMIA AND LYMPHOMA

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Background: Induction chemotherapy per the Children's Oncology Group (COG) protocols for pediatric acute lymphoblastic leukemia (ALL) and lymphoma includes vincristine, asparaginase, occasionally daunorubicin, and either dexamethasone or prednisone. Patients often experience varying degrees of steroid-induced side effects which may require additional medical intervention and increasing subspecialty involvement. Varying degrees of hyponatremia can be seen, often attributed to vincristine-associated syndrome of inappropriate antidiuretic hormone secretion (SIADH). Previous incidence estimates of severe hyponatremia (serum sodium levels less than 130 mEq/L) in pediatric ALL and lymphoma patients was 11.9%. Studies have not been conducted showing a difference in the incidence of hyponatremia during Induction between dexamethasone and prednisone.

Objectives: To quantify and compare the incidences of serum and urine electrolyte abnormalities in pediatric ALL and lymphoma patients who are receiving different steroid therapies and dosing regimens as part of induction chemotherapy.

Design/Method: A retrospective chart review of 86 pediatric and young adult patients less than 25 years of age with a diagnosis of ALL or lymphoma who received standard of care induction chemotherapy per COG protocols over the last 5 years. Patient biochemical profile data, including serum and urine electrolytes, were collected during the 60 day period after the start of induction chemotherapy.

Results: The incidence of severe hyponatremia was found to be 42%. Of the 86 patients, the mean minimum sodium level was 131 mEq/L . On average, minimum sodium levels occurred on day 15 of induction chemotherapy. Only 7% of patients received a diagnosis of SIADH. Twenty-seven percent of patients received a Pediatric Nephrology consultation, 20% received a renal ultrasound, and 37% required treatment for hyponatremia. There was no significant difference in the incidence of severe hyponatremia between steroid types ($p = 0.42$).

Conclusion: Severe hyponatremia is more common in our study than previously reported. These data may provide further evidence that hyponatremia is associated with steroid use instead of vincristine use as SIADH was not a common diagnosis in our patient population. Given the

frequency of severe hyponatremia and the variable approach for assessment and management, future directions include creating an algorithm in collaboration with nephrology to standardize the approach to assessment and management of hyponatremia during induction.

Poster # 159

TRAJECTORY OF HYPERGLYCEMIA IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

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Background: Medication-induced hyperglycemia is a known adverse event (AE) associated with pediatric acute lymphoblastic leukemia (ALL) therapy. It most commonly develops during induction therapy, likely due to glucocorticoid-induced insulin resistance and asparaginase-induced pancreatic B-cell dysfunction. However, hyperglycemia can also occur in later courses of chemotherapy, and the burden of this AE and impact on development of other AEs has not been well characterized.

Objectives: To describe the trajectory of hyperglycemia following induction chemotherapy for children with ALL, to identify patient-specific risk factors that may predict trajectory, and to delineate the management and risk of other AEs associated with hyperglycemia.

Design/Method: This single institution retrospective cohort study included patients aged 1-21 years with B or T ALL who received chemotherapy at Children's Healthcare of Atlanta from 2010 through 2018. Data were collected via automated and manual chart abstraction and included demographics, presence and grade of hyperglycemia by course (according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events v5), management, and development of other AEs by course. Trajectory was determined for each patient as resolution (before starting consolidation without later return), persistence (into at least consolidation), or recurrence (redevelopment during later courses following resolution prior to consolidation). Descriptive statistics were performed.

Results: Of the 450 patients included in this study, 60 patients (13.3%) had grade 2+ hyperglycemia during at least one course. Patients aged ≥10 at diagnosis and those classified as NCI High Risk were significantly more likely to have grade 2+ hyperglycemia at any time compared to those aged <10 ($p<0.01$) and Standard Risk ($p<0.01$). Fifty patients (83.3%) initially developed hyperglycemia during induction. Of those 50 patients, 35 (70%) experienced resolution, 7 (14%) had persistence, and 8 (16%) had recurrence. Recurrence most commonly occurred during delayed intensification (DI: 7 patients, 87.5% of those who recurred); 3 patients (42.8%) had hyperglycemia that then persisted into maintenance after DI. Grade 2+ hyperglycemia at any point was associated with higher rates of pancreatitis (18.3%) compared to those without hyperglycemia (5.6%, $p<0.01$). There was no association between rates of neutropenic fever or serious infections

and hyperglycemia.

Conclusion: Although there is a large burden of hyperglycemia during induction in pediatric ALL, most patients experience complete resolution by consolidation. It is uncommon to have persistent hyperglycemia beyond induction, and extremely rare to have persistence throughout all of chemotherapy. Given the trajectory of this important AE, efforts to mitigate the risk of hyperglycemia should focus on induction.

Poster # 160

HYPERTENSION AND BRADYCARDIA DURING INDUCTION CHEMOTHERAPY FOR LYMPHOBLASTIC LEUKEMIA AND LYMPHOMA

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Background: Induction therapy for pediatric acute lymphoblastic leukemia (ALL) and lymphoma consists of vincristine, asparaginase, occasionally daunorubicin, and either dexamethasone or prednisone. Bradycardia and hypertension are two common side effects of steroid use and may result in additional medical intervention or subspecialty involvement. Bradycardia is defined as heart rate less than 1st percentile for age and hypertension or blood pressure greater than 95th percentile for age persisting for 3 days or more. Previous literature has reported the incidence of bradycardia during induction to be 59% and hypertension incidence has been reported to range from 15-45%.

Objectives: To quantify and compare the incidences of bradycardia and hypertension in pediatric lymphoma and leukemia patients who are receiving steroids during induction chemotherapy.

Design/Method: A retrospective chart review of 86 patients less than 25 years old with the diagnosis of acute lymphoblastic leukemia or lymphoma undergoing standard induction chemotherapy per the Children's Oncology Group was performed. Patient blood pressure and heart rates were collected during a 60 day period after the start of induction. Descriptive statistics were obtained, overall incidence of hypertension and bradycardia were recorded. Incidence of bradycardia and hypertension with dexamethasone and prednisone were compared. Statistical significance was tested using chi square or Fischer exact testing when appropriate.

Results: Steroid-induced bradycardia was found in 60.5% of patients during induction and there was a statistically significant difference in the incidence of bradycardia when taking dexamethasone (73%) vs prednisone (32%)(p value 0.0005). Steroid-induced hypertension was noted in 87% of the study population. No statistical difference in incidence of hypertension was seen when comparing the use of dexamethasone to prednisone (p value of 0.5).Twenty-six percent of patients received treatment for steroid-induced hypertension. Additionally, 20% of patients received a renal ultrasound during induction to check for renal causes of hypertension and 28% of patients received a Nephrology consult. One patient (1.2%) developed hypertension during induction that lasted past the 60 day study interval requiring daily antihypertensives.

Conclusion: Steroid-induced hypertension are common findings during standard of care induction chemotherapy. These patients are more likely to receive additional medical interventions (i.e antihypertensive medication, renal ultrasound) or see additional subspecialists. Future work to include generation of clinical pathways for assessment and management of these common side effects.

Poster # 161

USE OF ROTEM TO CHARACTERIZE THE COAGULATION PROFILES OF NEWLY DIAGNOSED PEDIATRIC LEUKEMIA PATIENTS

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Background: Newly diagnosed pediatric leukemia patients (NDPLP) can present with thrombocytopenia along with prolonged prothrombin (PT) and/or activated partial thromboplastin time (aPTT) with/ without bleeding symptoms. Most of these patients receive products such as fresh frozen plasma (FFP) prior to procedures for prolonged PT/aPTT which may not be warranted as abnormality in these tests do not predict bleeding risk. Thromboelastometry is a whole blood coagulation analyser providing insights into clot initiation and propagation via the intrinsic (INTEM) and extrinsic (EXTEM) pathways, fibrin platelet interaction and clot firmness/ lysis (FIBTEM, APTEM).

Objectives: We aimed to characterize the coagulation profiles of NDPLP undergoing induction chemotherapy using ROTEM assays at three different time points to determine correlation of platelets and routine coagulation tests with clot characteristics revealed by ROTEM to aid in tailoring blood product management.

Design/Method: Target recruitment of NDPLP (including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) aged 1-21 years of age after obtaining institutional approval and consent /assent was conducted. Samples for ROTEM assays, PT/aPTT, fibrinogen and platelet counts were obtained at diagnosis, day 15 and day 29 of induction chemotherapy per Children's Oncology Group protocols.

Results: A total of 33 patients were recruited prospectively with mean age of 7.53 years (range:1.55-14.90) including females (n=17) and males (n=16) who were diagnosed with ALL (n=29) and AML (n=4). Mean platelet count at presentation was 60,000/cu.mm (range 15,000 – 158,000) and 12 had prolonged PT and prolonged aPTT (n=2). For ALL patients, ROTEM revealed prolonged Clotting time (CT) and Clot Formation Time (CFT) in both INTEM and EXTEM, consistent with coexisting thrombocytopenia. Mean fibrinogen levels at presentation were 424 mg/dL which correlated with normal FIBTEM MCF. Hypofibrinogenemia related to administration of PeG Asparaginase used in ALL but not AML protocols was noted on day 15 samples which correlated with increased INTEM and EXTEM CT/CFT and decreased FIBTEM (correlating with thrombocytopenia) without significant bleeding and normalized at the end of

induction chemotherapy.

Conclusion: Based on these preliminary analyses, ROTEM parameters revealed platelets as a driver of the coagulopathy of NDPLP receiving induction chemotherapy. Coagulation parameters (PT/ aPTT) despite being abnormal did not result in abnormal clot characteristics or clinical bleeding. Coagulopathy in NDPLP receiving induction chemotherapy may benefit from optimizing platelets with clinical bleeding using ROTEM to tailor replacement therapy.

Poster # 162

VARIABLES ASSOCIATED WITH OVARIAN INSUFFICIENY IN PEDIATRIC ONCOLOGY PATIENTS FOLLOWING CHEMOTHERAPY

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Background: Gonadotoxic effects of chemotherapy is a critical concern in Pediatric Oncology given most patients survive their cancer. Future fertility is an important concern in this population supporting the need for additional research on chemotherapy gonadotoxicity. Moreover, a recent Children's Oncology Group study identified gonadotoxicity calculation as a barrier to fertility preservation referral, highlighting the need to better understand factors associated with ovarian failure allowing oncologists to proactively intervene and effectively counsel patients and families.

Objectives: The objective of this retrospective single-center study was to identify associations with ovarian failure in pediatric patients with cancer based on age, cancer type and cyclophosphamide equivalent dose (CED). We hypothesize patients $\geq$ 13 years at time of cancer diagnosis would be more likely to experience ovarian failure, compared to patients less than 13 years old.

Design/Method: We retrospectively collected data on pediatric patients with cancer treated between 2008-2017. Inclusion criteria included female gender, age 0-25 at time of cancer diagnosis, diagnosis of a malignancy requiring chemotherapy, and documented ovarian hormone levels following chemotherapy completion. We identified eligible patients using our Division's Comprehensive Operational Database. Patients were excluded if they received hormone replacement therapy, received therapy with clear gonadotoxic effects (e.g. stem cell transplant, pelvic radiation), had brain or breast cancer or died within 2 years of completing therapy.

Results: In total, 245 female patients were identified using the specified inclusion and exclusion criteria. Of these, 57 had documented ovarian hormone levels following chemotherapy. Ovarian failure was classified as having 2 out of 3 abnormal hormone levels (FSH >30mIU/mL, LH >10mIU/mL, Estradiol >50pg/mL). Five patients (9%) met criteria for ovarian failure. These 5 patients were all $\geq$ 13 years old at time of cancer diagnosis and found to have a lymphoma or solid tumor diagnosis.

Conclusion: This is the first study to our knowledge to analyze ovarian hormone levels for pediatric patients with cancer. There was a significant association between ovarian failure and age $\geq$ 13 years at time of cancer diagnosis even in the setting of current treatment regimens.

Additionally, those documented with ovarian failure received a CED between 0-28.4 gm/m^2, suggesting other factors contribute to ovarian dysfunction, warranting further investigation. Future prospective studies can expand on this study by collecting ovarian hormone levels prior to and throughout chemotherapy treatment, and by collecting other markers of ovarian reserve (e.g. anti-Mullerian hormone).

Poster # 163

GONADOTOXIC RISK STRATIFICATION IN LEUKEMIA/LYMPHOMA FRONTLINE PHASE III PROTOCOLS IN COG 2000-2021

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Background: Oncofertility is a growng field in pediatric, adolescent, and young adult oncology (AYA). As fertility preservation counseling is done by a variety of specialists with varied training it is important that information provided on gonadotoxic risk of oncologic therapy be uniform. The Pediatric Initiative Network (PIN) of the Oncofertility Consortium published recommendations for the stratification of treatment-related risk for future infertility that can be used to counsel patients. These recommendations are not integrated into upfront protocols, hindering timely risk counseling and referral for fertility services.

Objectives: Provide a comprehensive guide in gonadotoxic risk categorization for pediatric/AYA patients newly diagnosed with leukemia/lymphoma and treated on current era COG protocols.

Design/Method: Leukemia/lymphoma phase III new diagnosis treatment protocols from the COG were identified from 2000-2021. Protocols were evaluated for gonadotoxic therapies (alkylating agents, heavy metals, hematopoietic stem cell transplant (HCST), or hypothalamic or gonadal radiation). Cumulative alkylating agent dose was determined for each arm and converted to cyclophosphamide equivalent dosing (CED). Patients were grouped as follows: pre-pubertal female, pubertal female, male. The level of risk (minimal, significant, or high) for gonadal dysfunction/infertility was then determined using the PIN Risk Stratification System. Regimens without alkylating agents were considered unlikely to be at risk. Dose calculations and risk stratifications were confirmed by a second reviewer.

Results: In total, 26 protocols with 97 treatment arms were reviewed: acute lymphoblastic leukemia (ALL), 11 protocols (52 arms); acute myeloblastic leukemia (AML), 7 protocols (18 arms); Hodgkin lymphoma (HL), 5 protocols (16 arms); non-Hodgkin lymphoma (NHL), 3 protocols (11 arms). Overall, 26% of leukemia and lymphoma protocols were considered to place patients at a high level of risk in at least one patient group and treatment arm. The percent of protocol arms by disease that placed a patient at high risk in at least one group was 23.1% for ALL, 0% for AML (no HCST), 72.7% for NHL, and 31.3% for HL. Males were most commonly at high risk in 25/97 arms (25.8%) followed by pubertal females in 4/97 arms (4.1%) and prepubertal females in 2/97 arms (2.1%). All patients who received direct gonadal radiation or HCST were

considered high risk.

Conclusion: This comprehensive list provides uniform gonadotoxic risk stratification across institutions using the PIN Risk Stratification System. The majority of protocols evaluated in this project do not have a high risk of gonadotoxicity.

Poster # 164

SYSTEMIC VINCRISTINE EXPOSURE IN THE JUVENILE PERIOD AFFECTS LOWER URINARY TRACT FUNCTION

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Background: Vincristine (VCR) is one of the most common chemotherapy agents used in pediatric oncology. Despite well-known VCR-induced peripheral neuropathy (VIPN), there has been limited investigation into the potential impact of VIPN on lower urinary tract (LUT) function.

Objectives: The objective of this study was to investigate the effects of systemic VCR exposure in childhood on LUT function by using a juvenile murine model.

Design/Method: Using IACUC approved protocols, CD-1 mice (3.5-wk-old) received an intraperitoneal injection of 0.5 mg/kg of VCR twice per week for 4 weeks. Control mice were treated with the same volume and schedule of saline. Physiological recordings of LUT and detrusor function were conducted by in vivo, cystometry in conscious unrestrained mice as well as an in vitro organ bath at 1 month after the last treatment. Bladder morphology was examined by light and fluorescence microscopy. Changes in gene expression in the bladders and the lumbosacral dorsal root ganglia (Ls-DRG) were examined at the mRNA and protein levels.

Results: Cystometry revealed that VCR exposure induced increased functional bladder capacity, micturition volume and bladder compliance. Cystometry also demonstrated sex dimorphic changes in response to VCR; an elevation of maximal intravesical pressure at micturition in females but not in males, and a significant increase in non-void contractions in males compared to the control mice. An increase in basal activity was observed in bladder strips from males who received VCR, suggesting that VCR induced detrusor overactivity. Molecular studies revealed that VCR exposure induced downregulation of a serotonin receptor, Htr3b, in the female bladders. In males, IL-2 was upregulated in both the bladders and Ls-DRG alongside elevated expressions of Trpa1 and Integrin α1 in the bladders of mice exposed to VCR compared to the control group.

Conclusion: Systemic VCR exposure in juvenile mice affected LUT function with sex-dimorphic changes in gene expression in the bladder and Ls-DRG, which may clinically present as gender-specific signs of LUT dysfunction. Translating these findings to clinical relevance, these results indicate that systemic VCR exposure in childhood cancer survivors may impact LUT function and thus we recommend follow-up urological assessment of these children who receive VCR as part of their anti-cancer treatment.

Poster # 165

THE EFFECT OF METHOTREXATE ON NEUROINFLAMMATION GENE EXPRESSION AND ASSOCIATED NEUROLOGIC SEQUELAE

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Background: Methotrexate treatment in pediatric patients has been associated with long-lasting detrimental neurological and psychological sequela following cancer survival (late-effects). The mechanism of methotrexate toxicity is unknown but may be related to the up- and down-regulation of neuroinflammatory-associated genes.

Objectives: The goal of our project is to reveal candidate risk genes and pathways contributing to methotrexate-induced neurocognitive and psychiatric late effects. We hypothesize that pediatric methotrexate treatment causes changes in neurological and psychosocial development associated with abnormal gene expression in brain white matter from autopsy specimens.

Design/Method: This study is composed of a two-pronged design: 1) a retrospective neurological and psychometric analysis of living cancer survivors who have completed methotrexate treatment and 2) genetic analysis of white matter tissue samples obtained from autopsies of deceased patients who had received methotrexate for leukemia or osteosarcoma.
The retrospective chart review consists of the medical records of cancer survivors aged 2-22 years enrolled at the Treatment After Cancer and Late Effects Center at Children's Hospital New Orleans. Specifically, we are examining neurological, audiological, and psychometric testing results before, during, and after treatment.
Genetic analysis is being conducted via RNA extraction from formalin-fixed, paraffin embedded (FFPE) brain specimens from autopsies of patients who received methotrexate treatment as well as normal controls. Nanostring, a variation of targeted RNA microarray testing, is being used to detect abnormal up- or down-regulation of neuroinflammation-associated genes. Bioinformatics using Ingenuity Pathway Analysis (IPA) is being used to determine affected biological pathways and networks.

Results: The retrospective chart review demonstrated that patients who received IV or intrathecal methotrexate are at higher risk of experiencing neurocognitive effects.
Preliminary genetic testing of white matter autopsy samples revealed that six genes were three- to eight-fold over- or under-expressed when compared to age-matched controls: GJA1 (non-syndromic hearing loss), HSPB1 (Charcot-Marie-Tooth disease), AGT (angiotensin), OLFML3 (microglia suppression), P2RY12+ (clotting), and CD24 (myelin sheath).

Conclusion: The present study will provide information regarding gene-environment interactions and thus reveal candidate risk genes and pathways contributing to neurocognitive and psychosocial late-effects. This understanding may provide better identification of those at risk for methotrexate toxicities and thus improve quality of life with access to precision medical interventions,

educational materials, and social support.

Supported by the National Institutes of Health, National Institute of Neurological Diseases and Stroke (NINDS)-BP-ENDURE.

Poster # 166

LET'S GET MOVING: INTEGRATION OF EARLY MOBILITY PROGRAM WITH ROUTINE CANCER CARE

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Background: Cancer-directed treatments increase the risk for physical deconditioning. Children with cancer have limited opportunities for physical rehabilitation and exercise during active cancer therapy.

Objectives: Provide assessment and rehabilitation services to children receiving active cancer treatment in outpatient pediatric oncology clinic through an integrated outpatient mobility program. The goal of the program was early identification, intervention, education, and prevention of physical deconditioning in cancer patients, as well as developing personalized rehabilitation programs for our patients.

Design/Method: We conducted a retrospective chart review for preintervention planning and implemented intervention based on results. We prospectively studied the effect of our intervention.

Results: Preintervention:
645 charts were reviewed between January 2019-January 2020. 157 patients receiving cancer treatment were identified, 120 (76%) of these developed treatment-related disabilities, and 51(42.5%) patients enrolled in outpatient physical therapy.

Coordinating rehabilitation services due to multiple treatment locations was identified as the primary barrier.

Intervention: We established a multidisciplinary team to provide assessment and rehabilitation services in the pediatric oncology clinic. These services were coordinated with the patient's office and infusion appointments. During the mobility clinic appointments, patients underwent initial evaluation, and the therapists provided them with home exercises and durable medical equipment. Based on the results of the initial evaluation, an outpatient physical therapy referral was made. In addition, the patients got braces or orthotics if indicated. Subsequent assessments occurred at 3–6 monthly intervals.

Post Intervention: Since the initiation of this project, 52 patients have been enrolled for initial assessment by a trained physical therapist in our outpatient department. Ten patients had a second assessment, and three patients had a third during subsequent visits. The most common physical

disability noted was ankle flexibility, secondary to peripheral neuropathy from chemotherapy. Other disabilities noted were quadriceps and upper extremity strength loss. Among the ten patients who underwent subsequent assessments, some showed improvement in ECOG performance, while others demonstrated further decline. This was attributed to adherence to physical activity. The mobility clinic program also helped establish physical therapy services for patients who were not receiving these services. A quarterly survey of the program from caregivers and patients provided positive feedback on the ease of availability of services.

Conclusion: We demonstrate a successful mobility program for patients undergoing active cancer treatment in the outpatient setting. This program has helped identify physical disabilities and assist patients in accessing therapy services to address the impact of oncology treatment. We hope future assessments will demonstrate that the patients can regain their baseline functions with therapy interventions.

Poster # 167

MICROBIAL CELL-FREE DNA CORRELATES WITH CLINICAL RESPONSE IN PATIENTS WITH INVASIVE FUNGAL INFECTION

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Background: The diagnosis and treatment of invasive fungal infections (IFI's), a life-threatening complication of cancer therapy or hematopoietic cell transplantation (HCT) is challenging. A convenient, non-invasive method to monitor pathogen-clearance and response to therapy of IFI could help define the appropriate therapy. Because non-invasive plasma microbial cell-free DNA (mcfDNA) next-generation sequencing (NGS) can detect and predict IFI we hypothesized that mcfDNA NGS might be used as a measure of burden of infection to monitor response to antifungal therapy.

Objectives: The objective of this work is to characterize the correlation of mcfDNA abundance with clinical response to treatment in patients with IFI.

Design/Method: In a prospective study, serial remnant plasma samples were collected from pediatric patients undergoing treatment for relapsed/refractory leukemia. IFI's were classified with EORTC criteria by 2 independent experts; episodes empirically treated for suspected IFI, but not meeting possible criteria were classified as suspected. All samples collected within 30 days after clinical diagnosis of non-fungemic IFI were tested for fungal mcfDNA by NGS using a research-use only assay optimized for detection of fungi by Karius (Redwood City, CA). Because of overlapping clinical syndromes, non-fungal DNA was not considered in this study. Chart review of antifungal therapy and clinical response was conducted and correlated with mcfDNA persistence

Results: There were 15 episodes of potential IFI in 14 participants with at least 1 sample available within 1 day of diagnosis (5 suspected, and 4 probable and 6 proven by EORTC definitions). Of 10

probable or proven IFIs, 8 (80%) had a relevant fungal pathogen identified by mcfDNA NGS at diagnosis. Six of these 8 participants had available samples in the post-diagnostic (≥2 days) monitoring period (2 probable, 4 proven). All six participants had persistent fungal mcfDNA of the corresponding IFI for 13 to 31 days. In four participants the mcfDNA demonstrated an early phase peak within the first 5 days of diagnosis. In four participants there was a decline of mcfDNA correlating with favorable clinical response to antifungal therapy and clearance of infection; in two patients there was a rise in mcfDNA correlating with poor clinical response and progression of infection.

Conclusion: In these episodes of IFI, concentration of specific plasma fungal cfDNA detected by NGS corresponded to clinical response, and might be helpful to monitor treatment-efficacy - and potentially in the future as a test of cure - of IFI in immunocompromised hosts, and may help provide more precise and tailored management of these life-threatening infections.

Poster # 168

BLOODSTREAM INFECTIONS & MICROBIOLOGY DURING INDUCTION OVER A DECADE AT A COMMUNITY CANCER CENTER

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Background: Bloodstream infections (BSIs) remain a significant cause of morbidity and mortality in children with leukemia. They are at an increased risk of infectious complications secondary to intense chemotherapeutic regimens during induction resulting in prolonged and profound neutropenia. There is limited literature regarding pathogens and antibiotic resistance from smaller institutions similar to ours.

Objectives: The primary objective of this review was to describe the microbiology of BSIs, and second to evaluate our rates of BSIs during induction chemotherapy as compared to larger institutions.

Design/Method: Retrospective chart review of 82 eligible patients between the age of 1 and 21 years with newly diagnosed leukemia between May 1, 2010 and May 31, 2020. Patients who did not complete the entirety of induction chemotherapy at our hospital were excluded. A microbiologically documented infection was defined as a causative pathogen isolated from the blood in the setting of fever and/or neutropenia. Neutropenia was defined as an absolute neutrophil count (ANC) of less than $0.5x10^9$ cells/L.

Results: Of the 82 patients, 12 (14.6%) patients had a BSI during induction chemotherapy. The most common organisms identified were Gram-positive cocci (75%), Gram-negative bacilli (16.6%), and Gram-negative cocci (8.3%). Methicillin-susceptible *Staphylococcus aureus* (MSSA) was the most frequently isolated organism (42%) overall. No methicillin-resistant *Staphylococcus aureus* (MRSA) was identified. Of the Gram-negative bacteria isolated, *Escherichia coli* (8%) and *Pseudomonas aeruginosa* (8%) were identified. No extended spectrum beta-

lactamase (ESBL) or multi-drug resistant organisms were identified. No fungi were isolated.

Conclusion: The incidence of BSIs in children during induction chemotherapy at our institution is similar to what is reported from larger, academic centers. Gram-positive cocci comprise 75% of BSIs with no MRSA isolates in 10 years. Our antibiogram shows no resistant Gram-negative bacteria. This is in contrast to what is reported to larger pediatric cancer centers. Therefore, current empiric monotherapy with a fourth generation cephalosporin at the onset of febrile neutropenia remains adequate for our pediatric oncology patients.

Poster # 169

REDUCING EMPIRIC ANTIBIOTIC ADMINISTRATION IN PEDIATRIC ONCOLOGY PATIENTS WITH NON-NEUTROPENIC FEVER

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Background: Bacteremia is a serious complication in pediatric oncology, often heralded by fever. Patients have multiple risk factors for bacteremia, including the presence of an indwelling central venous catheter (CVC). While prior studies demonstrated low rates of bacteremia in pediatric oncology patients with CVCs presenting with fever without severe neutropenia (ANC >500/mcL), there is no standard practice for managing these patients, leading to variability within and across institutions. A retrospective review of patients undergoing cancer treatment with a CVC who presented to the outpatient clinic with non-neutropenic fever within the Department of Pediatrics at Memorial Sloan Kettering Cancer Center (MSKCC) revealed that 97% received at least one dose of parenteral antibiotics despite low rates of bacteremia (2.3%). Given these results, a prospective quality improvement intervention was initiated.

Objectives: Decrease empiric antibiotic administration in a population of pediatric oncology patients with a CVC presenting with fever (temperature ≥38ºC) without severe neutropenia determined to be at low risk for bacteremia.

Design/Method: An algorithm for assessing patients at low risk of bacteremia was developed through consultation with local experts. All patients ≤35 years undergoing treatment for malignancy presenting to the Pediatric Ambulatory Care Center at MSKCC with a CVC and non-neutropenic fever were assessed for eligibility. In patients who met low-risk criteria, blood cultures were sent, and we recommended discharge home without administration of empiric antibiotics. Patients were followed for 72 hours from initial visit (considered one episode), and all subsequent events within this time period were noted. Visits were reviewed weekly and positive blood cultures tracked daily.

Results: Between 4/12 – 12/19/2021, 167 episodes met criteria for inclusion. Of these, only 9.6% (n=16) received antibiotics at initial visit. Analysis of outcomes in patients not receiving antibiotics (n=151) revealed a 3.3% rate of bacteremia within the episode, while an additional 2.6% were

admitted for infectious concerns without a positive blood culture. There were no infection-related deaths or ICU admissions in any patient in whom antibiotics was withheld during this period. As a balancing measure, we assessed time to antibiotic administration in patients with non-neutropenic fever, which remained under our 1-hour goal (median: 49 minutes).

Conclusion: We have shown that it is safe to withhold antibiotics in a select population of oncology patients with a CVC who present with non-neutropenic fever. Given evolving data about antibiotic risks – including antimicrobial resistance, microbiome dysbiosis, and medication costs – there is great appeal in such efforts to limit unnecessary antibiotic usage.

Poster # 170

DOES FEVER RESPONSE TO ACETOMINOPHEN PREDICT BLOOD STREAM INFECTIONS IN FEBRILE NEUTROPENIA?

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Background: Bloodstream infections (BSIs) in febrile neutropenia (FN) are associated with significant morbidity and healthcare costs but the majority of patients with FN do not have documented BSI and may not require inpatient admission. There is a need to identify clinical parameters for risk stratification and prediction of BSIs in these patients. Acetaminophen is a widely available treatment of fever in patients with FN. Despite acetaminophen's widespread utilization, little research exists on whether fever response to acetaminophen can be used as a predictor of BSIs in FN.

Objectives: To investigate the relationship between fever response to acetaminophen and culture confirmed bacteremia in patients presenting with FN.

Design/Method: A retrospective review of patients (ages 1-21 years) presenting with FN and bacteremia at Rady Children's Hospital (2016-2018) was performed. Demographic information, degree of neutropenia (ANC < 500 or >500 cells/µL), blood culture data, amount/timing of acetaminophen doses and patient temperatures 1-, 2- and 6-hours after acetaminophen were examined. Patients were stratified into one of three malignancy categories: leukemia/lymphoma, solid tumor, hematopoietic stem cell transplant (HSCT). Each patient was matched with a matched control (sex, age, category of malignancy and degree of neutropenia) who presented with FN and had documentation of negative blood cultures. Fourteen patients (52%) served as their own control using data from a separate admission for FN. Patients were excluded if they developed FN after admission.

Results: Twenty-seven patients with FN and bacteremia met inclusion criteria. Median age at presentation was 12.4 years (IQR 4.6-16.7), compared to 11.5 years (IQR 4.2-16.8) for the controls. Sixteen were female (59%). Sixteen patients were categorized as leukemia/lymphoma (59%), 7 as solid tumor (26%) and 4 as HSCT (15%). Twenty-five patients (93%) had a presenting ANC < 500 cells/µL. Temperature 1-hour post initial acetaminophen was found to be associated with blood culture positivity (p=0.039). Logistic regression demonstrated that temperature 1-hour

post acetaminophen had significant predictive value for blood culture positivity when controlling for acetaminophen dosing (mg/kg) and temperature prior to acetaminophen administration (p=0.022). Sensitivity and specificity were 0.39 and 0.61 respectively.

Conclusion: While temperature 1-hour post-acetaminophen differed with blood culture positivity and was a significant predictor of bacteremia when controlling for potential confounding variables, subsequent analysis demonstrated that fever response in isolation lacks sufficient predictive value to impact clinical decision making in FN. Future studies are needed to assess the utility of fever responsiveness as an adjunct to existing modalities of risk stratification in FN.

Poster # 201

MEMORY T CELL POPULATIONS IN HUMAN LEUKEMIA

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Background: Incorporating the immune system into cancer management is an area of robust research. Treatment modalities aimed at activating cytotoxic T cells against malignancies include immune checkpoint inhibitors, bispecific T-cell engagers, and chimeric antigen receptor (CAR) tumor-specific T cells. Most anti-cancer T cell research is narrowly focused, but knowledge about the nature of diverse sub-populations of T cells in cancer, particularly memory T cells, is vital prior to potential incorporation into therapies. T memory stem cells (Tscm) are of interest due to their longevity and powerful abilities of self-renewal and creating the full spectrum of memory $CD8^+$ T cells, including central memory (Tcm) and effector memory cells (Tem).

Objectives: To determine potential presence and frequency of memory T cell populations in human leukemia at diagnosis and after induction chemotherapy.

Design/Method: Children's Mercy Cancer Center Biorepository provided samples from 16 patients with premature B cell acute lymphoblastic leukemia (pre-B ALL) from peripheral blood (PB) and/or bone marrow (BM). Timepoints were diagnosis and day 29 (D29) of induction chemotherapy. Flow cytometric analysis of cytotoxic memory T cell populations was performed and analyzed using descriptive statistics and the t-test.

Results: Despite sample variability, the absolute cell counts were not significantly different. The live cell percent was lower at diagnosis than D29 (PB- 57.2% vs 79.4%, p=0.001; BM- 41.7% vs 77.0%, p<0.001). T cell frequencies were lower at D29 (PB- 14.8% vs 5.74%, p=0.014; BM- 9.5% vs 5.9%, p=0.217). $CD4^+$ and $CD8^+$ T cells were not significantly different between diagnosis and D29. Among $CD8^+$ T cells, naïve cells markedly increased from diagnosis to D29 (PB- 53.6% vs 82.2%, p<0.001; BM- 38.8% vs 80.3%, p<0.001) with a corresponding significant decrease in Tem (PB- 15.1% vs 4.2%, p=0.002; BM- 21.6% vs 4.7%, p<0.001). Tscm (reported as a % of CD8+ T cells) were detected in all samples at diagnosis (PB range- 0.49-12.2%; BM range- 0.12-4.4%). After induction, two patients had no Tscm detected. The remainder demonstrated varying numbers of Tscm (PB range- 0.038-23.4%; BM range- 0.013-17.4%). Differences between diagnosis and D29 were not significant; however, percentages of Tscm were lower in 9 of 12 patients after

chemotherapy.

Conclusion: Induction chemotherapy led to decreased differentiated $CD8^+$ T cells with recovery of mostly naïve cells by D29. Furthermore, we established the presence of Tscm in most pediatric pre-B ALL samples. The decline of Tscm in most patients requires functional analyses to determine their role in leukemia and potential for use in immunotherapy.

Poster # 202

A ROLE FOR SIGLEC 15 IN IMMUNE DSYREGULATION IN LYMPHOMAS

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Background: With use of intensive multiagent chemotherapy, 5-year event free survival for Non-Hodgkin's lymphoma (NHL) in pediatric patients is ~90%. However, among those with refractory or relapsed disease, survival is dismal at <30% and remains a clincal challenge despite the use of intensive salvage regimens. As such, identifying novel agents that increase survival in this population of patients highlights an unmet need. Siglec 15 (Sig15) a member of the sialic acid binding immunoglobulin-like lectin family of proteins, has recently been identified as a critical immune suppressor that is highly expressed in human cancers and intra-tumor myeloid cells. Importantly, inhibition of Sig15, either through genetic knockout or knockdown, had a restorative effect on local anti-tumor immune responses and abrogated tumor progression. While reported in solid malignancies, a role for Sig15 in promoting disease progression in hematologic malignancies has not yet been described.

Objectives: Characterize the expression of Sig15 n lymphomas and identify the mechanism(s) by which Sig15 upregulation mediates immune dysregulation in lymphomas.

Design/Method: We have evaluated Sig15 expression in primary human lymphoma patient samples as well as various lymphoma (human and mouse) cell lines using western blot, quantitative PCR as well immunohistochemistry (IHC) and immunofluorescence methods. We are evaluating the effect of inhibiting expression of Sig15 through genetic downregulation in human lymphoma cell lines as well as the established murine lymphoma cell line A20 on T cell function and proliferation using methods such as flow cytometry and ELISA.

Results: Analyses of public RNA-seq data sets demonstrates higher Sig15 expression in NHL cells compared to normal B cells. Western blot confirms higher Sig15 expression in lymphoma cell lines compared to peripheral blood mononuclear cells. IHC of a tumor microarray and validation samples from children shows high Sig15 expression in NHL samples with distinct staining patterns based on subtype. Specifically, Sig15 appears to be highly expressed and associated with the cell membrane in most Diffuse large B cell lymphomas and Burkitt lymphoma, with more variable expression in Anaplastic large cell lymphoma, primarily in the cytoplasm at low levels and/or in cells with morphology consistent with macrophages. Lastly, knockdown of Sig15 in A20 cells

abrogates disease progression in immune competent but not immune deficient recipients.

Conclusion: Together, our data is consistent with a role for Sig15 in immune evasion in lymphoma. Further, this implicate Sig15 as an immune checkpoint that may be inhibited therapeutically to promote an immune response to lymphoma cells.

Poster # 203

A NOVEL SIX1/EYA2 INHIBITOR IMPAIRS CALM-AF10 LEUKEMIA CELL PROLIFERATION

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Background: The *CALM-AF10* translocation is found in 5-10% of T-cell acute lymphoblastic leukemias (T-ALL) and some acute myeloid leukemias (AML) in children. *CALM-AF10* leukemias, like *KMT2A*-rearranged infant leukemias, are characterized by increased expression of *HOXA* genes. To identify novel target genes, we performed next generation sequencing on *CALM-AF10* transduced hematopoietic stem cells and murine *CALM-AF10* leukemia cells treated with the CRM1 inhibitor Leptomycin B (LMB), which impairs CALM-AF10 binding to *HOXA* genes. Eleven genes were common to both gene sets, including 7 *Hoxa* genes and the *Six1* homeobox gene. While SIX1 and its cofactor EYA2 are overexpressed in solid tumors, the role of SIX1 in leukemias is uncertain.

Objectives: To evaluate the role of a recently described inhibitor of the SIX1/EYA2 interaction in *CALM-AF10* leukemias.

Design/Method: *SIX1* gene and protein expression were assessed in *CALM-AF10* and Jurkat (T-ALL) leukemia cell lines. Cell-Titer-Glo Assays and liquid culture proliferation assays evaluated the effect of a SIX1/EYA2 interaction inhibitor (compound 8430). We assessed cooperativity between 8430 and KPT-330, a CRM1 Nuclear Export Inhibitor, using SynergyFinder2 (https://synergyfinder.fimm.fi/). This approach yields a δ-score, indicative of the degree of drug synergy.

Results: *SIX1* gene and protein expression are increased in *CALM-AF10* and Jurkat leukemias. Treatment with 8430 resulted in a 13.7%, 34.3%, and 52.2% decrease in viability at doses of 20 mM, 30 mM, and 40 mM, respectively, in *CALM-AF10* leukemia cells at 48 h post-treatment; similar reductions were seen in Jurkat leukemia cells. Every other day treatment for 6 days with 30 mM 8430 resulted in a 92.6% and 50.4% reduction in cell numbers compared to DMSO treated *CALM-AF10* and Jurkat leukemias, respectively. Combined treatment with 30 nM or 60 nM of KPT-330 was synergistic with different doses of 8430 in *CALM-AF10* cells (δ-scores 17-19) and Jurkat cells (δ-scores 6-8).

Conclusion: The *SIX1* homeobox gene is highly expressed during development, and its expression is silenced post-embryogenesis. Through an initial unbiased screen, we found that *Six1* is

upregulated in the presence of CALM-AF10. A role for Six1 in *CALM-AF10* leukemogenesis is supported by the ability of a SIX1/EYA2 inhibitor to slow the proliferation of *CALM-AF10* leukemia cells. Importantly, based on the observation that 8430 reduces proliferation of Jurkat T—ALL cells, SIX1 inhibition may also be relevant in other leukemias, such as *KMT2A*-rearranged leukemias. Finally, our demonstration that 8430 synergizes with KPT-330 suggests the possibility of a novel therapeutic approach for *CALM-AF10* and other leukemias.

Poster # 204

CLINICAL BENEFITS OF TUMOR GENOMIC PROFILING IN PEDIATRIC HEMATOLOGIC CANCERS: A CLINICAL SERIES

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Background: Hematologic or liquid tumors, such as leukemias and lymphomas, are traditionally treated with non-discriminatory chemotherapy. These treatment regimens are often limited by drug-related toxicities and/or lack of efficacy; molecular profiling of tumors can be used to identify targetable oncogenic drivers that expand therapeutic options. Unfortunately, knowledge of targetable biomarkers and/or mutations derives from studies of adult liquid tumors and does not always translate to efficacious treatment for pediatric liquid tumors. Further, there is a lack of consensus on when profiling should be done and how it should be used to guide therapies for such patients.

Objectives: We describe a single institution's experience with using molecular profiling for liquid tumors, including potential clinic benefits and shortcomings.

Design/Method: Patients diagnosed with leukemia or lymphoma between April 2011 and August 2021 that underwent tumor profiling were retrospectively reviewed. Data collected included diagnosis, age at diagnosis, gender, ethnicity/race, therapies utilized, clinical outcome, and tumor profiling results. Profiling results included biomarker analysis of microsatellite status and tumor mutation burden; results also included actionable genetic variants, approved or off-label therapies matched to identified variants, and potential clinical trials.

Results: Twelve patients met inclusion criteria with a median (range) age of 6.58 (1.04-18.93) years. Five (41.7%) patients were diagnosed with acute lymphoblastic leukemia (ALL), 6 (50.0%) with acute myeloid leukemia (AML), and 1 (8.3%) with anaplastic large cell lymphoma. A majority of patients had stable microsatellite status and low tumor molecular burden, 9 (75%) and 8 (66.7%) patients, respectively. Ten (83.3%) patients had relapsed disease prior to tumor profiling, of which 3 (30%) experienced refractory disease. Eight (66.7%) patients had targetable alterations identified on profiling, and 3 (25%) received targeted therapy based on these genetic variants. At time of study conclusion, 6 (50%) patients were alive and 6 (50%) were deceased. Of the 3 patients that received targeted therapy, 2 (66.7%) were living and 1 (33.3%) was deceased.

Conclusion: For a portion of our relapsing and/or treatment-refractory patients, genetic profiling was useful in finding a targeted therapy that resulted in stable disease or remission. While

prospective studies are encouraged to explore clinical benefits of and actionable genetic variants found in genetic profiling studies, tumor sequencing for leukemias and lymphomas expand availability of therapeutic options. Further, sequencing during initial cancer diagnosis with tests tailored to biomarkers and mutations prevalent in pediatric liquid tumors provide clinical benefits.

Poster # 205

THE ROLE OF SETD2 MUTATIONS IN PEDIATRIC B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: *SETD2* loss-of-function mutations occur in 5 to 10% of pediatric B-ALL supporting its tumor suppressor role. *SETD2* is an epigenetic modifier responsible for tri-methylation of lysine 36 on histone H3 (H3K36me3), critical for transcription regulation, DNA replication and DNA repair. Previous work in acute myelogenous leukemia (AML) indicated a role in intrinsic chemoresistance due to an impaired DNA damage response. However, using a variety of preclinical models we previously demonstrated that loss of *SETD2* in B-ALL does not lead to cell intrinsic chemoresistance. It is possible that *SETD2* loss results in a hypermutation phenotype thereby increasing subsequent mutations that drive clonal evolution.

Objectives: To determine the role of *SETD2* loss-of-function in mutation rate, transcriptional output and chromatin accessibility.

Design/Method: Isogenic B-ALL cell lines (697 and KOPN-8) were generated with *SETD2* knockout using CRISPR/Cas9. Western blot confirmed decreased H3K36me3 mark in engineered cell lines. Three subclones each (*SETD2*-KO and *SETD2*-WT KOPN) were treated with 6-TG for 9 days followed by whole exome sequencing. Treated cells were compared to their pre-treated clones to determine the amount of 6-TG-induced mutations. RNA and ATAC sequencing were performed on *SETD2*-KO and *SETD2*-WT B-ALL cell lines. Genes/peaks with absolute fold change ≥ 0.32 and p-value ≤ 0.05 were selected for pathway analysis with Enrichr and KEGG 2021 to determine pathways significantly altered.

Results: We observed no significant difference in total 6-TG induced mutations in the WT compared to the KO clones. Specifically, we did not see an increase of G to A and C to T transitions, a fingerprint for thiopurine-mediated defects in mismatch repair. Upon KO, we found 2,649 and 764 differentially regulated genes in KOPN-8 and 697, respectively. While there was minimal overlap of the differential genes, p53 and Rap1 signaling pathways were shared. For chromatin accessibility, we found 6,204 and 7,145 differential ATAC peaks upon KO in KOPN-8 and 697, respectively. ATAC peaks were preferentially increased within gene bodies and decreased within intergenic regions.

Conclusion: *SETD2* loss-of-function in B-ALL cell lines does not confer cell intrinsic resistance, nor increased mutagenesis, in response to DNA damage agents in contrast to AML. Our data

suggest that cell specific transcriptional reprogramming by *SETD2* loss may converge on downstream pathways known to be involved in cancer progression. *SETD2* induced chromatin changes may lead to poised open chromatin allowing for plasticity in activating gene expression in response to the evolutionary pressures of therapy.

Poster # 206

ESTABLISHING THE CALM-AF10 INTERACTOME: POTENTIAL LEUKEMOGENIC ROLES FOR EPS15,DVL2, AND CTTN

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Background: Although the prognosis for many pediatric leukemias has improved, leukemias associated with the t(10;11) *CALM-AF10* translocation remain difficult to treat. *CALM-AF10* leukemias exhibit increased expression of proleukemic *HOXA* genes, which 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. Importantly, CRM1 does not contain a recognized DNA binding domain, and it is not understood how the CALM-AF10/CRM1 complex interacts with regulatory regions of *HOXA* genes.

Objectives: Use a biotin ligase (BioID2) proximity-labeling approach to detect candidate CALM-AF10-interacting proteins that potentially mediate binding to *HOXA* genes.

Design/Method: HEK293 cells were transfected with a *BioID2-CALM-AF10* expression plasmid and grown in the presence or absence of biotin. Mass Spectrometry (MS) was performed to identify candidate interacting proteins, and potential interactions with CALM-AF10 were validated via co-immunoprecipitation in HEK293 cells transiently transfected with *CALM-AF10*. We confirmed that candidate proteins are present in murine *CALM-AF10* leukemia cells via Western blotting. To efficiently knockout (KO) candidate proteins, we generated a human U937 cell line – which harbors a (*CALM-AF10* translocation) – with stably incorporated *Cas9*. To assess whether KO of *EPS15* affects *HOXA5* expression, we performed RT-qPCR.

Results: Three independent MS experiments identified 12 biotin-labeled proteins that interact with CALM-AF10. Importantly, we identified DOT1L, a protein known to interact with AF10, and NUP214, a nuclear pore protein with a potential role in *CALM-AF10* leukemias. We chose EPS15, DVL2 and CTTN for further study, since each of these proteins is known to play a role in leukemogenesis. All three proteins co-immunoprecipitate with CALM-AF10. Western blotting showed that all three proteins are expressed in murine *CALM-AF10* leukemia cells. We knocked out EPS15 protein expression in U937 cells, and showed that *HOXA5* expression is reduced with *EPS15* KO.

Conclusion: Using a biotin ligase-dependent proximity-labeling approach, we identified candidate CALM-AF10-interacting proteins. Our identification of DOT1L validates the approach, since DOT1L is known to interact with CALM-AF10. We are further investigating three candidate proteins – EPS15, DVL2 and CTTN – all of which are expressed in murine *CALM-AF10* leukemia

cells and interact with the CALM-AF10 fusion protein. KO of *EPS15* in U937 cells results in decreased *HOXA5* expression, suggesting the importance of EPS15 in CALM-AF10 leukemogenesis. Evaluation of the roles of these proteins in leukemia cells may lead to identification of novel pathways involved in *CALM-AF10* leukemogenesis.

Poster # 207

REGULATION OF HETEROCHROMATIN LANDSCAPE IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Ikzf1 encodes a zinc finger, DNA-binding protein that functions as a tumor suppressor in acute lymphoblastic leukemia (ALL). Deletion and/or loss of Ikaros function results in the development of high-risk leukemia. In the nucleus, Ikaros forms complexes with histone deacetylase complex, NuRD, and it participates in the formation of heterochromatin. The role of Ikaros-mediated formation of heterochromatin in tumor suppression in leukemia is unknown.

Objectives: Our primary objective was to determine the role of Ikaros-mediated formation of heterochromatin during induction of tumor suppression in leukemia

Design/Method: We analyzed the dynamic regulation of global heterochromatin distribution in *Ikzf1*-null T-ALL and, on each day following *Ikzf1* re-introduction into T-ALL cells, over of 3 days. Using epigenetic sequencing techniques, we determined global genomic occupancy of Ikaros, global heterochromatin distribution, chromatin accessibility, and gene expression in mouse *Ikzf1*-null T-ALL, and at day #1, #2, and #3 following re-introduction of *Ikzf1* via retroviral transduction.

Results: Results showed that mouse *Ikzf1*-null T-ALL cells have severely impaired HDAC1 DNA occupancy and reduced H3K27me3. Re-introduction of *Ikzf1* via retroviral transduction resulted in the restoration of H3K27me3 facultative heterochromatin, along with HDAC1 DNA occupancy. Global genomic analysis of constitutive heterochromatin showed redistribution of H3K9me3 global occupancy, with reduced H3K9me3 occupancy at pericentromeric loci in *Ikzf1*-null T-ALL. Reintroduction of *Ikzf1* enhances H3K9me3 enrichment in pericentromeric loci, with enhanced H3K9me3 occupancy at the promoters of several genes that regulate cellular proliferation. Dynamic analyses demonstrate the long-lasting effects of Ikaros's DNA binding on heterochromatin distribution and chromatin accessibility.

Conclusion: In conclusion, the results suggest that Ikaros DNA occupancy is essential for tumor suppression in T-ALL, which occurs via the recruitment of histone deacetylase 1 (HDAC1), Polycomb repressive complex 2 (PRC2) and formation of facultative and constitutive heterochromatin.

Poster # 208

TARGETING MARKERS OF CHEMORESISTANT SUBCLONES IN PEDIATRIC ACUTE MYELOID LEUKEMIA

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Background: Pediatric acute myeloid leukemia (AML) continues to have high rates of treatment failure prompting investigation into mechanisms of resistance and relapse. We compared 6 AML samples from diagnosis and relapse using single cell RNA-sequencing to identify genes/pathways that are differentially expressed in subpopulations that expanded between diagnosis and relapse. Among those upregulated were the genes encoding CD36 and CD74. CD36 mediates fatty acid uptake for oxidative phosphorylation, and CD74 is the receptor for macrophage migration inhibitory factor (MIF), a cytokine which promotes intracellular ERK signaling and increased proliferation. Therefore, we investigated the anti-AML effects of MIF Antagonist IV and sulfosuccinimidyl oleate (SSO), an irreversible inhibitor of CD36-dependent fatty acid uptake, as these are both plausible mechanisms of chemoresistance.

Objectives: Our objective is to identify targetable markers of chemoresistance in pediatric AML that may contribute mechanistically to resistance or identify subpopulations which may contribute to relapse.

Design/Method: We utilized direct co-culture models with mOrange+ HS-5 stromal cells and AML cell lines to mimic the bone marrow microenvironment. After allowing for direct contact between the cells, they were treated with 50 uM SSO or 10 uM MIF Antagonist +/- 10 uM cytarabine. We measured the percent of viable cells by Annexin V labeling and FACS at 24 hours. Both MOLM-13 and MV-4-11 exhibited CD36 positivity at 53.39% and 41.87%, respectively. A greater difference in CD74 positivity was measured at 79.67% and 12.49% for MV-4-11 and MOLM-13, respectively. Three independent replicates were performed.

Results: Regarding CD36 directed treatment, there was a greater overall treatment response observed with SSO + cytarabine for MOLM-13 (mean viability 31.94%) compared to MV-4-11 (56.18%). Responses overall showed a progressive decline of viability following treatment of MOLM-13 cells with DMSO (80.76%), SSO (75.29%; p=0.168 v. control), cytarabine (45.33%; p=0.026), SSO + cytarabine (31.94%; p=0.011). Likewise for CD74 directed treatment, we observed a greater overall treatment response following MIF Antagonist + cytarabine for MV-4-11 (11.26% viable) compared to MOLM-13 (31.73%). A progressive decline in mean viability was again seen following treatment of MV-4-11 cells with DMSO (86.11%), cytarabine (66.32%; p=0.092 compared to control), MIF Antagonist (24.66%; p=0.005), MIF Antagonist + cytarabine (11.26%; p=0.004).

Conclusion: MIF inhibition and blockade of fatty acid transport lead to statistically significant cytotoxicity in combination with cytarabine, compared to DMSO controls. These results show that there may be a role for these markers of interest as targets in personalized therapy.

Poster # 209

CO-TARGETTING CDK9 AND BCL-2 TO COMBAT CYTARABINE RESISTANT ACUTE MYELOID LEUKEMIA

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Background: Resistance to AraC (cytarabine) is a major obstacle for effective treatment and limits survival rates of children with acute myeloid leukemia (AML). Therefore, there is an urgent need to develop new approaches to either overcome AraC resistance or to combat AraC-resistant AML independent of AraC. Mcl-1 and c-Myc play critical roles in survival and proliferation of AML cells and overexpression of these proteins are associated with chemotherapy resistance and poor prognosis. CDK9 positively regulates the expression of both c-Myc and Mcl-1. Thus, CDK9 inhibition by AZD4573, a novel CDK9 inhibitor, could be an important approach to downregulate c-Myc and Mcl-1. In addition, Bcl-2 is overexpressed in AML and its overexpression has been associated with chemotherapy resistance. Venetoclax (ABT-199), a Bcl-2-selective inhibitor, is FDA approved for the treatment of elderly patients with AML. Previous studies from our lab have demonstrated that downregulation of c-Myc and Mcl-1 synergistically enhances the antileukemic activity of Venetoclax against AML cells. Hence, we hypothesize that co-targeting of CDK9 by AZD4573 and Bcl-2 by Venetoclax could eradicate AraC-resistant AML cells.

Objectives: To determine the *in vitro* antileukemic activity of combined AZD4573 and Venetoclax therapy against AraC-resistant AML cells.

Design/Method: AraC-resistant MV4-11 and U937 AML cell lines were developed by exposing the cells to stepwise increasing concentrations of AraC over a period of 6 months. Annexin V/propidium iodide staining and flow cytometry analysis were used to measure apoptosis and Western blotting was performed to determine protein levels.

Results: AZD4573 downregulated c-Myc and Mcl-1 in a concentration-dependent manner and induced apoptosis in the pediatric AML cell line, THP-1, which is inherently resistant to AraC. Mcl-1 overexpression rescued AML cells from AZD4573-induced apoptosis, while c-Myc inhibition induced apoptosis in THP-1 cells, demonstrating that AZD4573 induces apoptosis via downregulation of c-Myc and Mcl-1. Despite the substantial downregulation of c-Myc and Mcl-1, AZD4573 failed to sensitize/resensitize AML cell lines with intrinsic resistance like THP-1 or acquired resistance like MV4-11 and U937 to AraC. However, the combination of AZD4573 and Venetoclax synergistically induced apoptosis in these AraC-resistant AML cell lines. In THP-1 cells, CRISPR knockdown of Mcl-1 significantly enhanced apoptosis induced by Venetoclax which was further enhanced when c-Myc was inhibited by its inhibitor, 10058-F4.

Conclusion: Our results demonstrate promising antileukemic activity of the combination of AZD4573 and Venetoclax against AraC-resistant AML cells. Future studies will determine the *in vivo* efficacy of this promising combination therapy against AraC-resistant xenograft NSGS mouse models.

Poster # 210

A NOVEL MURINE MODEL TO TEST IMMUNOTHERAPY FOR ACUTE MYELOID LEUKEMIA FROM FANCONI ANEMIA PATIENTS

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Background: Fanconi anemia (FA) is a genetic disorder characterized by predisposition to acute myeloid leukemia (AML). Unfortunately, FA-AML is a secondary AML with very poor prognosis. New therapies are needed for AML in FA patients. PD-1 is a protein identified on T-cells, and when bound to PDL-1 on tumor cells, it prevents T cell-mediated killing of the tumor cells.. Therefore inhibiting the PD-1/PDL-1 interaction can upregulate T-cells killing of cancer cells. Since we hypothesize that FA-AML can be treated with PD-1 checkpoint immunotherapy, we developed a novel FA-AML murine model to investigate new immunotherapeutic approaches.

Objectives: Develop a novel murine model to study immunotherapy approaches for Fanconi Anemia-mutated Acute Myeloid Leukemia.

Design/Method: FA-AML1 cells derived from a 2-year old boy was injected into the tail veins of NOD-SCID IL2 receptor gamma chain KO (NSG) mice at 8 weeks of age. The mice were monitored for AML engraftment by weight, HLA-DR expression and peripheral blood WBC counts. Once the FA-AML1 engraftment was confirmed, we reconstituted a human immune system in the mice with injection of peripheral blood mononuclear cells (PBMCs), confirmed by flow cytometry for CD8+ and CD4+ T cells. We treated mice with Nivolumab (PD-1 inhibitor) or PBS vehicle only control twice a week, and tumorigenic endpoints were obtained.

Results: FA-AML1 engraftment in NSG mice was confirmed 6 to 12 weeks. Successful engraftment was determined by positive HLA-DR expression by flow cytometry, markedly elevated WBC counts (average 14,000 cells/μL compared to normal Ref.Range 5.5-11 cells/μL), and increased spleen weight (27 fold increase compared to wild-type NSG mice). Overall survival was significantly increased in the Nivolumab-treated group (no PBMCs or treatment mean 166.6 +/- 22.3 days, PBMCs and PBS vehicle only control mean 187 +/- 17.5 days, PBMCs and Nivolumab treated mean 224.2 +/- 32.8 days). Organ histology showed leukemic infiltration in the spleen, liver and lungs. Spleen weight was significantly decreased in the Nivolumab-treated group (no PBMCs or treatment mean spleen weight 1.9g, PBMC and PBS vehicle only control mean 0.91g, PBMCs and Nivolumab treated mean 0.45g). No treatment-related toxicities such as skin or hair changes were observed.

Conclusion: We developed a novel humanized murine model of FA-mutated AML, which is an attractive tool for studying novel immunotherapy strategies for rare tumors such as FA-AML. Specifically in this work, PD-1 blockade effectively treats FA-AML, supporting further studies and clinical trials using PD-1 inhibitors to treat this high-risk leukemia.

Poster # 211

PHASE I/II TRIAL OF MITOXANTRONE AND CLOFARABINE IN CHILDREN WITH RELAPSED/REFRACTORY ACUTE LEUKEMIA

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Background: Despite excellent outcomes in pediatric leukemias, multiply relapsed or refractory patients have low response rates to reinduction therapy and low overall long-term survival. Clofarabine and Mitoxantrone have proven efficacy in children with leukemia.

Objectives: We sought to determine the safety and overall response rate in a Phase I/II trial of clofarabine in combination with mitoxantrone as reinduction therapy for refractory/relapsed pediatric leukemia.

Design/Method: Prospective, Phase I/II study (NCT01842672). Patients 0-30.99yr old with ALL or AML with relapse OR induction failure given 1 to 3 cycles of clofarabine (escalating doses 20, 30, 35 and 40mg/m2/day) Day 1-5, in combination with mitoxantrone 12mg/m2/day on Day 3-6. CNS prophylaxis with intrathecal cytarabine. MRD was defined by flow cytometry (≥ 0.01%).

Results: Total of 39 patients enrolled (18 Phase I, 21 Phase II). Median Age 13yrs (8months-23yrs). Demographics 23 ALL (9 = IF, 11 = Relapse 1, 3 = Relapse 2), 16 AML (8 = IF, 6 = Relapse 1, 2 = Relapse 2). During Phase I, there were 2 Grade III/IV toxicities at Dose Level 4 (1 hepatic toxicity, 1 prolonged myelosuppression). Median time to neutrophil recovery was 24 days. The Phase I MTD (RP2D) of this combination was established at 35mg/m2/dose Clofarabine. In Phase II one patient developed Grade IV prolonged myelosuppression. Thirty three of 39 (85%) leukemia patients achieved a CR after 1 cycle of therapy. Of these, 88% achieved MRD negativity. Thirty one of 33 patients achieving CR went on to receive alloSCT. One patient died prior to transplant. Seven patients died of transplant complications. One patient died of recurrent disease post-transplant. The remaining 24 patients continue to demonstrate complete remission with MRD negativity. The overall and event free survival at 1 year and 3 years for patients who responded to therapy is 85% (CI_{95} 0.84-0.97) and 77% (CI_{95} 0.64-0.98), respectively at a median follow up time of 48 months (range 4-95).

Conclusion: The combination of clofarabine and mitoxantrone reinduction therapy for relapsed or refractory acute pediatric leukemia has been demonstrated to be safe and well tolerated at a RP2D of 35mg/m^2 Clofarabine in children with poor risk acute leukemias. Our response data is encouraging with 85% CR rate with high MRD negativity in leukemic patients allowing patients to safely proceed to AlloHSCT with a 3yr EFS and OS of 77%. Long term follow up and a successor trial is planned and ongoing.

Poster # 212

PEGASPARGASE LEVELS IN INFANTS WITH ALL: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP TRIAL AALL15P1

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Background: Asparaginase is an essential component of therapy for acute lymphoblastic leukemia (ALL). Although pegaspargase pharmacokinetics and therapeutic drug monitoring by serum asparaginase activity (SAA) levels have been well described for older children and adults with ALL, there are very limited data in infants. This is of particular interest given infant BSA-based dosing varies from older children, and infant long-term outcomes remain poor.

Objectives: To describe SAA levels in infants with de novo ALL and evaluate for correlation with age/dose or treatment cycle.

Design/Method: AALL15P1 enrolled newly diagnosed infants with ALL between 2017-2020, utilizing an Interfant backbone with pegaspargase dosed at indicated units/m^2 according to course and age as follows: *Induction*: <7 days 1250; 7 days-6 months 1750; 6-12 months 2000; *Post-induction*: >6 months 1650; 6-12 months 1875; ≥12 months 2500. An optional study was available in which SAA levels were measured, with the recommendation to obtain levels on day 7 following administration.

Results: Sevety-eight patients enrolled on AALL15P1, and 34 patients submitted 60 SAA levels. Levels were measured during Induction (n=30), Interim Maintenance (n=17), and Delayed Intensification part 1 (n=13). Age at the time of pegaspargase administration varied from 1 to 17 months. There were no significant demographic differences between patients with at least one level reported and those without. All SAA levels were ≥ 0.1 IU/mL and the majority (n=55, 92%) were ≥ 0.4 IU/mL. Mean levels increased with prescribed dose (and thus age), with mean levels of 0.57 IU/mL for <6 months (n=10), 0.82 IU/mL for 6-11 months (n=31), and 1.31 IU/mL for ≥12 months (n=19) ($p<0.001$). This trend persisted when sub-analyzed by treatment cycle and age. There were no pegaspargase hypersensitivity reactions reported on AALL15P1.

Conclusion: This represents the largest reported cohort of infant ALL patients with SAA levels, inclusive of patients of various ages and doses. Importantly, all reported levels were ≥ 0.1 IU/mL, the commonly accepted minimum therapeutic level, and the vast majority were ≥ 0.4 IU/mL, believed to be the optimal therapeutic level, suggesting that, despite a reduced BSA-based pegaspargase dose when compared to older children, infants achieve adequate asparagine depletion. No SAA levels were indicative of silent inactivation and there were no patients with pegaspargase hypersensitivity reported, highlighting that the asparaginase immune response relationship may differ in infants compared to older patients. Ongoing analysis will assess for correlation of SAA levels with patient demographic factors and incidence of pegaspargase associated toxicities, and further evaluate pharmacokinetic modeling.

Poster # 213

NIVOLUMAB WITH AZACYTIDINE IN PEDIATRIC RELAPSED/REFRACTORY AML:PHASE I RESULTS FROM TACL CONSORTIUM

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Background: Approximately 40% of children treated for acute myeloid leukemia (AML) relapse, with 3-year overall-survival probability ranging from 16% to 34%. An improved understanding of the interaction between immune milieu and tumor cells has opened up avenues for innovative immunotherapies. Here we report the Phase I portion of a multi-institutional Phase I/II study conducted by Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) consortium, which is the first to test nivolumab in combination with 5-azacytidine in pediatric patients with AML.

Objectives: Primary objective of the Phase 1 portion was to establish a recommended Phase II dose (RP2D) of nivolumab in combination with 5-azacytidine in children and adolescents with relapsed/refractory AML. Correlative biology will identify biomarkers of response to nivolumab with checkpoint inhibition in immunoregulatory pathways, and explore correlation between DNA methylation and gene expression with 5-azacytidine.

Design/Method: Based on a modified 3+3 design, nivolumab was given on day 1 at dose level 1 (3 mg/kg/day), with possible de-escalation to dose level 0 (1 mg/kg/day), along with 5-azacytidine (75mg/m2) on days 1-7. After “priming”, a second dose of nivolumab was given on day 15 to enhance the effect of nivolumab on the regenerating CD4+/CD8+ T cells. Patients could receive 2 such cycles unless had progressive disease (PD). Primary endpoint of Phase I was to assess dose limiting toxicity (DLT) during Cycle 1, which could be hematologic or non-hematologic related to nivolumab.

Results: Eight patients were enrolled on the Phase I portion from December 2019 - December 2020. All 8 patients had > 2 prior treatment failures, with 4 patients experiencing no prior CR and 4 patients experiencing a CR < 12 months. Two patients had history of stem cell transplant. Two patients were not evaluable for DLT, as both only received 1 dose of nivolumab, due to PD. There were no DLTs noted in the 6 DLT-evaluable patients, and no patient discontinued therapy due to adverse events (AEs). Grade 3-4 AEs were primarily hematological. Febrile neutropenia in 3 patients was the most common AE with grade 3 or above. One patient developed grade 5 cardiac arrest not related to Nivolumab, which was due to PD. RP2D was established at dose level 1 (3 mg/kg/dose).

Conclusion: Nivolumab in combination with 5-azacytidine is safe and tolerable in heavily pre-treated pediatric patients with relapsed/refractory AML, and RP2D is same as in adult patients. Phase II portion of the study is ongoing to assess efficacy of this combination.

Poster # 214

PATHWAY ANALYSIS FOLLOWING SINGLE-CELL ATAC SEQUENCING OF INFANT ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Two-thirds of infants diagnosed with *KMT2A*-rearranged (*KMT2A-r)* acute lymphoblastic leukemia (ALL) relapse; however, the biological mechanisms underlying this relapse are unknown. Here, we used the assay for transposase-accessible chromatin with sequencing at single-cell resolution (scATAC-Seq) on samples collected at diagnosis from *KMT2A-r* infant ALL patients to identify genomic regions with greater chromatin accessibility.

Objectives: Our objective was to identify prognostically significant molecular pathways by comparing chromatin states between cases known to relapse and remain in remission.

Design/Method: We performed scATAC-Seq (10x Genomics Chromium, Multiome v1) on blood or bone marrow samples collected at diagnosis from 25 infants with KMT2A-r ALL; 19 of these cases later relapsed (the Rel group) while 6 did not (non-Rel). We identified differentially accessible genomic regions (DARs) using the Seurat package (v4.0.2) in R 4.0.3 with a log fold change cutoff of 0.25 and mapped these DARs to the nearest gene. QIAGEN Ingenuity Pathway Analysis (IPA, v1.20.04) was then used to generate a list of molecular pathways described by these differentially accessible genes ($p<0.05$), one for each group. We then compared the two lists to identify biological pathways with potential prognostic value.

Results: We sequenced an average of 1191 cells total per patient over six captures. We found 1868 DARs adjacent to 1605 genes in the Rel group relative to the non-Rel group. Conversely, 1443 DARs adjacent to 1265 genes were enriched in the non-Rel group. These genes were cross referenced to the KEGG database's "Pathways in Cancer" list (hsa05200). The top 3 differentially accessible peaks in the Rel group were adjacent to RET, WNT9A, and RUNX1. The top 3 peaks in the non-Rel group were adjacent to ADCY5, CCND3, and E2F3. Following IPA analysis, a total of 48 and 52 canonical pathways were described in the Rel and non-Rel groups, respectively. Two pathways of note in the Rel group, which also correlated well with previous single cell RNA sequencing data generated by our laboratory, included PI3K signaling in B lymphocytes and the PI3K/AKT signaling pathway.

Conclusion: Since increased activation of the PI3K/AKT pathway is specifically associated with chemoresistance in ALL, our findings suggest that this pathway could potentially be used as an indicator of potential relapse in infant ALL patients. Future studies will compare the above data to scATACseq data from paired infant *KMT2A*-r ALL samples collected at relapse to further investigate signaling pathway activation and clonal evolution in infant ALL.

Poster # 215

OUTCOMES IN A PREDOMINANTLY HISPANIC/LATINO PATIENT COHORT WITH PHILADELPHIA-LIKE B-ALL

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Background: Philadelphia (Ph)-like B-ALL presents a therapeutic challenge due to high rates of relapse. Common pathways involved include the JAK-STAT pathway and ABL class fusions. Recent clinical trials have incorporated the JAK-STAT inhibitor ruxolitinib and tyrosine kinase inhibitor dasatinib into treatment for patients with Ph-like B-ALL. In addition, the National Comprehensive Cancer Network has recommended enrolling patients on clinical trials which include ruxolitinib and dasatinib in front-line therapy for Ph-like B-ALL.

Objectives: We aim to describe the characteristics, treatment courses, and outcomes of patients at Rady Children's Hospital (RCHSD) with Ph-like B-ALL, including a subset who received targeted agents as part of their front-line regimen.

Design/Method: Case Series

Results: Since 2015, twelve patients with Ph-like B-ALL have been treated at RCHSD. Eight patients identified as Hispanic/Latino. Median age at diagnosis was 15 years. Of the Ph-like fusions identified through the LDA screen and confirmatory cytogenetic testing, IGH-CRLF2 was the most common, occurring in five patients. Two patients had IL7R mutations. For upfront therapy, patients were predominantly treated on or following COG protocols (AALL1521, AALL1131, AALL1732). Ten patients received additional targeted agents. Eight patients received ruxolitinib, and one patient received imatinib. One patient received dasatinib then switched to ponatinib upon second relapse, which was stopped after molecular testing did not identify the initial EBF1-PDGFRB fusion present at diagnosis. Overall, patients had poor outcomes, with seven patients experiencing relapse at a median of 37 months (range 19-61 months). Nine of ten patients receiving targeted agents experienced relapse, and one patient died of infectious complications during Delayed Intensification. After relapse, these patients underwent re-induction chemotherapy followed by blinatumomab, with four who underwent hematopoietic stem cell transplant (HSCT) or have plans for future HSCT and two who underwent both HSCT and CAR-T. Two patients who received targeted therapy ultimately died of complications from relapsed disease.

Conclusion: Our series of Ph-like B-ALL cases includes a predominantly Hispanic/Latino population with IGH-CRLF2 fusions, consistent with prior demographic trends for the Ph-like B-ALL population. Despite most of the patients receiving targeted agents with upfront therapy, they frequently experienced disease relapse. Further analysis of recent clinical trials incorporating therapy targeting JAK-STAT pathways and ABL class fusions will characterize the utility of these treatment options for patients with Ph-like B-ALL.

Poster # 216

AREA DEPRIVATION AND MINIMAL RESIDUAL DISEASE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: There are well-described health disparities in childhood acute lymphoblastic leukemia (ALL), particularly among socioeconomically-disadvantaged patients. Our group and others have demonstrated a relationship between low neighborhood socioeconomic status (SES) and worse overall survival (OS) in children with ALL. Area deprivation index (ADI) is a validated multidimensional tool for evaluating SES in a geographic area. However, the association of ADI with end of Induction (EOI) minimal residual disease (MRD), the strongest predictor of mortality in childhood ALL, has not been assessed.

Objectives: To determine whether ADI is associated with EOI MRD in a multi-center childhood ALL cohort.

Design/Method: ADI is derived from 17 American Community Survey indicators related to average neighborhood income, education, household characteristics, and housing. We computed ADI for children age 1-18 years diagnosed with ALL from 2006-2018 at three pediatric medical centers (Children's Healthcare of Atlanta, Texas Children's Hospital, Children's Hospital of Philadelphia) in the Leukemia Electronic Abstraction Research Network (LEARN), (N=505 with complete ADI and MRD data). ADI scores were used to classify patients into quartiles. The relationship between ADI score and positive EOI MRD was examined using logistic regression models, adjusted for sex, ethnicity, race, NCI risk group, and clinical trial enrollment status. Given limited access to cohort cytogenetic data and the impact of cytogenetics on MRD, we also performed a sub-analysis restricted to standard risk ALL (n=311), using post-induction risk stratification as a proxy for standard or high risk cytogenetics.

Results: Patients in higher ADI quartiles (lower neighborhood SES) were more likely to identify as Latinx or Black ($p \leq 0.001$), whereas the distributions of sex, NCI risk group, and clinical trial enrollment did not differ by ADI. In individual centers and the pooled cohort, there was no statistically significant association between higher ADI quartile and positive EOI MRD (2^{nd}: OR 1.18, CI 0.51-2.73; 3^{rd}: OR 0.55, CI 0.20-1.44; 4^{th}: OR 2.05, CI 0.89-4.83). The sub-analysis of standard risk ALL patients yielded similar findings. In the pooled cohort, MRD was significantly associated with male sex (OR 1.69, 95% CI 1.12-2.57) and NCI high risk status (OR 1.53, 95% CI 1.01-2.32).

Conclusion: Our findings confirm known associations between male sex, NCI high risk status, and positive EOI MRD, but did not identify an association between ADI and MRD. The impact of SES on adverse ALL outcomes may manifest at later stages of therapy. In addition to incorporating cytogenetic data, future studies should evaluate distal endpoints such as relapse and survival.

Poster # 217

KEY GENETIC CHARACTERISTICS OF PEDIATRIC AML BETWEEN BLACK/AFRICAN AMERICANS AND CAUCASIANS

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Background: Acute leukemia leads the way as the most common cancer in children. Acute Myeloid Leukemia (AML) constitutes 15-20% of all pediatric leukemia, with an average survival rate of 70%. Yet, significant differences exist in survival rate between races, specifically, Black/African American children (B) vs. White/Caucasian (C), with B having worse survival outcomes than C.

Objectives: Our aim is to identify a pattern of key genetic characteristics between these two races that could explain the different outcomes of children with AML.

Design/Method: Two large-scale cancer databases, cBioPortal and SEER*Stat, were prodded to identify molecular and statistical differences between B and C. Pediatric Acute Myeloid Leukemia (TARGET, 2018) was utilized within the cBioPortal database, and "SEER Research Data, 9 Registries, Nov 2020 Sub (1975-2018)" via SEER*Stat was utilized to access the frequency, rate, and survival.

Results: The TARGET database uncovered a statistically significant difference in survival rate, where at five years post-diagnosis, B (n=102) has a 50% chance of survival compared to C (n=644) at 70% (p-value: 2.63e-7). SEER*Stat data depicted similar rates between B and C at 0-14 years of age, but a 10% difference at ages 15-19: B at a 31.6% 5-year survival rate compared to C at 44.8%. SEER*Stat also identified that the rate of disease was about the same between B (n=297) and C (n=1501). cBioPortal analysis revealed that of the highest frequency of altered genes and most significant genes alterations between the two subgroups, the B subgroup seemed to dominate increased alteration frequencies of 24/26 genes observed. The top 3 gene alterations were from the olfactory gene family, OR4P4, OR4S2, and OR4C6, and an alteration correlated to a better survival rate than those unaltered. Furthermore, mRNA expression was considered between B and C, identifying 357 statistically significant genes with a q-value of <0.05; C had higher expression in majority of these genes. Lastly, the methylation of the two subgroups were significant in 343 genes with a p-value of <0.05, where B had the majority of genes with higher methylation.

Conclusion: The B and C subgroups contain intriguing molecular differences that may play a role in the prognosis of children with AML. It is clear that B, on average, does worse when diagnosed with pediatric AML. Focusing on the genetic characteristics of each subgroup is necessary to lessen the survival gap discrepancy and provide precise therapeutic options in the future.

Poster # 218

OPTIMIZING PRE-HYDRATION FOR HIGH DOSE METHOTREXATE IN B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: High Dose Methotrexate (HD MTX) is a critical component of high risk, B-cell acute lymphoblastic leukemia (HR ALL) treatment and typically requires 4 inpatient admissions on COG protocols. Adequate prehydration (specific gravity ≤1.010) and alkalization (pH ≥ 7) are necessary prior to treatment to prevent nephrotoxicity and delayed excretion of methotrexate. Failure to meet these criteria can delay start time and prolong hospital admissions. A retrospective chart review from July 2020 – July 2021, including 56 HD MTX cycles for 20 pediatric patients ages 2-20, with HR ALL, showed the mean start time was 7.61 hours (on day 1 and 29 – when a lumbar puncture (LP) starts the treatment day) and a mean of 7.28 hours on day 15 and 43, when patients are admitted from home (7.95 hours) or clinic (6.67 hours).

Objectives: Increase coordination between hospital departments (inpatient, post-op, nursing, outpatient) and optimization of supportive care to decrease the time to starting HD MTX and decreasing the length of hospitalization.

Design/Method: In Plan-Do-Study-Act cycle 1 (PDSA 1), the post anesthesia care unit (PACU) nursing staff and care providers were educated about the importance of expeditiously administering a normal saline bolus, a sodium bicarbonate bolus, and alkalinization fluids following the LP to facilitate starting HD MTX. Data was collected for 6 months from July 2021 – December 2021, after the education for 5 patients for 16 HD MTX cycles.
PDSA Cycle 2 (Future plans for admissions from clinic and home) – Increased education of outpatient team by coordinating starting normal saline and a sodium bicarbonate bolus in clinic and sending urinalysis before admission. For patients coming from home, educating patients about sufficient hydration with a calculated amount of fluid to drink (equivalent to a bolus) and oral sodium bicarbonate to be taken the night before. Increased education and communicaiton with inpatient pharmacy team to identifty areas for improved coordination of care.

Results: The initiation time for pre-hydration fluids to reach the patients was decreased by approximately 1.69 hours. The time to start chemotherapy decreased by 0.55 hours, on day 1 and 29 and the average discharge time decreased by 61 minutes when admitted from the PACU to the general pediatric unit.

Conclusion: Increased communication between care providers and providing education to staff yielded improvement in start times, improved hospital bed flow, and more efficient use of resources to optimize patient care during routine chemotherapy admissions for the patient and the family.

Poster # 219

PHASE II TRIAL OF OBINUTUZUMAB AND ICE CHEMOTHERAPY IN RELAPSED MATURE B-CELL NON-HODGKIN LYMPHOMA

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Background: Relapsed/refractory B-cell non-Hodgkin lymphoma (B-NHL) (diffuse large B-cell lymphoma [DLBCL] and Burkitt's lymphoma [BL]) is associated with a high degree of chemotherapy resistance leading to dismal outcomes. Obinutuzumab, a humanized, glycoengineered monoclonal CD20 antibody, exhibited enhanced ADCC and apoptosis compared to rituximab in pre-clinical testing against rituximab resistant BL and is approved for initial treatment and relapsed/refractory disease after rituximab containing therapy in follicular lymphoma and newly diagnosed patients with CLL.

Objectives: To investigate the safety and activity of obinutuzumab (O) in combination with ifosfamide, carboplatin, and etoposide (ICE) in children, adolescents and young adults with relapsed/refractory mature B-NHL.

Design/Method: Patients ages 3–31 years with relapsed or refractory CD20+ B-NHL were eligible. All patients received a window of 4 doses of obinutuzumab on days -14, -10, -6 and -2 prior to starting immunochemotherapy. Progression during the window phase allowed proceeding directly to O-ICE cycle 1. Patients received two 3-week cycles of O-ICE with 2 weekly doses of obinutuzumab each cycle. Patients received CNS directed IT therapy along with dexamethasone. Patients with a partial response (PR) or complete response (CR) after cycle one were allowed to proceed to hematopoietic stem cell transplant (HSCT). Patients without progressive disease (PD) proceeded to cycle 2. A third cycle of therapy was allowed as needed. Response assessments were as per the International Pediatric NHL Response Criteria (IPNHLRC). Study was registered as NCT02393157.

Results: Six patients with Burkitt Lymphoma, ages 7–20 years have enrolled to date. Patients included 1 CNS+, 1 in second relapse, and 1 with progression to Burkitt leukemia. Following a median of 2 cycles (range 1–3), there were 4 PRs, 1 CR, and 1 MR (ORR 83.3%). Five patients proceeded to HSCT. The mixed response patient later suffered from progressive disease and died prior to eligibility for HSCT. Three with PR died from disease complications following HSCT. One patient with PR and one with CR are alive following HSCT and remain disease free at 4 and 5 years post therapy. No O-ICE associated adverse events have been observed.

Conclusion: In this phase 2 study, the addition of obinutuzumab to standard salvage chemotherapy has been well tolerated in 6 patients, with the absence of grade 3 or higher adverse events, and 5 patients successfully proceeding to HSCT. Recruitment is ongoing.

Poster # 220

CHARACTERIZING AGE-RELATED DIFFERENCES IN PEDIATRIC HODGKIN LYMPHOMA

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Background: Current studies describing younger children with Hodgkin lymphoma are limited by geographical region, small sample sizes and variable age groups. Although published data is lacking, there appears to be a trend toward a higher male to female ratio and a higher proportion of mixed cellularity subtype when compared to older cohorts. These differences may indicate a distinct phenotype, opening the potential for additional age-dependent treatment regimens.

Objectives: To examine age-related differences in pediatric patients diagnosed with Hodgkin lymphoma, including differences in demographics, clinical presentation, and medical management.

Design/Method: This retrospective multicenter cohort study utilized the Pediatric Health Information System® (PHIS) database. The PHIS database contains clinical and resource utilization data for 49 of the largest and most advanced children's hospitals in the United States. Inpatient and emergency room encounters from January 2010 to September 2020 were reviewed and information was collected for all patients aged 0 to 39 years with a diagnosis of Hodgkin lymphoma. All data were summarized using descriptive statistics. Comparisons between age groups were achieved using Chi-square or Fisher's exact tests for qualitative variables and Kruskal-Wallis tests for quantitative variables.

Results: We identified 2,721 unique patients with a diagnosis of Hodgkin lymphoma who met inclusion criteria. Median age was 15.6 years (IQR 13.1-17.5 years), with 58.9% of patients with ages between 15-39 years. Younger age groups had a larger proportion of males ($p<0.001$) and Hispanic/Latino ethnicity ($p<0.001$). There was also a larger proportion of patients with mixed cellularity subtype in the youngest cohort (32% vs 4% in those aged 15-39 years, $p<0.001$). Treatment-related comorbidities, including mucositis, pain, bacterial infections and thrombosis, were all documented more frequently in those aged 15-39 years compared to younger age groups. Medical management, including chemotherapy and supportive care agents, also varied depending on age. There were no significant differences in number of admissions or total hospital days.

Conclusion: In this large retrospective national cohort of pediatric patients with Hodgkin lymphoma, we
found significant age-related differences in patient demographics, clinical presentation, and medical management. Given the age at presentation for younger patients, treatment-associated long-term side effects, including growth retardation and the occurrence of secondary malignancies, become even more worrisome. We propose that future studies should delineate between the pediatric age groups to determine if further treatment reduction could be advantageous within this population.

Poster # 221

INCIDENCE AND CHARACTERISTICS OF PTLD IN PEDIATRIC PATIENTS FOLLOWING INTESTINAL TRANSPLANT

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Background: Post-transplant lymphoproliferative disease (PTLD) is a complication associated with significant morbidity and mortality following transplant. PTLD has been associated with the degree of immunosuppression following transplant, Epstein-Barr virus (EBV), and age of the patient. Intestinal transplant patients have been described as among the most likely solid organ transplant recipients to develop PTLD.

Objectives: To report the incidence and describe the characteristics of PTLD in our pediatric transplant population in order to better understand risk factors associated with the development of PTLD.

Design/Method: A total of 428 intestinal transplants were done in 371 patients at our institution from 1990-2021. Among those transplanted, 82 patients developed PTLD (incidence of approximately 22%). A retrospective case-control study design was used to evaluate risk factors and outcomes in patients with PTLD following intestinal transplant. The 82 PTLD cases were matched with controls in a 1:1 ratio based on 1) age at transplant (within 2 years), 2) organs transplanted, and 3) transplant date (within 5 years). Descriptive statistics were used to summarize the data. Univariate analysis included use of Mann-Whitney tests to compare continuous variables between cases and controls and Fisher's Exact test to compare all categorical variables between cases and controls.

Results: The majority of PTLD cases were defined as extranodal (81%), polymorphic (68%), EBER positive on biopsy (87%), and could be seen on imaging prior to diagnosis via biopsy (75%). A total of 50% of PTLD cases were classified as early PTLD, meaning they occurred within one year of transplant, while the other 50% of cases occurred after 1 year post-transplant. Additionally, 28% of patients with PTLD ultimately lost their transplanted graft and had to be re-listed for transplant.

There was no significant difference in incidence of PTLD related to gender, ethnicity, indication for transplant, organs transplanted, induction immunosuppression agent, maintenance immunosuppression agent, or age at transplant. A total of 61% of patients diagnosed with PTLD received a graft from an EBV positive donor compared to 42% of the control group, a statistically significant finding (P=0.04). There was no significant difference in incidence of PTLD when comparing the average tacrolimus level in the month following transplant and the average level in the month prior to PTLD diagnosis.

Conclusion: Here we describe the characteristics of PTLD cases seen in the pediatric population who received intestinal transplants at UNMC. Our analysis was consistent with prior studies, showing increased incidence of PTLD in patients who received grafts from EBV positive donors.

Poster # 222

MONOMORPHIC POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER: A REVIEW OF TREATMENT APPROACHES IN CANADA

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Background: Monomorphic Post-Transplant Lymphoproliferative Disorder (mono-PTLD) is characterized by the pathological, monoclonal expansion of lymphoid cells, similar in appearance to lymphoma, occurring after solid organ or haematopoietic stem cell transplantation. Various treatment regimens are employed, including reduction of immunosuppression, rituximab, and chemotherapy. Treatment approach is not standardized across Canada.

Objectives: -To determine the epidemiology and disease characteristics of mono-PTLD occurring after solid organ transplant.
-To describe treatment regimens and outcomes among patients with mono-PTLD, after solid organ transplant, in Canadian Paediatric Oncology centres.

Design/Method: An, ongoing, multi-centre retrospective case review of children with mono-PTLD, diagnosed and treated at Canadian Paediatric Oncology centres. All patients included were < 19 years old, diagnosed in Canada between 2001-2021, with Diffuse Large B Cell-Lymphoma (DLBCL), Burkitt lymphoma, T/ NK cell lymphoma and Hodgkin lymphoma, occurring after solid organ transplantation. Patients with early or polymorphic PTLD were excluded. Data collected included patient characteristics, disease characteristics, treatment regimens used, overall survival and allograft outcomes.

Results: In two Canadian centres there were 47 eligible patients, diagnosed with mono-PTLD, during the study period. 57% (27/47) of patients were male. The most common solid organ transplant, preceding mono-PTLD, was cardiac, associated with 53.2% (25/47) of cases. DLBCL and Burkitt Lymphoma were the two most common subtypes of mono-PTLD; they occurred in equal proportions, each making up 46.2% of cases. In 63.8% of cases, primary disease site was the abdomen. 78.7% of cases presented with stage III or IV disease. And 59.6% of cases were EBV-Encoded Small Nuclear RNA (EBER) positive.
Most patients received rituximab (79%) and/or chemotherapy (83%) as part of their initial treatment plan. The most common regimen received was LMB-based multiagent chemotherapy (45%), followed by the chemo-immunomodulatory regimen of low dose cyclophosphamide, prednisone, and rituximab (17%), and other regimens (21%). A significant proportion of patients (32%) received second line therapy, for recurrent/relapsed disease. At a median follow-up of 48 months, overall survival of the group was 70%.

Conclusion: In this study, of paediatric patients with mono-PTLD, most had disease of a mature B cell phenotype: Burkitt Lymphoma and DLBCL occurred in equal proportions. Most patients presented with high-stage disease and received upfront treatment with both rituximab and chemotherapy. Overall survival was lower for patients with monomorphic PTLD than for immunocompetent patients with de novo non-Hodgkin lymphoma.

Poster # 223

Distinguishing Sepsis and Sepsis Associated HLH using T- cell activation profile

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Background: Sepsis-associated hemophagocytic lymphohistiocytosis (SHLH), is a fatal complication of sepsis where there is dysregulated immune hyperactivation. Although clinical similarities exist between the two syndromes, distinguishing them is critical, as urgent, aggressive immunosuppressive treatment is needed in SHLH which is detrimental in sepsis. The current diagnosis of SHLH is based on fulfilling HLH-2004 criteria which often results in diagnostic delays. We propose to evaluate immunological tests that measure pathophysiological alterations in peripheral blood T cells in pediatric patients with sepsis and SHLH.

Objectives: To study the peripheral blood T cell phenotype and activation profiles by flow cytometry in pediatric patients with SHLH compared to those with sepsis.

Design/Method: It was a pilot study that included patients with sepsis, sepsis HLH, primary HLH, and healthy controls. Blood samples were collected after written informed consent, utilizing protocols approved by the institutional review board of Christian Medical College, Vellore. Flow-cytometric immunophenotyping for T cells of cryopreserved PBMCs was done using activation markers CD 38 and HLADR.

Results: The total number included was 17 (Sepsis -6, S HLH-3, Primary HLH -3, and healthy controls -5).
The median % of activated CD 8 T cells (CD 38 +, HLADR+) was significantly higher in SHLH as compared to patients with sepsis (Median % SHLH vs Sepsis = 29.8 & 3.98 respectively; p= 0.024). However CD 4 activated T cells (CD 38 +, HLADR+) , even though the treads were similar, did not reach statistical significance (Median % SHLH vs sepsis = 6.29 & 3.07 respectively; p= 0.17). We also observed that there was a significant difference in CD 4: CD8 in both the groups (Median % SHLH vs Sepsis =0.84 & 1.98 respectively; p= 0.02). In primary HLH there was activation of both CD 4 and CD 8 T cells (28.2% and 39.5 %) where as in SHLH the activation was predominantly in CD 8 T cells (6.29% and 29.8%) however this was not significant.

Conclusion: T cell activation profile and CD4: CD8 ratios have the potential to distinguish SHLH from sepsis. Based on these findings, we hypothesize that there is overall activation of immune cells in SHLH compared to that seen in sepsis. To further explore regulatory immune mechanisms in these syndromes, we extended the study on a larger sample (SHLH 7 and sepsis 28) and did activation and exhaustion markers on T cells; activation and tolerance markers on monocytes; results of which are awaited.

Poster # 224

EMAPALUMAB EXPOSURE–SAFETY RELATIONSHIP IN PATIENTS WITH PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Background: Conventional therapy for the rare, life-threatening, immune disorder primary hemophagocytic lymphohistiocytosis (HLH) comprises immunochemotherapies, including etoposide and glucocorticoids, to suppress hyperinflammation. However, conventional therapies are associated with opportunistic infections and severe myelotoxicity. Emapalumab, a fully human, anti-interferon gamma (IFNy) monoclonal antibody, is FDA-approved for the treatment of adult and pediatric patients with primary HLH with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

Objectives: Describe a prespecified exploratory exposure-safety analysis was performed on data obtained from the pivotal phase 2/3 trial of emapalumab in patients with primary HLH.

Design/Method: Safety data from 34 patients with primary HLH participating in the pivotal multicenter, open-label, phase 2/3 study (NCT01818492) and its long-term follow-up study (NCT02069899) were included in this exposure-safety analysis. Patients were excluded if they had active infections that could be associated with elevated IFNy. Emapalumab was initially administered intravenously at 1 mg/kg every 3 days, on a background of dexamethasone 5-10 mg/kg/day with a planned treatment duration of up to 8 weeks. Dosing could be increased up to 10 mg/kg, if required, based on predefined laboratory and clinical response parameters. The incidence of adverse events (AEs) as a function of emapalumab exposure was determined using exploratory graphical and logistic regression analyses. Treatment-emergent AEs observed in the period between the start of the first emapalumab infusion through the last infusion and prior to conditioning for transplantation were recorded and included in this analysis.

Results: Mean (standard deviation) age at study enrollment was 2.24 (2.99) years. No relationship between the number of treatment-emergent AEs and exposure to emapalumab was identified. The predicted risk of severe AEs decreased as a function of the area under the emapalumab concentration-time curve, and the predicted risk of AEs related to infusion-related reactions and infections also decreased as a function of the mean concentration of emapalumab. No prognostic factors for the incidence of severe AEs or AEs related to infusion-related reactions were identified in a multivariate logistic regression analysis. Exposure to emapalumab did not appear to influence liver or renal function.

Conclusion: Exposure-safety analyses for emapalumab in patients with primary HLH indicate a favorable benefit-risk profile across the dose range used in this fragile pediatric population. Accordingly, emapalumab may offer safety advantages over conventional HLH therapies.
Supported by funding from Sobi.

Poster # 225

PEDIATRIC PATIENT DERIVED GERM CELL TUMOR XENOGRAFTS WITH HISPANIC PREDOMINANCE

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Background: Pediatric Germ Cell Tumors (GCT) are a group of diverse neoplasms which can arise both in the reproductive organs of both males and females as well as extra-gonadal site. These tumors can range from benign tumors comprised of teratoma elements to more malignant tumors with more aggressive embryonal or yolk sac components. Currently, most pediatric GCTs which require adjuvant therapy are treated with cisplatin-based regimens which can be associated with long term toxicity. Improved preclinical modeling would potentially be beneficial for novel therapeutic agents, however, patient derived xenografts (PDX) from GCTs remain difficult to reproduce.

Objectives: Our group developed patient derived xenografts of mixed germ cell tumors from pediatric patients with a Hispanic predominance. The generated xenografts were analyzed for validity to the parent tumor by histology and sequencing analysis.

Design/Method: Seven eligible patients with GCTs were consented to our institutionally approved repository which includes storage of tumor for research and PDX development and included four males who underwent radical orchiectomy, two females undergoing oophorectomy, and one male undergoing abdominal lymph node resection. Tumor samples were injected, and xenografts were generated in collaboration with the Houghton laboratory at UTHCSA. Demographic information, therapy and outcome measures for each patient were collected. Tumors were reviewed for histologic similarity, underwent DNA and RNA sequencing, and methylation profiling.

Results: Six out of seven patients were Hispanic. Five patients received chemotherapy. One patient underwent surveillance after diagnosis. One patient declined recommended chemotherapy and surveillance and was lost to follow-up post operatively. Seven tumor samples were shipped and all generated viable xenografts. Histological evaluation showed retention of the predominant embryonal histological subtype for two samples. One xenograft matched the lymph node mature teratoma homogeneity. Only one xenograft exhibited heterogeneity but did not match the corresponding original tumor's (OT) multicomponent malignant features. The three remaining xenografts retained only the nonmalignant features of the OT despite two OTs being immature teratomas and one OT being a mixed GCT with embryonal predominance.

Conclusion: All analyzed xenograft samples exhibited variable histological composition compared to OTs except for the mature teratoma. Ensuring that preclinical models reflect the original patient tumor is crucial in developing novel therapeutics. Sequencing analyses of the tumor and the patient derived xenograft is ongoing and will help to further elucidate the fidelity to the original tumor. The PDX samples generated here were from predominant Hispanic patients and will be additive to the ethnic diversity of pediatric GCT research.

Poster # 226

IMPACT OF A NOVEL PATHOGENIC PALB2 VARIANT ON DNA DAMAGE AND REPAIR IN EWING SARCOMA.

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Background: Ewing sarcoma is a fusion oncoprotein (EWS::FLI1)-driven primary bone cancer most commonly diagnosed in adolescents. EWS::FLI1 causes transcriptional dysregulation and can disrupt homologous recombination (HR)-mediated repair. Thus, at baseline, Ewing tumor cells demonstrate a degree of dysfunctional DNA damage repair. Approximately 10-13% of patients with Ewing sarcoma have germline mutations in DNA damage repair genes including HR genes, *BRCA1, BARD1, RAD51, RAD51D*, etc. It is unknown if these variants promote additional repair deficits. It is also not known if the presence of such germline variants impacts Ewing tumor response to HR-deficient targeted therapies. Recently, we discovered a patient who developed two distinct localized Ewing tumors almost a decade apart. This patient has a novel germline frameshift mutation in WD40 domain of the DNA damage repair gene *PALB2*. PALB2 functions in the early steps of HR and assists in loading of RAD51 onto single stranded DNA that is formed after DNA double-strand breaks. PALB2 mediates these steps through direct interaction with BRCA2 and RAD51 through its C terminal WD40 domain.

Objectives: As this specific *PALB2*variant has not been previously reported in any cancer, we aim to determine the impact of this mutation on the interaction between PALB2 and BRCA2/RAD51 and RAD51's ability to relocalize to DNA damage sites. Additionally, we sought to determine the impact of mutant PALB2 on Ewing cell response to DNA damaging therapies such as radiation.

Design/Method: To approach this objective, we utilized IncuCyte live cell imaging, PCR, co-immunoprecipitation assays, clonogenic survival assays, alkaline comet assays, and RAD51 foci formation assays.

Results: The presence of a type 1 EWS::FLI1 fusion in this tumor was confirmed by PCR. Using SMARTpool *PALB2*siRNA, we demonstrate that reducing PALB2 expression enhances Ewing cell sensitivity to DNA damage by PARP inhibition. We assess the impact of the PALB2 variant on its protein interactions with PALB2 binding partners, BRCA2 and RAD51, and detail the extent to which these interactions are compromised. Furthermore, since these interactions are essential for HR, we will determine the impact of this pathogenic PALB2 variant on cell survival, number of DNA breaks, as well as RAD51 foci formation.

Conclusion: Taken together, these findings will demonstrate the contribution of PALB2 to Ewing cell DNA damage response and define the functional consequences of the *PALB2*c.3469_3482del, p.(Gln1157Cysfs*28) variant on DNA damage repair.

Poster # 227

CRISPR/CAS9 MEDIATED TCR INSERTION RESULTS IN T CELL RESPONSES AGAINST EWING SARCOMA

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Background: Immunotherapy has the potential to treat metastatic cancer. The endochondral bone protein Chondromodulin-I (CHM1) facilities Ewing sarcoma (EwS) malignancy and mediates metastasis. In our previous work, HLA-A*02:01-restricted CHM1319-targeting TCR transgenic T cells specifically inhibited EwS *in vitro* and *in vivo* in mice and patients. However, conventional viral vector-mediated TCR insertion into T cells bears multiple hazards, including TCR mispairing, disruption of TCR dynamics, compromised functionality, and potential auto-reactivity or graft-versus-host disease (GvHD). Clustered regularly interspaced short palindromic repeats (CRISPR)/-associated protein-9 (CRISPR/Cas9) mediated gene editing provides the option of endogenous TCR knockout (KO), together with peptide-specific TCR insertion could avoid mispairing and show better killing capacity.

Objectives: Compare the phenotype and functionality of T cells after TCR transfer via CRISPR/Cas9 vs. retrovirus for the treatment of EwS.

Design/Method: CRISPR/Cas9 and retroviral transductions were performed the produce engineered T cells. ELISPOT was performed to detect IFN-γ release; phenotypes of the T cells were evaluated by FACS. Mice experiments were performed to compare the *in vivo* killing targeting HLA-A*02:01^{+} /CHM1^{319} A673 EwS cells.

Results: 1. CRISPR/Cas9 mediated T cell receptor insertion into the TRAC locus of CD3^{+} T cells targeting CHM1^{319} was achieved, endogenous TCRs were undetectable.
2. Non-viral transduction of CHM1^{319} specific TCR by CRISPR/Cas9 leads to specific IFN-γ release in HLA-A*02:01^{+} /CHM1^{319+} cell lines *in vitro*.
3. Compared to CRISPR/Cas9, more CD3^{+} molecules are expressed on the cell membrane via retroviral transduction.
4. The central memory phenotype (CD62L^{+}/CD45RO^{+}) population is higher after retroviral TCR insertion as compared to non-transduced T cells or CRISPR/Cas9 transduced T cells.
5. High efficiency of TCR transfection via retrovirus limits the endogenous TCR expression on the cell membrane, which may be the reason why there is no obvious GvHD in our patients.
6. There is a significant killing of EwS in mice in the retrovirus group (p=0.0125) and marginal killing (p=0.063) in the CRISPR group compared to controls. No significant difference was observed between CRISPR mediated compared to retroviral mediated TCR insertion (p=0.5354). Less CD3^{+} T cell homing to bone marrow and spleen was observed in the CRISPR group.

Conclusion: Non-viral transduction of CHM1^{319} specific TCR by CRISPR/Cas9 could avoid the mispairing of endogenous and exogenous TCR chains, and the resulting T cell product can specifically recognize the HLA-A*02:01-restricted CHM1^{319} peptide. It also shows specific rejection of HLA-A*02:01 EwS.

Poster # 228

UTILIZING TRANSCRIPTOME ANALYSIS TO IDENTIFY TARGETED THERAPY FOR EWING SARCOMA

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Background: The survival rate of patients with Ewing sarcoma (ES) has seen very little improvement over the past several decades and remains dismal for those with recurrent or metastatic disease. Current treatment for ES includes a combination of cytotoxic chemotherapeutic agents and local control with radiation and/or surgery. We hypothesize that based on RNA expression we will identify therapeutic targets in ES.

Objectives: The purpose of this study is to identify novel agents currently available with efficacy in Ewing sarcoma; and to identify synergistic combinations of available drugs for treatment of Ewing sarcoma.

Design/Method: Novel targeted approaches for the treatment of ES were identified using RNA sequencing performed on ES patient derived cell lines with bioinformatic analysis of gene expression. Targeted agents were tested on patient cell lines at escalating doses. At 48 hours cell viability was assessed with CellTiter-Glo 2.0 and analyzed with GraphPad Prism to determine the IC50. Western blot analysis was performed to evaluate the effect on proteins involved in cell cycle and apoptosis. Combination studies with standard chemotherapy were performed to evaluate for synergy using SynergyFinder 2.0.

Results: RNA analysis identified HDAC2, ALK, CDK4, and JAK1 as potential therapeutic targets. The pan-HDAC inhibitor, Panobinostat, was cytotoxic to all Ewing sarcoma cell lines tested with clinically relevant IC50s (<200nM), repressed expression of Cyclin D1, and induced Caspase 3 cleavage. ALK inhibition, by Ceritinib, and CDK4 inhibition, by Palbociclib, were cytotoxic at doses slightly higher than that of clinical relevance. HDAC and ALK expression levels correlated to cell sensitivity. JAK1 inhibition does not appear to have efficacy at clinically relevant dosing. Panobinostat synergizes with standard chemotherapy at clinically relevant doses.

Conclusion: This work highlights that RNA expression may identify potential targets which could be effective in treating Ewing sarcoma or potentially improve the efficacy of standard of care drugs. HDAC, ALK, or CDK4 inhibition show a decrease in cell viability in ES cell line models as single agents and may potentiate the effects of chemotherapeutics currently used in patients with ES. Future studies of these agents in combination with chemotherapy will aim to determine efficacy in xenograft models.

Poster # 229

SERIAL PASSAGE IN SARCOSPHERE CULTURE INCREASES CHEMORESISTANCE IN HUMAN OSTEOSARCOMA CELLS

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Background: Tumor chemoresistance limits treatment efficacy for a substantial proportion of patients with osteosarcoma (OS). Chemoresistance may be an intrinsic property of cancer stem cells associated with phenotypes, potentially regulated by epigenetic mechanisms, that enhance cell survival in the stem cell niche. To identify therapeutically-relevant mechanisms of chemoresistance we sought to determine whether culture in conditions that favor survival/proliferation of OS stem cells alters sensitivity to cisplatin.

Objectives: We first sought to establish a system for serial sarcosphere culture (SC) for OS cells. We next wished to determine the efficiency of sarcosphere formation in SC for OS cells at each of 3 serial passages in SC culture. Finally we wished to determine chemosensitivity to cisplatin for OS cells prior to SC following each of 3 serial passages in SC.

Design/Method: Sarcosphere Culture
MNNG-HOS human OS cells were seeded into ultra-low attachment culture dishes in serum-free DMEM/F12 medium with 1% methylcellulose supplemented with 20mM progesterone, 100 uM putrescine, and 1% insulin-transferrin-selenium A. Basic fibroblast growth factor and epidermal growth factor, each at 10 ng/ml, were added twice weekly. After 7 days in SC, cells were harvested, disaggregated with trypsin, washed, and re-seed in complete medium in standard tissue culture dishes for expansion prior to the subsequent passage in SC.

Sarcosphere-forming efficiency assay
Cells were seeded ($6x10^4$ cells/well) in CS and sarcospheres were counted visually on culture day 3. All wells were seeded in triplicate for each experiment.

Chemosensitivity assays
Cells were seeded into quadruplicate wells of 96 well plates (5000 cell/well) in complete medium. Cisplatin was added after 24 hours and cell survival was assayed using the CellTiter 96 assay (Promega) after 24, 48, and 72 hours of drug exposure.

Results: Sarcosphere-forming efficiency:
A nearly four-fold increase in sarcosphere-forming efficiency was observed from the initial seeding of OS cells in SC to the 3rd serial passage in SC.

Cisplatin chemosensitivity
A > 50% reduction in cytotoxicity was observed in OS cells following 48 hours across a broad range of cisplatin concentrations following 3 passages in SC compared to cells maintained in standard cell culture.

Conclusion: The increase in sarcosphere-forming efficiency suggests that serial culture in SC may enrich for OS cells with sarcoma stem cell phenotypes. The decrease in cisplatin chemosensitivity observed following serial SC culture suggests that chemoresistance may be a property of this stem cell phenotype. It will be necessary to test other cancer stem cell phenotypes in this system to substantiate these results.

Poster # 230

AEROSOLIZED GEMCITABINE MODULATES OSTEOSARCOMA TUMOR MICROENVIRONMENT AND INCREASES NK CELL EFFICACY

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Background: Lung metastases constitutes the main cause of death in patients with Osteosarcoma (OS). Patients with metastatic disease at diagnosis have a survival rate of less than 20%. Novel therapies are needed to improve survival rates. We demonstrated aerosol gemcitabine (GCB) to have therapeutic effect against OS. Previous studies support the use of GCB as a conditioning strategy together with immunotherapy. GCB has been shown to modulate the tumor microenvironment (TME) by increasing NK group 2 member D (NKG2D) ligand on tumor cells, decreasing myeloid-derived suppressor cells and stabilizing T-regulatory cells. We showed that aerosol delivery of GCB altered the TME and induced expression of surface proteins on OS nodules such as Fas, leading to T-cell mediated tumor killing.

Objectives: To determine if low-dose aerosol GCB can be used to alter the immunosuppressive TME in OS, thereby augmenting NK-mediated tumor cell killing and therapy efficacy.

Design/Method: We investigated baseline expression of NKG2DL in OS tumors (bone and lung metastases) from untreated patients by immunohistochemistry (IHC). We used flow cytometry to determine the effect of GCB on NKG2DL expression in various OS cell lines and the IncuCyte cytotoxicity assay to determine the cytolytic activity of NK cells when exposed to GCB treated OS-17 cells. We determined the *in vivo* effect of low-dose GCB in combination with NK cells using our human OS-17 OS mouse model. NSG mice were injected with $3*10^6$ GFP-luciferase OS17 cells IV and tumor growth was tracked by bioluminescent imaging. Mice were divided into four treatment groups: untreated, NK cells alone, GCB alone, and combination NK cell and GCB therapy. One mouse from each group was analyzed using the Xerra Imaging System to visualize NK cell localization relative to GFP tumor signal.

Results: We demonstrated various expression of NKG2DL in patients' primary bone tumor and lung metastases and a significant increase in NKG2DL expression in 3 of 4 OS cell lines. Pre-treatment of OS-17 cells with GCB increased susceptibility to NK killing. Low dose aerosolized GCB combined with NK cell therapy significantly decreased tumor burden in the lung. Localization and persistence of NK cells correlated with tumor burden in Xerra imaging.

Conclusion: Low-dose gemcitabine enhanced NK cell therapeutic efficacy against OS by increasing NKG2DL expression in tumor cells and potentially decreasing the immunosuppressive TME to make it more permissive to NK cell killing.

Poster # 231

METABOLOMICS OF URINARY METABOLITES IN CHILDHOOD RHABDOMYOSARCOMA TO DISCOVER NOVEL BIOMARKERS

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Background: Metabolomics has made it possible to analyze metabolic changes comprehensively and has been used to discover new biomarkers and elucidate pathogenesis in various cancer types. Childhood rhabdomyosarcoma is rare and refractory; therefore, novel biomarker discovery and therapeutic strategy development are expected through metabolomics analysis.
Metabolomics has made it possible to analyze metabolic changes comprehensively and has been used to discover new biomarkers and elucidate pathogenesis in various cancer types. Childhood rhabdomyosarcoma is rare and refractory; therefore, novel biomarker discovery and therapeutic strategy development are expected through metabolomics analysis.

Objectives: This study aimed to identify biomarkers for childhood rhabdomyosarcoma by comprehensively analyzing urinary metabolites from pediatric patients with or without rhabdomyosarcoma.

Design/Method: This study was conducted at Nagoya University Hospital, Nagoya, Aichi, Japan. Urine samples were collected from 8 pediatric patients with rhabdomyosarcoma. Urine metabolites were extracted using capillary electrophoresis mass spectrometry (CE/MS). Biomarker candidates were identified using the Wilcoxon rank-sum test, random forest method, and orthogonal partial least squares discriminant analysis between patients with and those without rhabdomyosarcoma. The pathway analysis was performed in these biomarker candidates.

Results: Approximately 500 metabolites, such as amino acids, nucleic acids, and lipids, were detected in those urine samples. In about 50 quantified metabolites, we identified some biomarker candidates which increased or decreased in patients with rhabdomyosarcoma compared to those without rhabdomyosarcoma.

Conclusion: Through metabolomics of urine metabolites in pediatric patients with and without rhabdomyosarcoma, we identified some urine tumor marker candidates for childhood rhabdomyosarcoma. In the future, in addition to urine samples, we plan to conduct a comprehensive analysis of the metabolites in blood and sarcoma tissue samples. We will detect the metabolic pathways specific to childhood rhabdomyosarcoma to investigate whether they can be disease-specific biomarkers or therapeutic targets.

Poster # 232

IDENTIFYING CELL SURFACE COMBINATIONS FOR TARGETING MALIGNANT PERIPHERAL NERVE SHEATH TUMOR CELLS

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Background: Malignant peripheral nerve sheath tumor (MPNST) is an aggressive, treatment resistant, soft tissue sarcoma, with generally poor outcomes. Given recent successes of CAR-T therapy on various solid tumors, there is increased interest in identifying unique surface markers. While no stand-alone surface marker of MPNST has been identified, there is increasing interest in identifying surface gene combinations that may serve as unique biomarkers or targets for this tumor.

Objectives: We aim to identify cell surface targets present on a majority of MPNST cells and as few as possible non-MPNST cells at a single cell resolution.

Design/Method: Four specimens from two MPNST patients were resected from lung metastasis and adjacent normal lung tissue. Single-cell RNA sequencing was performed, and a total of 2695 cell surface protein-encoding genes were evaluated. First, a combinatorial optimization method, Mad Hitter, (https://www.biorxiv.org/content/10.1101/2020.01.28.923532v4.full), was utilized to identify combinations of cell surface targets in two scenarios: 1) *basic scenario* requires their presence in >80% of MPNST cells and <10% of non-MPNST cells and 2) *stringent scenario*, identifying combinations that were present on >90% of MPNST cells and <5% of non-MPNST cells. Second, top individual surface targets were identified using a novel computational approach (https://www.biorxiv.org/content/10.1101/2021.09.29.462485v1.full) and evaluated with area under the curve (AUC). Third, target expression was compared to normal tissue in the genotype tissue expression (GTEx) database.

Results: Comparing lung metastasis MPNST cells to normal lung tissue cells from the same patient, we find that the best combinations in the basic scenario were *DLK1* and *SLC2A1* (patient one) and *MPZ* and *SLC3A2* (patient two). Of those found in the basic scenario for each patient, *DLK1* (AUC 0.99) and *MPZ* (AUC 0.93) alone had strong individual discrimination, respectively. In the stringent scenario, the optimal combination was 5 targets (patient one) and 12 targets (patient two). Of the four genes that appeared in both patients, *SLC2A1, SLC6A8, FGFR1, GPC3*, all were >97th percentile in expression compared to all other surface genes. Normal tissue with closest surface target expression was pituitary and nerve (>90th percentile).

Conclusion: Targeting lung metastasis would require combinations of 2 targets in the basic scenario, but 5 and 12 targets in the stringent scenario, the latter of which may be currently impractical. For each patient, different single targets showed strong discrimination, highlighting the need for personalized therapies. Expression of combined target surface genes identified is higher than all normal tissues, but off target effects should be carefully evaluated for any therapeutic approaches.

Poster # 233

SURVIVAL ANALYSIS OF YBX1-MEDIATED GENES IN NEUROBLASTOMA

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Background: Neuroblastomas (NB) arise from pluripotent sympathetic cells and present in the adrenal medulla, spine, or other regions along the neuraxis. While NBs are the most common solid tumor cancer in infancy, they still are relatively rare. The transcription factor Y-box-binding protein 1 (YBX1) has been shown to have a pro-oncogenic role in some cancers, and with advances in sequencing its binding targets have been better characterized and have expression data in a wider range of cancers.

Objectives: This *in silico* study analyzed YBX1 expression and its associated regulatory targets to identify whether YBX1 is implicated in survival outcomes and aberrant biological pathways in NB cases.

Design/Method: Genes which contained one or more binding sites for YBX1 in their promoter region based on ChIP-seq data were obtained from the MSig database. Kaplan-Meier plots of overall survival in NB cases in relation to YBX1 and YBX1-regulated gene expression levels were generated using 7 NB datasets on the R2 genomic platform (GSE45547, GSE3960, GSE49710, GSE62564, GSE85074, GSE16476, and from PMID:17075126). Genes identified to be statistically significant ($p<0.05$ post FDR correction) in terms of survival outcome were selected for enrichment analysis through Cytoscape to determine which biological pathways might mediate survival outcome ($p<0.01$ for significance). Additionally, network analysis was conducted based on physical and predicted interactions to generate a list of other genes which might act in concert with YBX1-mediated genes to affect survival.

Results: Significant survival differences in the NB cases were observed based on YBX1 and 55 of its regulatory targets ($p<0.05$). Enrichment analysis showed eleven pathways through which YBX1 and its targets can affect survival in NBs such as DNA geometric changes and anion transport ($p<0.01$). Network analysis highlighted genes with a wide array of functions, such as those involved in the autophagy pathway (*ATG7*) and those in platelet activation (*PAFAH1B2/3*) among others.

Conclusion: YBX1 and it's regulatory targets mediate pro-oncogenic processes in NB cases through numerous pathways, with many genes having a significant relation to survival outcome. Additionally, further analysis on those significant YBX1-regulated genes reveal other mechanisms through which survivability is impacted, such as possible increased platelet activation leading to the hypercoagulable state observed in some NB cases. The possible impact the transcription factor YBX1 and its targets have in NB survivability warrant further wet-lab research, especially in regards to therapeutic approaches.

Poster # 234

THE CELLULAR EFFECTS OF PHYSIOLOGIC DOSING OF DFMO IN NEUROBLASTOMA TUMORIGENESIS

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Background: The majority of high-risk neuroblastoma (NB) patients who experience relapse succumb to disease despite intensive treatment regimens. Difluoromethylornithine (DFMO) is an irreversible inhibitor of ornithine decarboxylase-1 (ODC1), the rate-limiting enzyme in the production of polyamines. ODC-1, polyamines and LIN28 protein are elevated in many cancers including NB. DFMO when used as maintenance therapy in high-risk NB prevents relapse and increases event-free and overall survival.

Objectives: This study aims to determine the effect of DFMO on cell cycle, viability, neurosphere formation, LIN28 expression and senescence at physiologic doses.

Design/Method: We performed this study using five established NB cell lines (CHLA90, SHSY5Y, SMS-KCNR, BE2C and NGP). To investigate the effect of DFMO on cell cycle and viability, 5×10^6 cells were seeded in 6-well plates and treated for 48 and 72 hours. Cells were stained with a custom panel combining cell cycle, apoptosis and viability markers. Flow cytometry was conducted on BD Fortessa cytometer and FACS data analyzed by FlowJo. To investigate effect on neurosphere formation, two cells per well were seeded in 96-well plates for four weeks. The frequency and the size of neurospheres were monitored and imaged weekly using Incucyte® ZOOM. Western blot was used to measure protein expression. Additionally, an *in-situ* senescence assay was performed using a beta-galactosidase staining kit. Escalating DFMO doses of 0, 0.1, 0.5 and 2.5mM were used for all assays which were performed in triplicate and replicated at least twice. Statistical analysis was done using GraphPad Prism and the level of significance set at p=0.05.

Results: Data from our study show DFMO treatment is not cytotoxic but is cytostatic at physiologically relevant doses (0.1-0.5mM). There was no dose dependent loss of cell viability or induced apoptosis up to 2.5mM. Cell lines underwent an S/G2 cell cycle arrest at doses ranging from 0.1mM to 2.5mM, with CHLA90, SMS-KCNR, and BE2C showing greater sensitivity than NGP and SHSY5Y. There was a dose dependent decrease in the frequency and size of neurospheres as well as in LIN28 expression in all cell lines at the tested doses. Significant changes were observed in four of the cell lines (CHLA90, SHSY5Y, BE2C, and NGP) at 0.5mM and 2.5mM. We further observed a dose dependent increase in senescence using the beta-galactosidase assay.

Conclusion: While previous studies show cytotoxicity with IC50's >5-15mM, are not achievable in patients. This study suggests that DFMO, at physiologically relevant dosing, inhibits neuroblastoma by targeting cellular process integral to tumorigenesis.

Poster # 235

RECEPTOR TYROSINE KINASE-LIKE ORPHAN RECEPTOR-2: A NOVEL CELLULAR THERAPY TARGET FOR NEUROBLASTOMA

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Background: Neuroblastoma (NBL) is the most common extra-cranial solid tumor in childhood. High-risk NBL has poor survival despite the addition of tandem-autologous stem cell rescue; therefore, novel treatments are needed. Receptor Tyrosine Kinase-like Orphan Receptor 2 (ROR2) is highly expressed in NBL and is part of the Wnt signaling pathway which enhances cell growth and promotes epithelial-mesenchymal transition and metastasis.

Objectives: We aimed to design *in silico* and assess *in vitro* efficacy of a ROR2 chimeric antigen receptor (CAR) targeted cellular immunotherapy for NBL.

Design/Method: CAR constructs were designed *in silico* by fusing specific single-chain domains with transmembrane and intracellular costimulatory domains. The ROR2 constructs were cloned into third generation lentiviral vectors using the HEK293 cell line. ROR2 CAR transgenes were transduced into primary human T-cell and NK-92 cells. CAR expression in both T-cells and NK-92 cells was detected via flow cytometry using biotinylated ROR2 protein. Cytotoxicity of the ROR2 CAR effector cells towards target cell lines SY5Y (NBL, $ROR2^{(+)}$) and JeKo-1 (mantle cell lymphoma, $ROR2^{(-)}$) was evaluated via luciferin-based assays. A titration curve of effector to target ratios (E:T) was used to elucidate an IC50 or the E:T ratio resulting in 50% cytotoxicity of the target cells.

Results: Three separate ROR2 constructs (ROR2a, ROR2b, and ROR2c) were designed and optimized *in silico*. Each construct had a unique single chain domain but all three were designed with the same CD8α transmembrane domain, and 4-1BB and CD3ζ co-stimulatory domains. The ROR2 CAR T-cells were expanded for 12 days and ROR2 CAR expression was 61.7%, 59.2% and 59.2% for ROR2a, ROR2b and ROR2c, respectively. The IC50 against SY5Y cells after a 24-hour assay was 0.27, 0.19, and 0.37 for ROR2a, ROR2b and ROR2c CAR-T cells, respectively. The ROR2 CAR NK-92 cells were expanded for 14 days, and then sorted using flow cytometry to achieve a more homogenous population for each ROR2 construct. The IC50 against SY5Y cells after a 4-hour assay was 18.3, 0.67, and 1.07 for ROR2a, ROR2b, and ROR2c CAR NK-92 cells, respectively. None of the ROR2 CAR T-cells or CAR NK-92 cells displayed statistically significant cytotoxicity towards JeKo-1 (p-value <0.0001).

Conclusion: Our three ROR2 CAR constructs were successfully transduced into both primary T-cells and NK-92 cells and displayed specific cytotoxicity towards ROR2 positive cell lines. Further testing, including *in vivo* testing, is planned to further optimize the ROR2 constructs for both CAR-T cell and CAR-NK cell therapy for NBL.

Poster # 236

ESTABLISHMENT OF A PROGNOSTIC IMMUNE SIGNATURE IN NEUROBLASTOMA

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Background: Neuroblastoma (NBL) is the second most common solid tumor of childhood and is unique among pediatric malignancies as it exhibits great clinical heterogeneity. High risk patients continue to have a poor prognosis despite multimodal therapy including antibody therapy. It is now well established that the immune system plays a vital role in regulating tumor proliferation and metastasis as well as response to immunotherapy. Therefore, we sought to characterize the immune landscape of NBL.

Objectives: To characterize and determine the prognostic value of the tumor microenvironment immune phenotype in NBL.

Design/Method: We used immune cell fraction estimation analysis to profile the tumor immune microenvironment of NBL samples using RNA-seq data in the TARGET database (N=141). We sought to further characterize the immune profiles of NBL via in silico analysis using previously identified immune signatures, namely the Immunologic Constant of Rejection (ICR), which captures active Th1/cytotoxic response associated with favorable prognosis, and TCGA immune subtypes.

Results: We found repressed immune cell estimates in MYCN amplified NBL consistent with previous reports. In contrast to previous reports, we found increased M1 macrophages and decreased tumor-associated (TAM) and M2 macrophages in MYCN non-amplified high risk (NA HR) NBL compared to the non-high risk cohort. There was, however, no correlation between overall fractions and overall survival in the entire cohort. While a high ICR score showed no prognostic significance in the entire cohort, a high ICR score was associated with improved overall survival (OS) in HR (HR 0.6, p=0.039) as well as NA HR (HR 0.47, p=0.01), metastatic (HR 0.58, p=0.026), and non-infant NBL (HR 0.61, p=0.04). We clustered NBL samples into six immune subtypes (C1-C6) akin to what has been previously described in adult tumors from The Cancer Gene Atlas (TCGA) database. Inflammatory (C3) subtype was associated with best OS (median OS not reached) in NBL. Contrary to what has been described in the adult literature, worst OS was seen in the wound healing (C1) subtype (median OS 40 mos, HR 2.93, p=0.005) and is associated with increased expression of angiogenic genes. The prognostic significance of the C1 subtype held true for all NBL subgroups.

Conclusion: We demonstrate that NBL can be classified by ICR and immune subtype. We further provided evidence of the prognostic significance of ICR and immune subtype. Future goals are to validate our findings in larger NBL cohorts and to seek to refine NBL risk stratification by incorporating immune biomarkers.

Poster # 237

TARGETING MTOR AND MEK OR ERK INHIBITS THE GROWTH OF PDX MODELS OF NF1-DEFICIENT PEDIATRIC SARCOMA

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Background: The neurofibromin gene 1 (NF1) is a tumor suppressor and negative regulator of RAS. Germline alterations that result in NF1 inactivation predispose to sarcomas such as malignant pleural nerve sheath tumors, embryonal rhabdomyosaroma, and gastrointestinal stromal tumors. Dysregulation of NF1 leads to enhanced signaling from RAS effector pathways including MEK-ERK, PI3K-AKT and mTOR. We explored targeting MEK or ERK in combination with mTOR as potential therapy for pediatric sarcomas with NF1 loss.

Objectives: To investigate the effectiveness of targeting mTOR and MEK or ERK at blocking growth of PDX models of NF1-deficient pediatric sarcoma

Design/Method: We developed patient-derived xenograft (PDX) and cell line models with NF1 mutation from tumor samples obtained from a child with a known germline *NF1* alteration diagnosed with a high grade malignant peripheral nerve sheath tumor with rhabdomyosarcomatous differentiation (a.k.a. malignant Triton tumor). Tumor samples were profiled by the MSK-IMPACT platform, which revealed somatic inactivation of the other *NF1* allele by a nonsense mutation (*NF1* R816*). We examined the efficacy of inhibitors of MEK (trametinib), ERK (ulixertinib) or mTOR (rapamycin) alone or in combination on growth *in vitro* and *in vivo*. Protein phosphorylation was examined by western blotting. Activated receptor tyrosine kinases (RTK) were profiled using phospho-proteomic arrays.

Results: Two PDX models (IO-PPBpdx1 and IO-PPBpdx2) and two matched cell lines (IO-PPBcl1 and IO-PPBcl2) were generated from the patient samples. Phospho-proteomic profiling of IO-PPBcl1 detected very low activation of RTKs. Higher MEK1/2, ERK1/2, S6 and 4EBP1 phosphorylation was detected in IO-PPBcl1 cells compared to non-tumor cells. Growth of IO-PPBcl1 was more sensitive to rapamycin (IC_{50}=0.001 μM) than trametinib (IC_{50}=600 nM) when grown in 10% fetal bovine serum (FBS) but equally sensitive at lower FBS concentration (2%). ERK1/2 and S6 phosphorylation was more sensitive to a combination of rapamycin and trametinib, than either agent alone. Treatment of mice bearing IO-PPBpdx1 tumors with rapamycin (4 mg/kg QD, $p<0.0001$), trametinib (1 mg/kg QD, $p<0.0001$) or ulixertinib (50 mg/kg BID, $p=0.003$) monotherapy resulted in significant reductions in tumor growth. However combinations of trametinib or ulixertinib with rapamycin was more effective at blocking tumor growth. The two therapeutic combinations were similarly effective.

Conclusion: In patient-derived models of NF1-mutated sarcoma, we observed activation of the MAPK and MTOR pathways. Combined inhibition of MEK or ERK and MTOR were effective at inhibiting tumor growth. These results confirm the possibility of targeting different elements of the MAPK and MTOR pathways to increase the response for NF1-mutated sarcomas.

Poster # 238

MERTK INHIBITIOR, MRX-2843, IS A POTENTIAL NOVEL THERAPY IN PEDIATRIC BONE SARCOMAS

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Background: Osteosarcoma (OS) and Ewing sarcoma (EWS) are the two most common pediatric bone sarcomas. Outcomes remain poor in patients with advanced or relapsed disease and current treatments rely on multi-modal therapy that has significant short- and long-term side effects. New, less toxic and more effective treatments are urgently needed. One potential therapeutic target is MERTK. MERTK tyrosine kinase is overexpressed in numerous cancers where it promotes tumor cell survival, metastasis, and resistance to cytotoxic and targeted therapies. MRX-2843 is a first-in-class MERTK-selective tyrosine kinase inhibitor currently in clinical trials.

Objectives: Evaluate MRX-2843 as a novel therapy in preclinical OS and EWS models.

Design/Method: Cell cultures were treated with GAS6 ligand and/or MRX-2843. Expression and phosphorylation of MERTK and downstream signaling proteins were determined via immunoblotting. Phosphorylated MERTK was detected after MERTK immunoprecipitation. Changes in relative cell density were determined with Cell Titer Glo reagent after treatment with MRX-2843 for 72 hours.

Results: MERTK protein was expressed and activated in 3 of 4 OS cell lines and 5 of 5 EWS family cell lines tested. In EWS cell lines, stimulation with MERTK ligand GAS6 resulted in activation of downstream oncogenic signaling pathways, including JAK/STAT and MAPK/ERK. Treatment with MRX-2843 decreased phosphorylation of MERTK in a dose dependent manner, with an IC50 of 8.4 nM (95% CI; 2.6 – 13.6 nM) in A673 cells, and reduced downstream STAT6 signaling. Similar findings were observed in the TC106 EWS cell line. Moreover, publicly available data from CRISPR-based library screens indicate that EWS cell lines are particularly dependent on MERTK. Indeed, MRX-2843 had potent anti-tumor activity against all 5 EWS cell lines, leading to decreased cell density in culture with IC50 values ranging from 178 – 297 nM. Of note, inhibition of MERTK phosphorylation correlated with anti-tumor activity in both the A673 and TC106 cell lines, implicating MERTK inhibition as a mechanism of MRX-2843 anti-tumor activity. MERTK-expressing osteosarcoma cell lines (HOS, SAOS2, and U2Os) were sensitive to MRX-2843 with IC50 values ranging from 261-1176 nM, while the SJSA-1 cell line, which does not express MERTK, was not affected by treatment with MRX-2843.

Conclusion: These data validate MERTK as a promising therapeutic target in EWS and support development of MRX-2843 for treatment of EWS and OS, with potential to directly inform and enable a clinical trial in pediatric patients and, ultimately, to improve both outcomes and quality of life for patients with these diseases.

Poster # 239

SINGLE-CELL TRANSCRIPTOMICS INDENTIFIES METASTATIC DEVELOPMENT GENE NETWORK IN EWING SARCOMA CELLS

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Background: A patient-derived Ewing sarcoma ES36 cells and also patient-derived human fibroblasts provide a unique opportunity to explore the relationships between primary Ewing sarcoma cells and the healthy fibroblastic population.

Objectives: Assess the difference of gene expression between human fibroblasts and primary Ewing sarcoma culture

Design/Method: ES tumor tissue was dissociated from as described earlier (doi.org/10.1007/978-1-0716-1020-6_13), washed from blood cells, and plated at adhesive factor-coated T75sm^2 flasks in the presence of complete DMEM media supplemented with 10% FBS. Cells were characterized morphologically and by staining with CD99 antibodies. Human fibroblast cell culture was established by Dr. Levina et al and described earlier (PMID: 11739665). Cells were trypsinized, filtered to remove aggregates and single-cell sequencing was done using 10X Genomics 3' gene expression assay v3.1. Data processing and analysis was done using 10X Genomics Cell Ranger pipeline, Seurat R package, and consensus non-negative matrix factorization.

Results: Using Seurat Find Neighbors, cells in the aggregated dataset were classified into 12 distinct clusters. All clusters were comprised of cells with neoplastic or normal phenotype, except two clusters more enriched in ES36 cells. All samples were represented by clusters high for CD99 expression. ES36-enriched clusters exhibited a high level for MMP14 and MMP2, zinc-dependent enzymes, regulating migration and invasion. ES36-enriched clusters also showed higher expression of genes regulating oxidoreductase and dehydrogenase activity. Two of twelve ES36-based clusters had elevated expression of caveolin-1, HMGA1, EDIL3, integrins betta 1 and 3. Additionally, multiple zinc-containing metalloproteins such as carbonic anhydrases type 2(CAII), 9(CAIX), and 12(CAXII) efficiently catalyze the reversible hydration of carbon dioxide in tumor cells. In our study, we observed along with CAII absence among ES36 transcripts, a low-level of CAXII expression presented in unique clusters 10 and 12. The further GEO (GSE63155) bioinformatic analysis complements single-cell sequencing data, suggesting that activation of CAII and/or CAXII during ES propagation may require the involvement of the tumor microenvironment to develop metastases.

Conclusion: Utilizing single-cell gene expression profiling, we showed that ES36 cell clusters appear to maintain an endothelial and metastatic phenotype, which can be formed as a result of bilateral regulation of the microenvironment. Subpopulations of ES36 cells exhibited enrichment of beta 1 and 3 integrins, EDIL3, HMGA1, and features of the metastatic phenotype.

This research study was supported by the Russian Scientific Fund (21-15-00213)

Poster # 240

RETROSPECTIVE REVIEW OF CLINICAL COURSE AND GENOMIC SEQUENCING OF PEDIATRIC MPNST

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Background: Malignant peripheral nerve sheath tumors (MPNST) are rare pediatric cancers that develop in patients with and without Neurofibromatosis type 1 (NF1). Prognosis is based on the extent of surgical resection and whether the patient has localized or metastatic disease. There is currently no standard treatment for pediatric patients with MPNST; as a result, understanding the genomic basis of this disease to identify novel targets for treatment is necessary.

Objectives: The objective of this study was to evaluate the clinical presentations, genomics, and outcome differences between NF1 and non-NF1 patients with a diagnosis of MPNST at a single institution.

Design/Method: This study conducted a retrospective chart review of patients less than 25 years of age at diagnosis treated at our institution from January 2003 to December 2021. We reviewed presentation, pathology, imaging, genomics, treatment and clinical outcomes in patients with MPNST.

Results: Eighteen patients were included in this study, 11 with NF1 (61%) and 7 without (39%). The mean age at diagnosis was 13.5 years (range: 2.9-24.7) with patients with NF1 being older at diagnosis (16.2 vs 9.3 years, $p<0.05$). Patients with NF1 also had larger tumors at diagnosis (9.2 cm vs 4.7 cm in maximum dimension, $p <0.05$). Of the 18 patients in the study, 15 received at least a gross total resection (83%), 14 received radiation therapy (78%) and 9 received chemotherapy (50%). There was no statistically significant difference in treatment approach between patients with and without NF1. Four patients died of their disease, 2 with NF1 and 2 without. Fourteen patients are alive without evidence of disease. Eight patients underwent integrative clinical sequencing including matched tumor/normal DNA and tumor RNA sequencing, 5 of whom had NF1. Two patients had unique gene fusions identified, one with NF1 and one without. In all patients sequenced, we identified actionable genomic alterations, with 3/8 receiving precision targeted therapy.

Conclusion: Patients with NF1 and MPNST presented at a later age with larger tumors than patients without NF1. Genomic sequencing identified actionable genomic targets for therapy in all sequenced patients, but precision therapy was only used in 3 patients. Broader utilization is needed to determine the impact on outcomes. Two novel gene fusions were identified and may be areas for future research. Larger prospective studies are needed for this rare disease.

Poster # 241

TREATMENT OF EXTRARENAL, EXTRACRANIAL MALIGNANT RHABDOID TUMORS: A RETROSPECTIVE CASE SERIES

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Background: Malignant rhabdoid tumors are a rare, aggressive soft tissue malignancy characterized by mutations of *SMARCB1/INI1* that traditionally present in young children and are associated with poor outcomes. Rhabdoid tumors are most common in the kidney or brain, making extrarenal, extracranial malignant rhabdoid tumors (EERTs) especially uncommon. Given the rarity of EERTs, there is a paucity of data on treatments and outcomes in this population.

Objectives: The purpose of this study is to review a single institution's experience with EERTs, including clinical features, treatment factors, and outcomes.

Design/Method: We performed a retrospective chart review of nine patients diagnosed with EERT since 1989. Diagnosis was established by loss of *INI1* in seven patients and histologically in two. We extracted data on presentation, tumor stage, chemotherapy regimen, radiation, resection, treatment related morbidity, and survival.

Results: Nine patients (3 male, 6 female) were diagnosed with EERT at a median age of 67.4 months (range 3 months to 22 years). Primary tumor locations included paraspinal muscles (3), liver (2), vertebral bodies (1), retropharyngeal soft tissue (1), orbit (1), and forehead (1). At presentation, five had stage IV disease and four had stage II disease. Eight patients received early local control with three receiving radiation alone, two receiving resection alone, and three receiving both resection and radiation. All patients received chemotherapy, including six who initially received a regimen of alternating cycles of vincristine/doxorubicin/cyclophosphamide and ifosfamide/carboplatin/etoposide (VDC/ICE), two who initially received a modified IRS III backbone, and one who was originally diagnosed as hepatoblastoma and treated accordingly before changing to VDC/ICE after the diagnosis was changed. Five patients are alive after therapy (55.6%), and all are at least 3 years off therapy. Of the five survivors, one presented with stage IV disease, three received radiation and resection, one each received radiation or resection alone, and four were treated with VDC/ICE. Two patients with incomplete resections also received maintenance chemotherapy following VDC/ICE with vinorelbine/cyclophosphamide and vincristine/actinomycin respectively. Of the four non-survivors, all died from progressive disease with three patients never obtaining disease control and one patient with recurrent disease not responsive to salvage regimens.

Conclusion: EERTs are a rare malignancy with a guarded prognoses and no standard treatment guidelines. This case series highlights the successful treatment of EERTs with VDC/ICE and early local control, suggesting that VDC/ICE should be considered for treatment of EERTs. Maintenance chemotherapy may also have a role for patients with incompletely resected tumors.

Poster # 242

SURVIVAL OUTCOMES BASED ON SURGICAL APPROACH TO PULMONARY METASTASECTOMY IN PATIENTS WITH OSTEOSARCOMA

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Background: Approximately 20% of patients with osteosarcoma present with pulmonary metastases at diagnosis and over a third of patients with localized disease will develop lung metastases. Surgical control of macroscopic disease both at primary and metastatic sites in osteosarcoma is considered essential for cure. Despite the advantages of thoracoscopic approach to limit morbidity, thoracotomy is considered standard for pulmonary metastasectomy in osteosarcoma. Limited information is available on the impact of each approach on survival.

Objectives: To evaluate survival outcomes of different surgical approaches in the management of pulmonary metastases in osteosarcoma.

Design/Method: A retrospective review of all patients with osteosarcoma diagnosed between January 2004-December 2018 who underwent pulmonary metastasectomy.

Results: Of 61 patients with osteosarcoma who underwent pulmonary metastasectomy, 37 (61%) were localized and 24 (39%) were metastatic at diagnosis. The 5-year EFS and OS were 17.2% and 71.4%, respectively. There was no difference in survival outcomes between the two groups (5-year EFS localized vs. metastatic, 11% vs 29%; p=0.262; 5-year OS 67% vs 78%; p=0.735). There was also no difference in survival outcomes based on primary tumor histologic response (5-year EFS good histologic vs. poor histologic response, 30% vs 12%; p=0.262; 5-year OS 84% vs 63%; p=0.133).

Of 24 patients with metastatic lung disease at diagnosis, pulmonary lesions were unilateral in 9 and bilateral in 15. There was no significant difference in the 2-year EFS (62% vs 33%; p=0.262), or the 2-year OS (89% vs 73%; p=0.499) between unilateral vs. bilateral disease. Twenty-one patients underwent pulmonary metastasectomy, 9 (43%) had thoracotomy, 6 (28.5%) had thoracoscopy and 6 (28.5%) had thoracoscopy with thoracotomy. There was no difference in survival outcomes between surgical approaches (2-year EFS thoracotomy vs thoracoscopy vs both, 42% vs 33% vs 50%; 2-year OS 64% vs 83% vs 83%).

In the 43 patients with first pulmonary relapse or progression that underwent metastasectomy; 18 (42%) had thoracotomy, 16 (37%) had thoracoscopy and 9 (21%) had thoracoscopy with thoracotomy with no significant difference in survival outcomes (2-year EFS thoracotomy vs thoracoscopy vs both, 23% vs 47% vs 25%; p=0.363; 2-year OS 93% vs 78% vs and 58%; p=0.593).

Conclusion: Our patients with osteosarcoma pulmonary metastases have comparable poor survival outcomes despite varying surgical approaches to pulmonary metastasectomy. Evaluation of surgical morbidity in this cohort is ongoing. Our study reinforces the clinical equipoise between thoracotomy and thoracoscopy, which will be prospectively investigated in the Children's Oncology Group randomized trial AOST2031.

Poster # 243

RHABDOMYOSARCOMA CLINICOPATHOLOGY AND OUTCOMES BY AGE GROUP AT A SINGLE INSTITUTION

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Background: Rhabdomyosarcoma (RMS) is a cancer of immature striated muscle cells and the most common soft tissue tumor in children. It represents 5% of all childhood cancer with a peak incidence <6 years old. RMS also occurs adults, although it only makes up 2% of soft tissue sarcomas in patients ³16 years of age. Results from previous COG trials suggest that age is a negative prognostic marker in RMS, but there is limited data comparing clinical, and pathologic features and outcome between young children, adolescents, and older adults.

Objectives: Compare the different clinicopathologic characteristics and treatment outcome of rhabdomyosarcoma between different age groups at a single institution.

Design/Method: We performed a retrospective chart review of 63 rhabdomyosarcoma patients treated at our institution between 2000 and 2016. We compared stage and group classification at diagnosis, tumor location, histological subtype, treatment modalities, and outcomes among four different age groups (>13, 13-20.99, 21-39.99, and >40 years of age).

Results: Our data shows a bimodal age distribution, with peaks at 0-5 years and 60-80 years. There was a male predominance among children (1.6:1 M:F) and older adults (1.7:1 M:F) but a female predominance in adolescents (2.3:1 M:F) and young adults (1.7:1 M:F). Head and neck were the most common tumor site among young children, extremities were the most frequent location for older adults, and adolescents had more pelvic, retroperitoneal, and intrathoracic tumors. These groups also were more likely to have higher staged tumors at presentation (stage 4 in 50% of adolescents and 80% of young adults, vs 17.9% in children and 26.3% in older adults). Young children's tumors had almost exclusively alveolar and embryonal histology, while adolescents and young adults (AYAs) primarily developed alveolar rhabdomyosarcoma. Older adults had tumors with diverse histologies, such as pleiomorphic and spindle cell. A small number of adults were treated with only chemotherapy or surgery, while all children and adolescents received multimodal therapy. Consistent with previous literature, 5-year overall survival was significantly greater among young children than any other group (82.8%). Young adults and adolescents had the lowest survival rates (0% and 10% respectively), while older adults fared slightly better with 26.3% 5-year survival.

Conclusion: Our data shows that there are clear clinical and pathologic differences in RMS between age groups with AYA and older adult patients experiencing worse survival outcomes. These results support the need for continued investigations on novel treatments for RMS in this high-risk population.

Poster # 244

Downstaging and Resection After Neoadjuvant Therapy for Fibrolamellar Carcinoma

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Background: Fibrolamellar Carcinoma (FLC) is a rare form of primary liver cancer affecting children and young adults. It typically presents at an advanced stage with minor or nonspecific symptoms. Currently, the only treatment for FLC is surgery with complete resection and negative margins (R0) offering the only known possibility of cure. However, up to one-third of patients are unresectable at presentation. Unresectable patients are considered incurable and have short life expectancies. An effective neoadjuvant chemotherapy could potentially increase the amount of resectable FLC patients and, in turn, increase chances of sustained surgical remission and potentially cure. Although clinical trials are ongoing, there are no proven adjuvant or neoadjuvant therapies for FLC patients. Our retrospective study of 27 unresectable FLC, most multiply relapsed, showed that for some patients, achieving surgical remission is possible after induction chemotherapy with gemcitabine-oxaliplatin-lenvatanib (GEMOX-LEN).

Objectives: We describe our experience with the novel neoadjuvant chemotherapy combination, GEMOX-LEN, for unresectable FLC patients.

Design/Method:
We treated 27 patients with unresectable FLC, most of whom have had previous surgeries and therapies, with a neoadjuvant gemcitabine 1000mg/m2, oxaliplatin 100mg/m2 every 2 weeks, and daily oral lenvatanib 8mg. Data was collected from April 2019 to January 2022. Response to treatment was measured using RECIST 1.1.

Results: After induction treatment with GEMOX-LEN, 14 patients became surgical candidates, 10 never became surgical candidates, 3 are still receiving GEMOX-LEN. The average and median RECIST 1.1 response was -35% and -24%, respectfully. Of the 14 surgical candidates, four are scheduled for surgery in the next 2 months, seven had R0 surgeries, one had 95% tumor debulking, one was aborted after inter-operative discovery of carcinomatosis not seen on imaging, and one had such a significant response (94% reduction by RECIST) that remaining tumors were eradicated by SBRT radiation and 3 microwave ablations. The most common toxicities were neuropathy (36%), cytopenias (24%), and nausea (28%) - all NIH grade 1 or 2.

Conclusion: It is too soon to say if GEMOX-LEN induction combination chemotherapy will make incurable FLC patients curable or even prolong their life. However, it does offer a tolerable option for patients wishing to try to get an aggressive surgery and possible hope for the future. Prospective trials are needed to confirm these retrospective results.

Poster # 245

CLINICAL EFFICACY OF PAZOPANIB IN HIGH-RISK PEDIATRIC SOLID TUMORS:A MULTICENTER RETROSPECTIVE STUDY

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Background: The improvement in pediatric cancer survival has reached a plateau with conventional treatment, prompting the development of innovative therapies. Pazopanib, a multi-targeted tyrosine kinase inhibitor (mTKi), has demonstrated anti-tumor activity in adult bone and soft-tissue sarcomas (STS) but has not yet been approved for pediatric tumors.

Objectives: The primary objective was to evaluate the efficacy of pazopanib alone or in combination with topotecan (ToPaz). The secondary objective was to describe pazopanib tolerance for the entire population.

Design/Method: This observational multicenter retrospective study included patients with solid tumors, ≤25 years old at diagnosis, from all 4 pediatric oncology centers in the province of Quebec, treated with pazopanib out of a clinical trial, in monotherapy, ToPaz or with poly-chemotherapy before January 1st, 2021.

The efficacy outcomes were overall response rate (ORR) (complete (CR) or partial response (PR)), disease control rate (DCR) (CR, PR or stable disease (SD) for ≥8 weeks), progression-free (PFS) and overall survival (OS). We also compared the efficacy depending on molecular alterations identified, targetable by pazopanib or not, and compared the toxicity between monotherapy or combination therapy. Cox proportional hazard models were used to identify predictors of survival.

Results: For efficacy analysis, 19 patients with relapsed/refractory tumors were eligible: 14 bone tumors (osteosarcoma=7, Ewing sarcoma=7) and 5 STS (rhabdomyosarcoma=2, others=3). Four patients received ToPaz. At pazopanib initiation, the median age was 16.9 years [range=6.0-26.2], 18 patients had metastatic disease with a median of 2 prior therapeutic lines. With 6.2 months [0.8-26.0] of median follow-up, no PR or CR were observed, but 10 patients had SD for a DCR of 52.6%. The median PFS and OS were 3.0 months [95%-CI=1.1-5.8] and 6.2 months [95%-CI=2.8-13.6], respectively. The efficacy did not differ according to molecular alterations. Multivariable analysis showed an inverse relationship between the number of prior treatment lines and PFS and OS (hazard ratio=1.73 (p=0.04) and 1.76 (p=0.03), respectively).

Toxicity analysis on the 23 patients showed 6 treatment discontinuations because of toxicity, 4 grade ≥3 adverse events and no treatment-related mortality. There was no statistical difference in pazopanib-related toxicity depending on the regimen.

Conclusion: In this hard-to-treat pediatric bone tumors and STS population, over 50% had controlled disease with a median OS ≥ 6 months and an improved survival for patients who had received fewer prior therapeutic lines. Future studies are warranted to determine the best timing to initiate mTKi and to identify biomarkers of efficacy.

Poster # 246

INCREASED PEDIATRIC KIDNEY TUMOR INCIDENCE RATES IN THE LOUISIANA ACADIAN PARISHES

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Background: Malignant renal tumors account for 7% of the pediatric cancer burden in 2021, increased from the 4% reported between 1975 to 1995; Wilms tumors (WT) accounted for 90% of these tumors. Despite a stable world-wide incidence of WT from 1996 to 2010, it appears that pediatric kidney cancer rates are disproportionately increased in the Louisiana Acadian parishes, which are home to nearly 800,000 individuals of Cajun descent. The Cajun population, known for their unique dialect and culture, is a non-Hispanic white founder population that migrated to Louisiana from the French Canadian territory of Acadia in the late 1700s.

Objectives: In this study, we examined the incidence rate of kidney tumors in the Cajun population; hypothesizing that an increase may be due to heritable cancer syndromes or undiscovered cancer susceptibility genes. We examined the pathology, treatment, outcomes, and survival rates among these Acadian Parish pediatric patients.

Design/Method: Our methods included an analysis of the Louisiana Tumor Registry in order to understand how many pediatric kidney tumors are diagnosed in Louisiana. We then conducted a retrospective review of hospital records from Children's Hospital of New Orleans (CHNOLA) from 2000-2018. We examined medical records at CHNOLA of all pediatric kidney tumors treated during that time and focused on the 22 Acadian parishes. Medical Records data included demographics, pathology, genetic testing, and treatment data. Data from Louisiana Tumor Registry and CHNOLA was compared to Surveillance, Epidemiology, and End Results (SEER) national incidence data.

Results: Upon analyzing the Louisiana Tumor Registry from the years of 2000 to 2018, we found an increased incidence rate of renal tumors in the white pediatric population from Acadian parishes (per 1,000,000) compared to the white pediatric population in all of Louisiana and in the SEER national incidence data. The percentage of non-Hispanic white children in the Acadian parishes ranges from 23.9 to 75.1%, while the percentage of non-Hispanic black children in the Acadian parishes ranges from 4.5 to 65.6%. The data is as follows: 11.6 (Acadian Parish whites) versus 7.6 (Louisiana whites) versus 6.5 (SEER). Contrarily, the incidence rate of renal tumors in the Black pediatric population from Acadian parishes is notably lower at 5.6 (per 1,000,000).

Conclusion: While Southern Louisiana is notoriously referred to as "Cancer Alley" due to the presence of hundreds of chemical and petroleum plants, the increased incidence in Acadian Parish white children but not Black children suggests that environmental causes are not the sole contributing factor at play.

Poster # 247

IMPACT OF A PATIENT-PROVIDER EDUCATIONAL INITIATIVE ON TREATMENT OF PEDIATRIC NEUROBLASTOMA

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Background: Treatment strategies for pediatric neuroblastoma have been tailored according to risk stratification, predicted response to therapy, and risk of relapse. As we acquire a better understanding of clinical and biological risk factors, it is important to consider treatment by compartmentalizing neuroblastoma and planning in concordance with the perspectives and goals of patients and their families.

Objectives: To empower patients and families and to share their perspectives with the clinical team while making treatment decisions according to disease compartments.

Design/Method: Two, 1-hour online video-based programs were hosted in September and October, 2020 for patients/families and HCPs, respectively. The patient activity was conducted in collaboration with Solving Kids Cancer. The HCP activity was held as a satellite symposium in conjunction with the International Society of Paediatric Oncology (SIOP) virtual congress. Practice and knowledge gaps among HCPs, and knowledge, communication and self-efficacy behaviors among patients were assessed. Each activity was interactive, consisting of slides, polling and live questions, and remains on-demand for 12 months. Assessments were administered at 3 time points (pre-, immediate post-, and 2 mos. post-activity). Data from these questions, responses to live polling questions, and learner-submitted questions during live Q&A were analyzed to determine engagement, lessons learned, and continuing education gaps. Patient/Family data were captured and shared during the HCP program at SIOP.

Results: As of December 2021, 214 HCPs and 7,246 patients participated in the ongoing activities. Post education, HCP learners anticipated the education would positively impact practice behavior (76%) and patient clinical outcomes (70%). HCP Improvements in pre/post knowledge and competence questions were realized in all 3 questions. Patients/families listed “anxiety about disease progression” and “anxiety about treatment efficacy” as their greatest challenges. Additional qualitative and quantitative data were collected regarding patient/family perceptions on treatment options, preparation for side effects, experience with therapies, and preferences for shared decision-making. Updated data will be shared, including 2-mos. follow-up, aligned HCP and patient/family data, and practice pattern data.

Conclusion: Providing patient/family perspectives to HCPs for pediatric neuroblastoma care can impact clinical practice behaviors, patient/family healthcare communication and confidence, and treatment knowledge for effective management, including for patients with CNS/leptomeningeal metastases. Together, aligned education directed to HCPs and patients can improve the ability to provide evidence-based treatment for patients.

This tethered initiative was supported by an educational grant from Y-mAbs Therapeutics, Inc.

Poster # 248

YOGA: A NON-PHARMACOLOGIC THERAPY TO REDUCE DINUTUXIMAB-INDUCED PAIN IN PATIENTS WITH NEUROBLASTOMA

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Background: Anti-GD2 antibody therapy has become a key component of treatment for patients with high-risk neuroblastoma in the frontline and relapsed settings. Dinutuximab (DIN) targets GD2 on neuroblasts, but also binds to normal cells of neuroectodermal origin, such as peripheral nerves. Pain is therefore a common toxicity. While opioid analgesics are the mainstay of pain management, incorporating an integrative therapy such as yoga may help reduce pain, overall distress, and perhaps decrease opioid usage in patients receiving DIN. We evaluated the feasibility of yoga therapy in patients receiving DIN at a large children's hospital.

Objectives: The primary objective was to assess the feasibility of providing individualized yoga therapy by a certified therapist to patients with neuroblastoma hospitalized for DIN administration. Secondary aims included evaluating the efficacy of yoga therapy, as assessed by patients, caregivers, and clinicians, in addition to measuring the level of pain/distress pre- and post- yoga therapy.

Design/Method: In this pilot study, children ≥3 years of age with neuroblastoma participated in yoga therapy while receiving DIN infusions at the Children's Hospital of Philadelphia. Yoga therapy was deemed feasible if patients participated in individualized yoga therapy during ≥60% of admissions for DIN. The patient was considered to have participated in yoga therapy if the therapist entered the patient's room, interfaced with the patient for ≥15 minutes, and engaged the patient in at least one yoga intervention.

Results: Twelve participants were enrolled in the feasibility cohort and there were 32 evaluable encounters (i.e. a single admission for DIN). Seven of 12 participants were female, 2/12 were Hispanic, and 8/12 were white. Median age at enrollment was 4 years (range: 2-14 years). Yoga therapy was feasible in 25/32 (78%) encounters. Most participants engaged in yoga practices including: asana (physical postures), pranayama (therapeutic breathwork), and somatic-based inquiry (mindfulness). Nine of 12 caregivers completed surveys. Seven caregivers agreed/strongly agreed that yoga was valuable to their child and eight caregivers strongly agreed that they wanted their child to continue to participate in yoga. Four caregivers engaged their child in yoga at least once without the yoga therapist. Twenty-one of 23 clinicians reported that they would recommend yoga therapy for other patients receiving DIN.

Conclusion: This pilot study establishes the feasibility of yoga therapy during DIN infusions in patients with neuroblastoma. These results are promising, as yoga therapy may help decrease DIN-associated pain and distress. Efficacy is currently being evaluated in additional patients receiving this therapy.

Poster # 249

MUTATIONAL LANDSCAPE OF ALTERNATIVE LENGTHENING OF TELOMERES IN PEDIATRIC BRAIN CANCER

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Background: To achieve replicative immortality, most cancer cells develop a telomere maintenance mechanism, such as reactivation of telomerase or alternative lengthening of telomeres (ALT). ALT occurs in roughly 10-15% of cancers, and previous work has shown that ALT occurs more frequently in pediatric high-grade astrocytic tumors (HGATs), neuroblastomas, and osteosarcomas. ALT has previously been associated with mutations in the chromatin remodeling gene ATRX, as well as mutations in p53. Maintenance of telomere length is thought to be critical for tumor survival.

Objectives: To determine which pediatric brain tumors utilize ALT and whether somatic and germline mutations are associated with ALT.

Design/Method: We detected ALT by c-circle analysis (CCA) on Pediatric Brain Tumor Atlas (PBTA) tumors that had corresponding whole genome sequencing (N = 685) and performed additional validation by ultrabright telomeric foci *in situ* on a subset of these tumors (N = 35). We computationally determined ALT status using TelomereHunter and examined whether ALT was associated with somatic or germline alterations in cancer, including known cancer predisposition and/or DNA repair genes.

Results: We identified ALT by CCA in 8% (2/25) of atypical teratoid rhabdoid tumors, 5% (4/75) of ependymomas, and 37% (29/77) of HGATs. Using the CCA readout, we validated the utility of TelomereHunter to stratify HGAT tumors by ALT status and achieved 89.3% sensitivity and 81.3% specificity. ATRX mutations were found in 58% (29/47) of patients with HGAT and ALT. Germline variants in mismatch repair (MMR) genes, but not other DNA repair or cancer predisposition genes, were associated with an increased occurrence of ALT. Four patients with HGAT had a germline MMR variant, and 100% of these were ALT+. Sixty patients with HGAT did not have germline MMR variants, and 35% of these patients were ALT+ (p=0.02).

Conclusion: We demonstrate that ATRX is only mutated in 58% of ALT+ HGAT, suggesting that other means of ATRX loss of function or other mutations may be associated with the development of ALT in these patients. Additionally, we show that germline variants in MMR genes are associated with an increased rate of ALT+ tumors, suggesting that loss of MMR function may result in a permissive state that promotes the development of ALT. Future studies will focus on elucidating the relationship between MMR function and ALT development, as well as identifying other mutations that drive the maintenance and development of ALT. By gaining a greater understanding of ALT, we may be able to identify potential candidates for ALT directed therapies.

Poster # 250

OXALIPLATIN AS A HEARING-SPARING ALTERNATIVE IN AUTOLOGOUS STEM CELL TRANSPLANTS IN CNS MALIGNANCY

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Background: Intensive chemotherapy with tandem autologous stem cell transplants (autoSCT) is shown to improve survival for children with CNS malignancy. Platinum-based chemotherapeutic agents in these regimens, mainly cisplatin and carboplatin, have resulted in significant sensorineural hearing loss. Oxaliplatin, a more recently developed platinum-based agent, is considered less ototoxic. Empiric substitution of oxaliplatin for carboplatin in preparative regimens for autologous stem cell rescue have been tried. However, the survival and ototoxicity outcomes have not been studied.

Objectives: To compare the overall survival and ototoxicity of oxaliplatin versus carboplatin preparatory chemotherapy regimens in children who received tandem autoSCT for treatment of CNS malignancy.

Design/Method: We performed a retrospective chart review of all pediatric patients with primary CNS tumors who received tandem autoSCT from 2011 to 2018 at Children's Hospital Colorado. Demographics, clinical outcomes, and medication administration records for all cisplatin, carboplatin, oxaliplatin, vancomycin, furosemide, and aminoglycosides were extracted from electronic medical records. Hearing evaluations, performed at pre-transplant, after each transplant episode, and at 1-year and/or subsequent follow-up visits, were reviewed and graded by an audiologist. Comparisons were performed using Fisher's exact tests and log rank test statistics.

Results: A total of 32 pediatric patients with CNS tumors met inclusion criteria. Seven patients received oxaliplatin in place of carboplatin in one or more preparatory regimens. There was no statistically significant difference in overall survival between those who did or did not receive oxaliplatin (p=0.99). A total of 85 follow-up audiograms were available for assessment, including long-term follow up. Of the 13 audiograms that showed hearing loss, one (8%) had prior oxaliplatin exposure, compared to 18/72 (25%) audiograms without hearing loss had prior oxaliplatin exposure (p=0.28).

Conclusion: Oxaliplatin is effective and well-tolerated when used in lieu of carboplatin in preparatory regimen for autoSCT for pediatric CNS malignancy. This study is limited by its small size. A larger, multi-center study is warranted to confirm oxaliplatin's safety and effect on survival and ototoxicity in pediatric autoHSCT.

Poster # 251

PREDICTING CEREBELLAR MUTISM SYNDROME

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Background: Survival rates for pediatric cancers have greatly improved in this century, and this includes brain tumors. This increases the importance of understanding and preventing the development of treatment-related effects in the pediatric population. About 25% of patients who undergo cerebellar tumor resection develop a constellation of deficits in cognition, affect and executive function, known as cerebellar mutism syndrome. A recent study by Albazron et al, involving 195 subjects included showed that lesion anatomy was a critical variable for CMS, showing that: 1) damage to the cerebellar outflow pathway increases the risk of CMS ten-fold, and 2) a data driven lesion symptom map identified a region maximally associated with CMS.

Objectives: We aim to further evaluate the relationship of lesion location and the onset of severe cognitive and affective symptoms following pediatric cerebellar tumor resection. Specifically, our goal was to test the results of the Albazron study in an independent cohort, with pre-registered anatomical hypotheses. Particularly, we hypothesized that subjects with CMS would have lesion that overlap with the cerebellar outflow pathway and the CMS lesion symptom map to a greater extent than patients that did not develop CMS.

Design/Method: This was an observational study that included data from 56 patients under 21 years of age who underwent cerebellar tumor resection. Each patient had a post-surgical MRI and clinical assessment to determine the presence or absence of CMS. Each tumor resection cavity was manually segmented and transformed to a common template brain. The intersection of the lesion with the cerebellar output pathway and the CMS lesion symptom map was quantified and compared between individuals that did or did not develop CMS.

Results: Out of 56 patients, 10 developed CMS (18%). As hypothesized, the lesions of individuals with CMS overlapped with the cerebellar outflow pathway and the data-driven lesion symptom map to a greater extent than individuals that did not develop CMS ($p=0.0271$ & $p=0.013$, respectively).

Conclusion: Our analysis provides further support that the anatomy of the resection site is a critical variable in the development of CMS and it can predict the development of CMS across independent cohorts.

Poster # 252

CHILDHOOD GLIOMA OUTCOME DISPARITIES

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Background: Central nervous system tumors are the leading cause of cancer-related death in children. There is a lack of recent studies analyzing disparities in survival among American Indian, Hispanic, African American, and Asian/Pacific Islander children diagnosed with gliomas. These

populations may have unique barriers to health care, that may impact outcomes and survival rates. Previous studies have shown that Neurofibromatosis type I (NF1) can increase an individual's risk of gliomas; however, there are few recent studies conducting an analysis on how NF1 status impacts outcomes of childhood gliomas.

Objectives: To describe the relationship between race and event-free survival among children diagnosed with glioma prior to age 20 from 2005 to 2019.

Design/Method: Through partnership with a children's hospital at an academic medical center and the institutional cancer registry, we have identified a list of patients with glioma following the 2016 World Health Organization Classification of Tumors of the Central Nervous System (n=152). The patients' diagnosis, Neurofibromatosis Type 1 (NF1) status, treatment and outcomes were obtained from the registry and electronic medical records. We evaluated differences in survival time from diagnosis to death or the end of the study period by race/ethnicity and glioma category using Kaplan-Meier analysis with the log-rank test.

Results: We identified children with glioma who were non-Hispanic (NH) American Indian (4.6%), NH white (68.4%), Hispanic (13.2%), NH African American (9.2%), or NH Asian/Pacific Islander/Other (4.6%) from the hospital's cancer registry. Forty-two percent (42%) of children with gliomas were female and the median age at diagnosis was 8 years. We observed that 12.6% of children with low-grade glioma also had NF1. Median survival time from gliomas differed by race/ethnicity ($p=0.04$), with NH American Indian children having the poorest survival outcomes. Median survival time differed by glioma type ($p<0.0001$), with high grade gliomas having the poorest outcomes. Thirteen percent (13%) of children with high-grade gliomas and 97% of children with low-grade gliomas survived at least five years from diagnosis.

Conclusion: For our next step, we plan to conduct a more in-depth analysis of the specific outcomes associated with low-grade gliomas and high-grade gliomas. This project will generate important preliminary data for future studies, which will evaluate strategies to address barriers to care faced by different racial and ethnic groups.

Poster # 253

PATIENT-LEVEL ANALYSIS OF PEDIATRIC CNS TUMOR SURVIVAL BASED ON DEMOGRAHPIC/SOCIOECONOMIC VARIABLES

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Background: Our previous population-based study using SEER data showed poorer survival of pediatric central nervous system (CNS) cancer based on Black race, Hispanic ethnicity, and residence in high poverty areas in the United States.

Objectives: Given that clinical and patient-level socioeconomic factors are difficult to assess in population-based studies, our objective in this study was to scale down our focus to evaluate the

effects of patient-level demographic, socioeconomic, and clinical factors on pediatric CNS tumor survival at Children's Hospital Colorado (CHCO).

Design/Method: This was a retrospective cohort study of 858 patients diagnosed with a primary CNS tumor from 1986-2020 seen at CHCO. We evaluated the effects of diagnosis year, age, gender, race, ethnicity, primary language, insurance at first surgery, rurality, tumor type, tumor site, presence of metastatic disease, and socioeconomic concerns (based on initial social worker assessment) on overall survival using univariate and multivariable Cox proportional hazards survival analyses.

Results: As expected, we found that clinical features like aggressive tumor type (high-grade glioma, atypical teratoid/rhabdoid tumor, medulloblastoma, and ependymoma), brainstem location, and metastatic disease were most predictive of poor survival. Brainstem followed by thalamus and then cerebral hemisphere locations were most predictive of poor survival for malignant tumors, while ventricular location was most predictive of poor survival for low-grade tumors. On univariate analysis, family report of financial concerns to social workers was correlated with poor survival, but this effect was no longer significant on multivariable analysis controlling for demographic and clinical factors. Multivariable analysis showed a statistically significant increase in mortality for patients of Asian/Pacific Islander descent. Significant survival disparities were not observed based on Black race, Hispanic ethnicity, Spanish primary language, lack of private insurance, or rural/urban residence. Survival improved significantly over the study period.

Conclusion: In this patient-level, single-institution study of pediatric CNS tumor survival, we found the Asian/Pacific Islander race was associated with poorer survival, while we did not find evidence of survival disparities based on Black race, Hispanic ethnicity, rural/urban residence, insurance type, or socioeconomic status when controlling for clinical factors. These differences from national results may be due to smaller study size and/or specific characteristics of the hospital and regional healthcare system. Future work will assess intermediate outcomes, treatment variables, and the role of tumor biology.

Poster # 254

META-ANALYSIS OF HIGHLY EXPRESSED GENES IN EPENDYMOMA CASES

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Background: Ependymoma is a rare cancer which arises primarily from the glial cells found within the ventricular system in pediatric cases. Previous studies have shown limited utility with histopathological classification, and increased efforts have been focused on molecular subtyping both for risk stratification as well as drug target discovery.

Objectives: Utilizing publicly available datasets, this study examines highly expressed genes shared among pediatric ependymoma cases to identify common pathways and biological processes.

Design/Method: Utilizing the R2 genomic visualization platform, expression data was analyzed from 8 publicly available ependymoma datasets (GSE141460, GSE13267, GSE64415 GSE50385, GSE125969, GSE16155, and from PMID:20639864, 21840481). For each dataset, the top 100 genes based on log2-median expression level were taken and compared to calculate which genes were highly expressed across several datasets. Those genes ranking in the top 100 in 5 or more underwent enrichment analysis using Cytoscape to observe shared biological processes which saw high activity in ependymoma cases ($p<0.01$ was considered significant). The DisGeNET platform was used to observe if there were other malignancies or diseases which featured a significantly ($p<.01$) similar genetic profile to the ependymoma cases based on the curated gene list.

Results: In total, 47 genes appeared in the top 100 highly expressed list of at least 5 datasets. Within that curated list were some genes that coded for proteins discussed in previous cancer literature such as COX1/2 and vimentin, and other genes that are less investigated such as the glycoprotein encoding *CHI3L1* gene. Enrichment analysis highlighted several pathways such as VEGFA-VEGFR2 signaling, neutrophil degranulation, and cellular amide metabolism among eleven others. While the DisGeNET analysis showed that diseases such as tauopathies and retinal diseases have a significantly similar expression profile, no cancers shared comparable expression profiles.

Conclusion: Given its rarity and the difficulty of connecting histopathology to outcome, genetic analysis of ependymoma cases is an important step in better characterizing cases in regards to outcomes. Here we observe a cohort of consistently highly expressed genes, with some novel genes unexplored in either ependymoma or other cancers. The unique nature of ependymomas were affirmed given the results of DisGeNET, with the enriched pathways such as cytokinesis regulation and chaperone mediated autophagy offering possible therapeutic targets and launching points for future wet-lab studies.

Poster # 255

TARGETING MALT1 IN GLIOBLASTOMA

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Background: Central nervous system malignancies account for 40 percent of cancer-related deaths in children. Pediatric glioblastoma (GBM) is a particularly devastating disease, with a 5-year survival of less than 20%. There is a clear need for improved treatment strategies.
MALT1 is an intracellular protease that functions as the effector molecule of the CARMA-BCL10-MALT1 (CBM) protein complex. The CBM was first discovered in lymphocytes where it mediates antigen receptor-dependent activation of NF-κB and production of cytokines to promote an immune response. However, gain-of-function mutations resulting in deregulated CBM activation underly multiple subtypes of lymphoma where it drives tumor progression. Beyond lymphoma, the CBM complex has recently been found to promote tumor progression in a variety of other cancers. Here, we investigate the role of MALT1 in GBM in order to determine if this intracellular protease represents a potential therapeutic target.

Objectives: We aimed to evaluate the contribution of MALT1 to GBM progression using a combination of bioinformatic and *in vitro* cancer cell-based analyses.

Design/Method: *In silico*, using the Gliovis portal, we investigated MALT1 expression in adult and pediatric GBM samples and analyzed the correlation with tumor grade and molecular subtype. *In vitro*, we evaluated the effect of treating GBM mouse (GL261) or human (U87MG) cell lines with either MALT1 siRNA or with the highly specific MALT1 protease inhibitor, MLT-748, on cell viability, clonogenicity, migration and cytokine release profile.

Results: Analysis of TCGA data demonstrated that MALT1 is overexpressed in pediatric and adult GBM and its expression correlates with tumor grade. MALT1 expression is significantly higher in mesenchymal GBM, a subtype with more aggressive features and a worse prognosis. *In vitro* analyses revealed that both mouse and human GBM cells demonstrate constitutive MALT1 proteolytic activity. Treatment with MALT1-siRNA or MLT-748 induced a discreet reduction in GBM cell viability, clonogenic potential and migration. We identified IL-11 as a cytokine whose secretion from GBM cells is dependent on MALT1.

Conclusion: Together, our studies support a potential role for MALT1 protease in promoting GBM pathogenesis. Bioinformatic analysis demonstrates that MALT1 expression correlates with features of GBM tumor aggressiveness. Studies of both mouse and human GBM cells reveal that inhibiting MALT1 abrogates multiple hallmarks of tumor progression and alters the immunomodulatory cytokine profile. These observations suggest that further study of MALT1 as a potential therapeutic target in GBM are warranted and may inform future clinical trials incorporating MALT1 inhibitors for the treatment of this devastating cancer.

Poster # 256

THE RISE OF WNT-SUBTYPE MEDULLOBLASTOMA

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Background: Medulloblastoma used to be thought of as a single disease, stratified only by surgical success and presence or absence of metastatic spread.
We now know that medulloblastoma has many subtypes, four commonly recognized (sonic hedgehog-activated [SHH], wingless-activated [WNT], group 3 and group 4) and up to 12 possible further classifications. This stratification of medulloblastoma subtypes is critically important in the diagnosis, counseling, and treatment of these pediatric patients. The WNT subtype for example, is associated with an excellent overall survival and event free survival, even in the presence of metastatic disease and thus has been identified as a candidate for therapy de-escalation. WNT medulloblastomas are thought to represent approximately 10% of all new medulloblastoma diagnoses.
Our experience with pediatric medulloblastomas at Nemours Children's Hospital in Wilmington, Delaware, has recently seen a surge of this patient population.

Objectives: Measure the frequency of WNT-activated medulloblastoma from 2017-2021 at

Nemours Children's Hospital in Wilmington, Delaware.

Design/Method: We performed a retrospective chart review of all patients treated over the past five years from 2017-2021 at Nemours Children's Health in Wilmington, Delaware. All patients were identified via an institutional database which was approved by the Nemours institutional review board including waiver of patient consent. Data extracted included gender, age at diagnosis, histology, medulloblastoma group, tumor location, and genetic testing including FISH and microarray.

Results: Since January 2017, we have diagnosed and treated 12 children with medulloblastoma. Seven of 12 (58%) of these patients have been of the WNT subtype. Median age at diagnosis was 9 years, range 8-12 years. M:F ratio was 2:5. WNT subtyping was performed at one of two CLIA certified labs using a neuro-oncology gene panel and gene microarray. All patients are alive, well and, without evidence of disease although follow up is short, median 9 months following diagnosis, range 2-51 months.

Conclusion: This cohort may represent sampling error due to small numbers. However, it is also possible that the original estimates of WNT prevalence were low or incorrectly excluded patients who were CTNNB1 mutation negative but monosomy 6 positive. Additionally, this cohort may represent a local cluster within the state of Delaware; a state that continues to have a higher rate of malignancy as compared to the average. It is also possible that as we advance our understanding of molecular sub-groups that WNT is in fact a separate disease entity, as are the other subgroups, whose intrinsic molecular heterogeneity individually drives prognosis and treatment.

Poster # 257

ATYPICAL TERATOID RHABDOID TUMORS FROM 1989-2020 IN UTAH: OUTCOME AND LATE-ONSET CANCERS

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Background: Atypical teratoid rhabdoid tumors (ATRT) are clinically aggressive Central Nervous System (CNS) malignancies accounting for only 1-2% of all pediatric CNS cancers, but 40-50% of CNS cancers in infants under 1-year-old. Biallelic *SMARCB1* or *SMARCA4* inactivation defines ATRT genetic alterations; germline (GL) mutations define Rhabdoid Tumor Predisposition Syndrome (RTPS). Aggressive multimodal therapy improves survival to 30-40%. While initially chemotherapy-responsive, most children succumb to tumor progression. Standard surveillance recommendations for patients with RTPS remain undefined.

Objectives: To describe treatments and outcomes of University of Utah/Intermountain Primary Children's Hospital of children with ATRT.

Design/Method: In this IRB-approved study, we queried the Intermountain Health Care Cancer Registry to identify patients ages 0-25 years old diagnosed with ATRT. We reviewed medical charts, tumor histopathology, somatic and tumor genomic analyses, and family pedigrees. Data were analyzed using descriptive statistics, univariate hazard ratios, log-rank tests, and survival curves. Multimodal treatment included maximal safe resection, standard-dose chemotherapy, individualized radiation, and high-dose chemotherapy/stem-cell rescue.

Results: Between 1998-2020, 37 children with ATRT were identified, including 20 sporadic, and 17 syndromic tumors from 11 families, the latter harboring SMARCB1 GL mutations. The overall survival (OS) was 40% and significantly higher in the sporadic cohort. There were 8 deaths in the sporadic versus 13 deaths in the familial cohort (P=0.004). However, 6 children in the familial cohort underwent supportive care only. The OS in all children undergoing tumor-directed therapy was 50%, with 7 deaths in each cohort (p=0.060). Univariate Hazard ratios identified age < 1-year-old, posterior fossa location, and metastases at diagnosis as significant adverse prognostic factors. While most children in the familial cohort were < 1-year-old when diagnosed, 3 children from one family were diagnosed at ages 28, 46, and 48 months.

Four members from 3 families with RPDS were subsequently diagnosed with cancers, including a 4-year-old with asymptomatic intraventricular ATRT detected by surveillance imaging. Three adults not undergoing scheduled surveillance imaging were diagnosed with symptomatic cancers: one with a molecularly distinct 2nd ATRT 15 years after initial ATRT, one with a localized undifferentiated sarcoma, and one with widely metastatic lung adenocarcinoma.

Conclusion: Aggressive multimodal tumor-directed therapy improves survival in children with sporadic and familial ATRT. GL testing should be performed in all patients diagnosed with ATRT, as ATRT can present well outside of infancy in individuals with RTPS. The onset of cancer in adults with RTPS underscores the need to establish effective screening strategies and expanded counseling.

Poster # 258

DETECTING AND CHARACTERIZING EXTRACHROMOSOMAL DNA IN MEDULLOBLASTOMA AT SINGLE CELL RESOLUTION

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Background: Extrachromosomal circular DNA (ecDNA) is an important driver of aggressive cancers, including medulloblastoma (MB), the most common malignant pediatric brain tumor. It can play a role in the development of treatment resistance and is associated with poor outcomes.

Objectives: To utilize 'multiome' single cell sequencing to understand intra-tumoral heterogeneity in medulloblastoma human tumors and in Patient Derived Xenografts (PDX) with respect to ecDNA sequence diversity copy number variation, and gene expression. Our aim is to better understand how different ecDNA variants and ecDNA-amplified oncogenes contribute to intra-tumoral heterogeneity in primary tumors and in PDX models and their effect on disease

progression

Design/Method: Analysis of multiome single-cell RNA- and ATAC- sequenced tumor and PDX samples derived from medulloblastoma patients.

Results: Whole genome sequencing (WGS) of a tumor derived from a SHH MB patient with heterozygous somatic TP53 mutation identified two distinct ecDNAs, a 3.2Mbp amplicon comprising 3 regions of chr1 and another 4.5Mbp amplicon comprising 23 segments originating from chr7 and chr17. We have now simultaneously analyzed the accessible chromatin and gene expression in single cells of the human tumor and of a PDX derived from this tumor, using multiome single-cell ATAC-seq and gene expression (10X Genomics). We then used multimodal analysis with the Seurat tool to describe the tumor cell type, gene expression, estimate ecDNA copy number and variant signature. As a result, we have determined that the ecDNA high copy number cells from the human tumor account for the majority of the cells in the PDX, indicating a clonal evolution.

Conclusion: EcDNA can be identified and quantified in both a patient and PDX model. By identifying differential genes, can determine cell types that contribute to intra-tumoral heterogeneity. Cells that are identified as ecDNA high in the human tumor are seen as the predominant cells in the PDX model, indicating a clonal selection and evolution.

Poster # 259

A PHASE 1 STUDY OF MEBENDAZOLE WITH BEVACIZUMAB AND IRINOTECAN IN HIGH GRADE GLIOMAS

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Background: High grade gliomas (HGG) continue to have a dismal prognosis despite multimodal therapy. Mebendazole (MBZ) is a benzimidazole drug developed for the treatment of human helminthic infections. In vitro data have suggested that MBZ has efficacy in numerous cancer models. MBZ is able to cross the blood brain barrier, making it a strong candidate for the treatment of CNS tumors. We conducted a phase 1 trial (NCT01837862) to evaluate the safety of Mebendazole in combination with bevacizumab (BVCZ) and irinotecan (CPT-11), which have demonstrated efficacy in HGG.

Objectives: To determine the maximally tolerated dose of MBZ when given in combination with BVCZ and CPT-11 in children and young adults with high-grade gliomas, as well as to describe the progression-free survival (PFS) and overall survival (OS) for this group.

Design/Method: Patients between 1 and 21 years of age with a diagnosis of HGG, including H2K27m mutated diffuse midline gliomas (DMG), were enrolled in a 3+3 design to escalating doses of MBZ in combination with BVCZ 10mg/kg/dose and CPT-11 150mg/m2/dose (or 350mg/m2/dose for subjects on enzyme-inducing anticonvulsant drugs). Subjects were eligible in the upfront setting after completion of radiation or at the time of progression. MBZ was taken

orally twice per day continuously and BVCZ and CPT-11 were given intravenously on days 1 and 15 of a 28-day cycles.

Results: Between 2015 and 2020, 10 subjects were enrolled at MBZ 50mg/kg/day (n=3), 100mg/kg/day (n=4), and 200mg/kg/day (n=3). One subject assigned to 100mg/kg/day was not evaluable. Seven subjects had a diagnosis of DMG, one subject had anaplastic astrocytoma, and one subject had a spinal HGG. All subjects received radiation and two subjects were treated in the relapse setting. There were no dose limiting toxicities. All subjects were removed from treatment due to progressive disease. The most frequent G3/G4 AEs were neutropenia (n=3), and lymphopenia (n= 4). The overall response rate was 33% with two subjects achieving a partial response and one subject achieving a complete response which was sustained for 10 months. The PFS and OS from the start of study treatment were 4.7 months and 11.4 months, respectively.

Conclusion: MBZ was safe and well tolerated when administered with BVCS and CPT-11 at doses up to 200mg/kg/day. Further studies are needed to determine the efficacy of this treatment.

This research was supported by drug supply from Janssen R&D.

Poster # 260

PEDIATRIC LOW-GRADE GLIOMAS-RAPID PROGRESSION FOLLOWING DISCONTINUATION OF BRAF/MEK TARGETED THERAPY

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Background: Pediatric low-grade gliomas (PLGG) encompass diverse pathological entities and comprise 30% of pediatric central nervous system (CNS) tumors. Nonresectable PLGG represents a complex chronic medical condition, posing significant short and long-term therapeutic challenges. Despite initial responses to cytotoxic chemotherapy, disease progression is common. Recently developed panel-based molecular assays permit timely identification of specific targetable genetic alterations, most commonly involving the Ras/MAP kinase pathway, including *KIAA1549*::*BRAF* fusion and *BRAF* pV600E alterations. Medications targeting the specific pathogenic alteration or the activated pathway have resulted in remarkable responses, thus extending therapeutic options for treating children with these challenging tumors. However, drug selection, treatment duration, response durability, and late effects are not well-characterized.

Objectives: To describe the University of Utah/Primary Children's Hospital experience involving children with nonresectable, symptomatic, progressive PLGG molecularly characterized by BRAF/MEK alterations.

Design/Method: We conducted a review of medical records, imaging studies, tumor pathology, and genomic evaluations. Treatments included vemurafenib, dabrafenib, trametinib, and Day101 given alone or in combination. Data were analyzed using descriptive statistics.

Results: Between 2017-2021, 19 children (17 with prior progressive disease (PD) despite cytotoxic chemotherapy) ages 0.5-18 years-old, with nonresectable, symptomatic, progressive PLGG with documented BRAF alterations were treated with BRAF/MEK-targeted agents for ≥ 6 months. Nine remain on therapy with sustained minor or partial responses; 1 experienced mixed imaging response but clinical deterioration; 1experienced PD.

Eight patients completed planned therapy: 3 with Ganglioglioma WHO grade I and *BRAF* pV600E mutation; 5 with Pilocytic Astrocytoma WHO grade I; 2 with *KIAA1549*::*BRAF* fusion, and 3 with *BRAF* pV600E mutations. Mean and median age at diagnosis were 6.2 and 5 years, respectively (range 0.75-17.5 years). Mean therapy duration was 23 months (range 12-36 months). Two patients remain off-therapy with sustained partial responses (PR) for 9 and 12 months, respectively. However, 6 patients, each of whom had sustained ≥50-75% tumor size decrease on therapy, experienced rapid clinical and imaging PD at a mean of 4.1 months following treatment discontinuation. We restarted MEK/BRAF-targeted therapy in each patient. Within 1-3 months, each patient experienced robust clinical improvement associated with radiographic imaging response of MR or PR and no significant adverse treatment effects.

Conclusion: While targeted BRAF/MEK inhibition yielded robust, durable responses in these children with non-resectable PLGG with BRAF/MEK pathway alterations, rapid symptomatic PD following therapy discontinuation was common. Short interval MRI following targeted therapy completion is thus indicated. Rapid re-initiation of targeted therapy is effective. Optimal treatment duration remains undetermined. Continued surveillance is imperative.

Poster # 261

SINGLE-AGENT BEVACIZUMAB IN THE TREATMENT OF SYMPTOMATIC CERVICOMEDULLARY BRAINSTEM LOW GRADE GLIOMA

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Background: Bevacizumab-based therapies have been utilized effectively as single or combination therapy of refractory/recurrent pediatric low-grade gliomas. Its efficacy for symptomatic cervico-medullary low-grade gliomas (cmLGG) in the upfront and recurrent setting is less known.

Objectives: To report our retrospective single institutional experience from 2015-2021 with single agent bevacizumab in the upfront and recurrent setting for symptomatic cmLGG using standard or increased interval dosing. Clinical and radiographic responses were analyzed.

Design/Method: Retrospective review of 6 consecutive patients with symptomatic cmLGG treated with single agent bevacizumab at Rady Children's Hospital San Diego from May 2015 to April 2021.

Results: Six consecutive patients (4 female, 2 males, ages 2-12 years) with newly diagnosed (n = 3) and recurrent/refractory (n = 3) symptomatic non-disseminated cmLGG (5/6 biopsy proven, 2

BRAFV600E, 2 BRAF-KIAA1549) were treated with bevacizumab from 2015 - 2021. All patients demonstrated a radiographic response most pronounced on post gadolinium T1-weighted magnetic resonance imaging (2 complete, 4 partial) at a median of 8 weeks (range 2-12). Clinical response was seen in all patients with improvement in cranial nerve abnormalities (3 recurrent/refractory, 1 newly diagnosed), strength (2 recurrent/refractory, 2 newly diagnosed), pain (2 recurrent/refractory) and anorexia (1 newly diagnosed). Treatment was overall well tolerated with discontinuation in one patient due to transient proteinuria, which subsequently resolved. Following treatment with bevacizumab, 3 patients experienced disease progression while on carboplatin, one of whom was successfully rechallenged with bevacizumab. At a mean follow up of 7 months, all patients are stable without disease progression.

Conclusion: Single-agent bevacizumab may be effective in the management of symptomatic newly diagnosed and recurrent/refractory cmLGG that warrants further evaluation in a clinical trial setting.

Poster # 262

MACROCYTOSIS WITH CARBOPLATIN MONOTHERAPY IN PEDIATRIC LOW GRADE GLIOMA: A SEVEN PATIENT CASE SERIES

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Background: Carboplatin is used to treat solid tumors of the head, neck, and ovary in adults. In pediatrics, it may be used as monotherapy to treat low grade glioma. Macrocytosis can be used as an indicator of oral medication compliance and has been associated with improved outcomes in certain adult solid tumors treated with carboplatin. Macrocytosis during treatment with carboplatin monotherapy for LGG has not been reported.

Objectives: To describe the clinical course of seven pediatric patients receiving carboplatin monotherapy for LGG who developed macrocytosis (>2 standard deviations above normal, based on age) during treatment, which resolved without intervention.

Design/Method: Seven patients, ages 3-13 years old, with confirmed LGG received carboplatin (560mg/m^2) monthly for a planned 12-month course. The first patient was identified while receiving treatment, then two more were found prospectively; the remaining four patients were discovered upon retrospective chart review. Their electronic medical records were reviewed for clinical and laboratory data including hematologic parameters, carboplatin start and end dates, onset and resolution of macrocytosis, levels of folate, B12, fetal hemoglobin, and thyroid-stimulating hormone (TSH), and interventions for macrocytosis.

Results: Five patients had optic pathway gliomas, four of whom also had Neurofibromatosis type 1. The other two had LGG of the brainstem. One patient received only eight doses due to an allergic reaction, after which carboplatin was discontinued. Of the six patients who received all 12 doses, two had 25% dose reductions due to neutropenia. The median time to macrocytosis was 15

weeks after the start of the carboplatin. The three of the patients were identified while receiving treatment had a work up of this finding. All three patients had normal folate levels, one had a low B12 level (185 pg/mL) and was given supplemental oral cyanocobalamin, and two had slightly elevated fetal hemoglobin (2.5-3%). Of the two patients who had thyroid studies, one had high TSH, likely related to other endocrinopathies from prior CNS radiation. The median time to resolution of macrocytosis was 16 weeks after completion of the carboplatin.

Conclusion: These seven patients with LGG developed a reversible macrocytosis following the start of carboplatin monotherapy. Only one of the three patients who had a work up for the macrocytosis received a supplemental vitamin as an intervention for an elevated mean corpuscular volume. Larger studies are needed to determine whether this temporary macrocytosis warrants a hematology work up and whether this finding has any implications for treatment outcome.

Poster # 263

INCREASED EPIGENETIC AGE IN CHILDHOOD CANCER SURVIVORS

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Background: Pediatric cancer survivors remain at risk for numerous late effects of therapy and have shown signs of increased frailty. The specific mechanisms at play are unclear but epigenetic modulation may play a role.

Objectives: To evaluate epigenetic age (biological age compared to chronological age) in childhood cancer survivors and healthy matched siblings

Design/Method: This cross sectional pilot study included ten pediatric solid tumor survivors who received intensive chemotherapy with or without radiation and were a minimum of five years from treatment and ten healthy biological siblings. Peripheral blood was obtained from each subject and evaluated for DNA methylation patterns, including the Horvath markers, to provide a predicted epigenetic age (biological age compared to chronological age) for each subject. Participants and their parents provided health and lifestyle information including body mass index (BMI) and completed Pediatric Quality of Life (QOL) questionnaires. Epigenetic age for both groups was compared using paired t-test. Spearman analysis was used to correlate BMI and QOL with epigenetic age in both groups.

Results: Seven males and three females comprised the survivor group, and four males and six females comprised the sibling group. Mean chronological age for survivors was 12.1 ± 4.1 years and 13.6 ± 4.44 years for the sibling cohort (mean ± SD). Solid tumor diagnoses in the survivor cohort included rhabdomyosarcoma (n=2), neuroblastoma (n=5), Ewing sarcoma (n=1), and Wilms tumor (n=2). Mean time from end of therapy to time of consent and blood draw for survivors was 7.92 years (range 5 – 14.92 years). Childhood cancer survivors showed increased epigenetic age, with an increased biological age compared to chronological age, when compared to the healthy sibling cohort (1.85 ± 4.02 years vs 0.16 ± 2.83 years) (mean ± SD). This difference in epigenetic aging was statistically significant (mean difference 1.69 ± 2.08 years, p=0.030). There was a

moderately strong positive correlation between BMI and increased epigenetic age for survivors (Spearman correlation 0.54) but not for healthy siblings (Spearman correlation 0.28).

Conclusion: Childhood cancer survivors have increased epigenetic age when compared to their healthy siblings. Epigenetic modulation via DNA methylation may be a potential mechanism underlying this aging process and the well-known frailty phenotype seen in childhood cancer survivors.

Poster # 264

INDEPENDENCE AND SOCIAL ATTAINMENT IN IRRADIATED LONG-TERM SURVIVORS OF CHILDHOOD CRANIOPHARYNGIOMA

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Background: Craniopharyngioma is a locally aggressive sellar/suprasellar brain tumor with a bimodal distribution most often effecting children and elderly adults. Craniopharyngioma is often associated with the hypothalamic-pituitary axis, visual pathways, and primary cerebral arterial circulation. Tumor and treatment pose severe and wide-ranging complications that threaten functional independence and social attainment.

Objectives: The aim of our study was to report on long-term outcomes in a cohort of irradiated survivors of childhood craniopharyngioma.

Design/Method: The medical records of 89 survivors were reviewed. All patients were treated with conformal photon radiation therapy (CRT) between 1999-2013. The median age at CRT was 7 years (range 1-17). The median age at the time of most recent assessment was 25 years (range 16-36). Quantitative and qualitative assessment of four primary categories was performed: physical and general characteristics, complications and comorbidities, psychosocial development, and education and professional outcomes.

Results: The most common impactful and concerning complications were impairment of vision (n=61), diabetes insipidus (n=57), CSF shunt (n=54), sleep disorders (n=49), and dyslipidemia (n=48). Most survivors were found to live with their immediate family (78.7%), have a driver's license (64.9%), and require academic accommodations (68.5%). Only 46.1% continued education beyond secondary school. Survivors were commonly found to have deficits in living independently, succeeding professionally, socializing, and maintaining age-appropriate neuropsychological function. The majority (89.9%) of survivors were found to be overweight or obese with a median BMI of 32.6 (range, 18.4-61.8).

Conclusion: Survivors of childhood craniopharyngioma experience wide-ranging complications and co-morbidities from tumor and treatment which impact quality of life, independence, and social attainment. Select survivors in our series were able to attain independence and higher education; however, many face poor general health, limited social function, lack of dependence,

and low achievement. Future studies should examine tumor and treatment-related risk factors as well as environmental hardship and socioeconomics to identify opportunities for interventions.

Poster # 265

THE ASSOCIATION OF HEALTH STATUS AND QUALITY WITH PHYSICAL ACTIVITY IN CHILDHOOD CANCER SURVIVORS

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Background: Childhood cancer survivors (CCS) are at risk for multiple therapy-related late effects. Physical activity can help minimize the burden of late effects, but CCS' rates of physical activity remain lower than those of siblings or age-matched peers. Perception of survivor health status and overall health quality may impact CCS' levels of physical activity.

Objectives: This study aimed to determine how survivor/parent-proxy perception of survivor health status and overall health quality are associated with physical activity in CCS**.**

Design/Method: This is a cross-sectional, retrospective study of CCS aged 6-21 years and ≥1 year off-therapy, who participated in an institutional CCS cohort from January 1, 2018, to September 30, 2020. Low self-reported physical activity was defined as <5 days per week with ≥60 minutes of activity per day. Perceived health status was assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health measure with poor health status defined as responses of "fair" or "poor" on questions related to overall, physical, and mental health. Late effects were defined as therapy-related or non-cancer chronic conditions present at survey completion; presence of ≥2 late effects was dichotomized as poor health quality. Multivariable logistic regression was performed to identify any associations between physical activity and a) perceived health status or b) health quality.

Results: Of the 285 CCS (mean age at survey: 14.7±4.2 years; mean age at diagnosis: 6.1±4.6 years), 71.6% reported low physical activity. Negative perceived overall, physical, and mental health was present in 5.6%, 10.5%, and 15.8% of CCS, respectively. Poor health quality was found in 49.8% of CCS. Multivariable analyses did not show a significant association between perceived poor overall health status (OR 1.8, 95% CI 0.46-7.03, p=0.396) and low physical activity, but did yield significant associations between perceived poor physical (OR 6.1, 95% CI 1.38-27.44, p=0.017) and mental (OR 3.5, 95% CI 1.27-9.61, p=0.015) health status and low physical activity, when controlling for survey respondent, sex, race/ethnicity, treatment intensity, and time off-therapy. There was no correlation between health quality and physical activity (OR 1.0, 95% CI 0.56-1.71, p=0.934).

Conclusion: Perceived negative physical and mental health status were associated with low physical activity, while health quality was not. Addressing perceptions of physical and mental health as part of future targeted physical activity interventions in CCS will be important in optimizing both the efficacy of these interventions and the long-term health outcomes of this population.

Poster # 266

RURAL HEALTH CHALLENGES IN OPTIMAL FOLLOW-UP CARE AMONG CHILDHOOD CANCER SURVIVORS

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Background: Children with cancer and their families from rural and non-urban areas face unique challenges across the continuum of care, from active treatment to survivorship. Oklahoma is a highly rural state with thirty-four percent of residents living in non-urban areas. Therefore, given the known burden of late effects, health equity for this population requires attention to potential geographic disparities in optimal follow-up care in order to mitigate adverse health outcomes.

Objectives: The primary purpose of this study was to construct a childhood cancer survivorship cohort in Oklahoma, through the integration of cancer registry, electronic health record, and geospatial data, and identify potential disparities in optimal follow-up care among survivors from non-urban areas.

Design/Method: The Oklahoma Childhood Cancer Survivor Cohort was based on all patients ≤18-years-old at diagnosis captured by the cancer registry between January 1, 2005 and September 24, 2014 (to allow for at least seven years of follow-up data for all survivors). Patients with documented death or relapse, non-analytic cases, and those not seen in the pediatric oncology clinic were excluded. The primary outcome was whether survivors were seen in the pediatric oncology clinic between 2020-2021. To assess the potential impact of the COVID-19 pandemic, clinic attendance from 2018-2019 was also analyzed. The primary predictor of interest was rurality, defined by Rural-Urban Commuting Area coding based on zip code. Other explanatory variables included age, gender, race/ethnicity, late effects risk strata, and primary diagnosis.

Results: A total of three-hundred and twenty-one survivors met eligibility criteria, of whom 41.1% (n=132) were not seen in the pediatric oncology clinic between 2020-2021. There were significant differences (p=0.036) in optimal follow-up care with 53% of survivors from large towns (n=64) and 45% of survivors from small town/isolated rural areas (n=49) without a documented clinic visit compared with 36% of survivors from urban areas (n=205). There were no significant differences in follow-up by race/ethnicity, gender, age at diagnosis, or late effects risk strata. In the two years preceding the COVID-19 pandemic, 31% of survivors were not seen in the clinic with observed differences among survivors from urban, large town, and small town/isolated rural areas at 25%, 47%, and 26% with suboptimal follow-up, respectively (p=0.011).

Conclusion: Survivors from non-urban areas were less likely to receive optimal follow-up care compared to survivors from urban areas. The COVID-19 pandemic worsened optimal follow-up care and disproportionately affected survivors from large town and small town/isolated rural areas.

Poster # 267

USER PREFERENCES FOR A CHILDHOOD CANCER SURVIVOR MOBILE APPLICATION: A CROSS SECTIONAL SURVEY STUDY.

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Background: The population of childhood cancer survivors (CCS) is growing, along with the number of CCS who will experience physiological and psychosocial late effects. CCS require long-term follow-up (LTFU) care and resources to increase their engagement, and ownership of health practices. CCS and their families have reported preferring an electronic or web-based educational messages. Mobile health (mHealth) interventions provide such a platform including the use of mobile applications (apps).

Objectives: There is an urgent need to develop new ways of healthcare delivery that are compatible with modern technology and societal preferences. The Childhood Cancer Survivor Program (CCSP) at the University of Minnesota (UofM) sought to describe the preferences of CCS usage of a mobile application specific to their survivor-focused care.

Design/Method: As a program evaluation quality improvement project, a cross sectional survey was conducted with 140 childhood cancer survivors (or their parents) of all ages (5-48) receiving care in CCSP at the UofM. Participants completed a survey through their routine clinical care at yearly appointments describing their preferences and expectations for a mobile application specific to their survivor-focused care. The survey included 9 items focusing on psycho-social care and care coordination created by review of the relevant CCS mHealth literature. The data collected were analyzed using descriptive statistics.

Results: Most participants (86%, 120/140) reported being very willing or willing to use an app on their phone that was specifically designed for CCS. Most survivors reported being very willing or willing to complete surveys (83 %, 116/140) and participate in research through an app (80%, 112/140). Survivors preferred to be contacted via text message (69 %, 97/140). Majority of participants (67%, 94/140) wanted UofM to be in charge of the app as opposed to an app that would be created by some other hospital/medical center. Some of the options survivors would find most useful in such an app were mainly related to connectivity with other survivors and increasing their knowledge about survivorship related health topics.

Conclusion: CCS from a single institution academic medical center report being willing to use mobile health interventions (app) as part of their routine survivor-focused care. Such intervention could have impact on survivor engagement, ease the transition from childhood to adult models of care, improve survivor knowledge of late effects and skill building in self-management. Apps could serve as an accessible and trusted repository of psychosocial resources and ultimately become part of a program's clinical research infrastructure.

Poster # 268

AYA ONCOLOGY CARE MODEL SHOWS INCREMENTAL BENEFIT AND CAN SMOOTH TRANSITION IN SURVIVORSHIP CARE

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Background: Adolescents and young adults (AYAs, defined as ages 15-39 years) with cancer have unique supportive care needs, including but not limited to psychosocial, fertility, and vocational support. There are limited data to identify the best care model to support the vulnerable AYA population. We sought to compare the impact of AYA physician visits versus interdisciplinary team (IDT) care on AYA-specific resource identification and utilization.

Objectives: The University of Wisconsin Carbone Cancer Center (UWCCC) launched its AYA Oncology Program in January 2021 with a novel telehealth two-step approach: a one-on-one oncology physician visit followed by an interdisciplinary team (IDT) meeting. The aim of this study was to evaluate the effectiveness of this model by quantifying resource utilization following each step to determine the incremental benefit from an AYA-specific clinic and the discrete benefit of interdisciplinary care.

Design/Method: The UWCCC AYA Oncology Program sees any patients who are currently aged 15-39 years, regardless of age at time of diagnosis. We performed a retrospective chart review of the first 35 patients who were seen by the UWCCC AYA Oncology Program to measure resource utilization prior to the AYA clinic and following the one-on-one physician visit and IDT meeting,

Results: Of the 35 patients analyzed, four were survivors of childhood cancer, with an average age of three years at time of diagnosis. Prior to their AYA clinic visit, patients in the entire cohort saw an average of 2.51 AYA-specific services. An average of 4.45 novel resources were identified by the AYA Oncology Program per patient, which represented a statistically significant increase in resource identification ($p < 0.001$). This included an average of 2.54 and 1.91 additional resources identified per patient through the AYA physician visit and IDT meeting respectively.

Conclusion: Initial data show a quantifiable benefit for AYAs with cancer to be seen by an AYA-specific interdisciplinary program. The UWCCC AYA Oncology Program is a model for effectively meeting resource needs for AYAs with cancer in a limited resource setting that has implications for expanding AYA cancer care. Improved resource identification may lead to more likely utilization of resources for long-term survivors; thus, AYA programs can perhaps serve as a conduit to smooth transitions from pediatric to adult care.

Poster # 269

IMPROVING KNOWLEDGE OF FOLLOW-UP CARE AND LATE EFFECTS IN SURVIVORS: A QUALITY IMPROVEMENT PROJECT

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Background: There are more than 400,000 pediatric cancer survivors living in the United States today while greater than 60% experience at least one treatment-related late effect altering their quality of life. Studies reveal more than half of survivors do not adhere to long term follow up care after treatment completion. We hypothesized that the majority of caregivers/survivors lack knowledge regarding the need for long term follow-up and risks for late effects. We developed an intervention to improve understanding of the need for life-long follow up along with patient specific late effects utilizing quality improvement methodology.

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 leukemia survivors within two years from completion of treatment. We designed a leukemia specific late effects educational brochure and surveyed caregivers or patients older than 13 with 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? During the visit, the oncology provider verbally reviewed correct answers (life-long, risk for late effects, and patient specific side effects, respectively) using the brochure. The survey was repeated at the next appointment and at a third time point >12 months from first survey to assess long-term retention of information. 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 three PDSA cycles with 14 patients total. Two time points were completed with the same respondent in 14 patients, and three time points in 10. From baseline to last visit, percent of correct responses for follow up duration increased from 29% to 50%. The proportion who identified at least two late effects correctly increased from 64% to 86%. Out of 14 patients, three reported anxiety when late effects were discussed.

Conclusion: Improving knowledge of follow-up care among pediatric leukemia survivors is a vital need. We showed an educational intervention can increase and sustain knowledge regarding need for lifelong follow-up in survivors and late effects. Anxiety was an unexpected finding.
We are currently measuring the frequency of anxiety with late effects discussion in a similar project with solid and brain tumor survivors.

Poster # 270

QUALITY OF LIFE IN CHILDREN WITH ADVANCED CANCER: A MULTICENTER LONGITUDINAL PILOT STUDY

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Background: Children with advanced cancer, defined as relapsed, progressive, or refractory disease, are at-risk for experiencing a spectrum of symptoms that can negatively impact quality of

life. Little is known about the effects of symptoms and important disease and clinical characteristics on quality of life over time in this population.

Objectives: The purpose of this multicenter pilot study was to describe quality of life in children with advanced cancer and the effects of symptom adverse events, disease status, and cancer-directed treatment on quality of life over six months.

Design/Method: A prospective and longitudinal descriptive study design was used to collect quality of life and symptom adverse event data biweekly from children aged 2-18 with advanced cancer of any type. Quality of life was measured using the PedsQL Cancer Module, and the Pediatric PRO-CTCAE was used to elicit information about symptom adverse events. Disease and clinical characteristics were extracted from the medical record. Descriptive statistics were used to describe sample characteristics, health-related quality of life and symptom attribute (frequency, severity, interference) mean scores. Higher quality of life scores correspond with better quality of life. Generalized linear mixed models using random effects were used to evaluate the effects of symptom attribute scores, disease status, and cancer-directed treatment on total quality of life scores.

Results: Forty-nine children participated in the study (mean age = 11.1 years [range: 2-18]) with diverse race/ethnicity (female (33%), non-white (29%), Hispanic or Latino (35%)) and disease type (hematologic malignancy (37%), solid tumor (45%), central nervous system tumor (18%)). The mean total PedsQL score was 73.86 for the total sample across all time points. Total PedsQL mean scores varied by diagnostic group. Children diagnosed with a hematologic malignancy had higher quality of life scores compared to children diagnosed with a solid tumor or central nervous system tumor (78.33 vs. 71.42 vs. 70.91, respectively). Generalized linear mixed models did not demonstrate meaningful effects of disease status (active disease and recent disease progression) and cancer-directed treatment on total PedsQL scores. Meaningful effects on reduced quality of life were found for fatigue severity as well as frequency of anorexia, anxiety, nausea, and pain.

Conclusion: The presence of poorly controlled symptoms is frequently overlooked to provide a curative approach, leading to reductions in quality of life. Given their negative effect on quality of life, clinicians should prioritize fatigue, anorexia, anxiety, nausea, and pain for monitoring and intervention during the advanced cancer trajectory.

Poster # 271

DEVELOPMENT OF A TRANSITION-TO-ADULT-CARE CLINIC FOR PEDIATRIC ONCOLOGY TEENS AND YOUN ADULTS

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Background: As many as 95% of pediatric oncology survivors will face at least one treatment-related chronic health condition by middle age. Transitioning from pediatric medical care to adult medical care can present a variety of challenges, including problems associated with accessing adult-appropriate health services and continued survivorship-specific care. In fact, only 32% of

adult childhood cancer survivors report receiving cancer/survivorship-focused care.

Objectives: To develop and evaluate a multi-disciplinary program aimed at improving the transition to adult care for pediatric oncology survivors and their families.

Design/Method: To develop our program, we 1) Conducted a literature review to identify the successes and difficulties encountered by similar transition clinics for children with chronic disease, and 2) Performed a needs assessment survey of both pediatric oncology survivors and guardians. Subsequently, a multi-disciplinary planning team, including physicians, nursing, and psychology specialists developed specific programing for the transition clinic, using both expert opinion and existing formats within the literature. Patient and guardian-reported effectiveness, acceptability and appropriateness are being collected via survey before, immediately after, and 6 months following program participation.

Results: The Pediatric-to-Adult Care Transition Program had its first quarterly clinic with four survivor participants and two parents. The pilot program consists of regular transition readiness assessments starting at age 16, attendance at a multidisciplinary, educational clinic at age 18-20, and a planned follow-up formal transition appointment one year later. The clinic consisted of a survivorship visit and specialized sessions for both survivors and guardians. Survivor sessions included practice relaying medical history, scheduling a doctor's appointment, and learning about mental health resources and school/work accommodations. Guardian sessions included sessions regarding communication with teenagers and fostering teenager independence. There were also joint sessions reviewing healthcare resource needs (e.g. insurance, transportation) and discussing genetics counseling. While based on few numbers to date, on 1-10 Likert scales, and survivors' level of preparedness of the transition to adult healthcare rose from an average 6 to 7, and guardians' rose from 5.5 to 6. Program usefulness was rated at 8.25 (patients) and 10 (guardians). There were no suggestions for modifications to the program.

Conclusion: Preliminarily, our pilot transition clinic was acceptable and well-received by both pediatric oncology survivors and their guardians. This program provides resources and skills development relevant to the transition from pediatric to adult medical care. As additional quarterly programs occur, we will continue to assess the utility of our transition program, while incorporating participant feedback.

Poster # 272

HEALTHY BONES HEALTHY LIFE: EFFECT OF PHYSICAL ACTIVITY ON BONE HEALTH IN PEDIATRIC CANCER SURVIVORS

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Background: While childhood cancer treatment efficacy has dramatically improved survival rates, treatment has devastating effects on bone health in pediatric cancer survivors (PCS). In healthy children, bones are strengthened by the mechanical stress of physical activity (PA). PA may

improve bone loss associated with cancer treatment. Data is limited on the effects of PA on bone health in PCS, and treatment guidelines to improve bone mineral density (BMD) and lifelong bone health are lacking.

Objectives: To evaluate the effect of PA on bone health and investigate the mechanism by which PA impacts bone health in PCS.

Design/Method: This prospective cohort study enrolls survivors (ages 5-18) of acute lymphoblastic leukemia (ALL) or lymphoma that are 1-13 months post-treatment. At baseline and at 6 months, metabolic health (laboratory evaluation and body composition), bone density (dual x-ray absorptiometry scans) and activity level (accelerometer data) are evaluated. To evaluate our primary outcome (effect of PA on bone health), the change in bone density between baseline and 6 months will be compared between participants classified as low and high activity level using a two-independent samples t-test.

Results: We report baseline data in our first 22 patients enrolled. The mean age at study entry is 10.2 years, and the mean age at cancer diagnosis is 7.7 years. Study participants are 59% male (n=13), 73% Caucasian (n=16), 73% have a history of B-cell leukemia (n=16) and 100% were treated with chemotherapy (n=22). Eleven patients (69%) had vitamin D deficiency. Three participants (14%) had low lumbar spine BMD Z-score (below -2.0), five participants (23%) had low femoral neck BMD Z-score and seven participants (32%) had low subtotal BMD. Participants spent mean 70.4% of time sedentary, mean 13.1% doing light activities and mean 18% performing moderate/vigorous physical activities. Participants spent mean 93.1% of time doing low vertical impact activities and mean 6.9% of time performing high vertical impact activities. Study recruitment, visit completion and analysis is ongoing.

Conclusion: Multimodal, longitudinal studies in PCS are feasible. Poor bone health is seen in ALL/lymphoma PCS after completion of therapy. Final results of this study may inform design of an interventional physical activity study to improve bone health in PCS.

Poster # 273

OVARIAN FUNCTION IN SURVIVORS OF RETINOBLASTOMA TREATED WITH INTRA-ARTERIAL MELPHALAN

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Background: Systemic exposure to alkylating agents, including melphalan, is associated with premature ovarian insufficiency and reduced fertility potential. Since 2006, intra-arterial melphalan has been used for ocular-sparing treatment of retinoblastoma. Data are lacking on whether intra-arterial melphalan is similarly associated with ovarian dysfunction.

Objectives: We sought to describe biochemical measures of ovarian function in pubertal female survivors of retinoblastoma treated with intra-arterial melphalan.

Design/Method: This is a single-institutional, retrospective study of female retinoblastoma survivors treated with intra-arterial melphalan between 2006-2019 with attained age ≥ 10 years and at least one set of gonadotropins (follicle stimulating hormone [FSH] and luteinizing hormone [LH]). Patients with history of stem cell transplantation were excluded. Data on treatment exposures, gonadotropins, and menstrual regularity were abstracted from the medical record. Normal gonadotropins values were FSH and LH <12 mU/ml.

Results: Eleven survivors were eligible (median age at diagnosis: 1 year, range 0.5-9; median age at study: 14.5 years, range 11-19). Seven patients (63.6%) had bilateral disease. Five patients (45.5%) had treatment with intra-arterial melphalan, carboplatin, and topotecan without any systemic chemotherapy. Four patients (36.4%) had intra-arterial melphalan and topotecan either alone or with systemic chemotherapy that did not include alkylating agents (IV carboplatin, n=1, IV carboplatin/etoposide/vincristine, n=2). All eleven patients had normal gonadotropins; six experienced menarche spontaneously and reported regular periods while five were pre-menarchal at last visit. No patient had symptoms of menopause.

Conclusion: In this small sample, all retinoblastoma survivors treated with intra-arterial melphalan had normal gonadotropins without menopausal symptoms. Longitudinal studies of larger cohorts will be required to confirm these findings.

Poster # 301

CLINICAL HEMATOLOGIC MANIFESTATIONS OF SARS-COV-2 INFECTION AND MIS-C IN HOSPITALIZED CHILDREN.

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Background: Hematologic complications of SARS-CoV-2 infection are well-recognised in hospitalized adults who develop a pro-thrombotic coagulopathy associated with increased mortality. Description of hematologic manifestations or their association with prognosis is limited in children with SARS-CoV-2 infection or multisystem inflammatory syndrome (MIS-C).

Objectives: Ascertain the following in hospitalized children with SARS-CoV-2 infection or MIS-C.

1. Prevalence of hemorrhage and thrombosis
2. Clinical description and management of hemorrhage and thrombosis
3. The relationship between patient's pre-existing comorbidities and occurence of hemorrhage and thrombosis
4. The role of hemorrhage or thrombotic events in causing mortality

Design/Method: An international multi-centered (15 hospitals in Canada, Iran and Costa Rica) retrospective registry was established to collect data on SARS-CoV-2 or MIS-C in hospitalized children between February 1, 2020 – May 31, 2021. This sub-study focused on hematologic manifestations. Study variables included demographics, pro-hemorrhagic or pro-thrombotic comorbidities, MIS-C diagnosis, clinical presentation, new hemorrhage or thrombosis during hospitallization, management and outcome.

Children were classified as having primary SARS-CoV-2 infection if it caused or prolonged the hospital admission and incidental SARS-CoV-2 if it did not affect hospital admission. MIS-C was diagnosed based on the World Health Organization (WHO) criteria. Hemorrhage severity was classified per the WHO criteria.

Results: Nine hundred and eighty-five children were enrolled and 915 (93%) had clinical information available; 385 (42%) had primary SARS-CoV-2 infection, 288 had MIS-C (31.4%) and 242 (26.4%) had SARS-CoV-2 identified incidentally. Ten children had thrombosis (5 primary SARS-CoV-2; 3 MIS-C; 2 incidental), 16 had hemorrhage (11 primary SARS-CoV-2; 4 MIS-C; 1 incidental) and 2 (MIS-C) had both. Comorbidities observed at a higher frequency in children with thrombosis and primary SARS-CoV-2 included congenital heart disease (p-value = 0.007) and central venous catheters (p = 0.04). Obesity (p-value= 0.002) and cytokine storm (p= 0.012) were significant pro-thrombotic conditions in MIS-C. Comorbidities identified at a higher frequency in children with hemorrhage and primary SARS-CoV-2 included age > 10 years (p = 0.04) and CVC (p= 0.03). Thrombocytopenia (0.001) and cytokine storm (0.02) were significant pro-hemorrhagic conditions in MIS-C. Prevalence of hemorrhage and thrombosis was similar between patients with primary SARS-CoV-2 infection (2.8%; 1.3%) and MIS-C (2%; 1.7%). Eleven patients died (1.2 %) with no deaths attributed to thrombosis or hemorrhage.

Conclusion: Hemorrhage and thrombosis with SARS-CoV-2 commonly occurred in children with pre-existing conditions. Thrombosis prevalence was lower than adults but higher than hospitalized children without SARS-CoV-2 infection. Complete understanding of SARS-CoV-2 related hematologic complications in children requires ongoing research.

Poster # 302

COVID-19 IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH CANCER

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Background: Pediatric oncology patients are at risk for poor outcomes with respiratory viral infections. Outcome data for COVID-19 in children and adolescent and young adults (AYA) with cancer are needed for both COVID-19 treatment and optimal modification of anti-cancer therapy. Moreover, COVID-19 data in pediatric cancer are sparse for obese/overweight patients, Hispanic/Latinx individuals, AYA, and chimeric antigen receptor T-cell (CAR-T) recipients, subgroups that are either predisposed to higher COVID-19 morbidity in the general population or adult oncology or at higher risk for adverse cancer outcomes (AYA, obesity).

Objectives:

- Define outcomes in children and AYA with cancer and COVID-19.
- Determine immune responses to COVID-19 infection in pediatric cancer.

Design/Method: We conducted a single center cohort study of patients younger than 25 years old with cancer and RT-PCR confirmed COVID-19. Fishers' exact test, and logistic regression were used for statistical analysis.

Results: We identified 87 patients with cancer and COVID-19. The median age was 12 years (0-24 years). The majority of the cohort was of Hispanic/Latinx ethnicity (n=63, 72%), and 42 patients were overweight/obese. Anticancer therapy included chemotherapy only (n=64), CAR-T (n=7), hematopoietic stem cell transplantation (HSCT, n=12), or CAR-T and HSCT (n=4).

There was no COVID-19 related mortality. Twenty-six patients (30%) required hospitalization for COVID-19 management; five required multiple hospitalizations. Nine patients (10%) had severe/critical infection, and 5 needed intensive unit care. Compared to COVID-19 infected patients without cancer, patients with cancer and COVID-19 were more likely to be hospitalized ($p<0.001$) and develop severe infection ($p<0.05$). COVID-19 resulted in anti-cancer therapy delays in 22 (34%) of 64 patients on active therapy (median delay =14 days).

Risk factors independently associated with hospitalization in a multivariable analysis included steroid exposure within 2 weeks prior to infection ($p=0.02$, OR=5.1), lymphopenia ($p=0.006$, OR=7.1), significant non-COVID infection ($p=0.046$, OR=6.6), and high COVID-19 viral load ($p=0.01$, OR=1.1). Ethnicity, age, obesity, and neutropenia were not associated with hospitalization. CAR-T recipients with B-cell aplasia tended to have severe/critical infection ($p=0.04$). A COVID-19 immune response was detected in 14 of 32 patients with available serology data.

Conclusion: A substantial proportion of children and AYA with cancer and COVID-19 require inpatient management. Morbidity may be particularly high in patients with CAR-T related B-cell aplasia. Unlike the general population, obesity and Hispanic/Latinx ethnicity were not associated with adverse outcomes. Viral load is a potential predictive biomarker for COVID-19 morbidity in pediatric cancer. Most patients with COVID-19 can be safely taken through anti-cancer therapy.

Poster # 303

COURSE AND TREATMENT OF COVID-19 INFECTION IN PEDIATRIC PATIENTS WITH ACTIVELY TREATED CANCER

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Background: The clinical course of actively treated pediatric cancer patients, who are simultaneously diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),

has been thought to be more severe than experienced by the general pediatric population; however, risk factors predictive of and treatment affecting clinical severity in this population have not been elucidated.

Objectives: We describe the clinical course, risk factors affecting clinical severity, and management of coronavirus disease 2019 (COVID-19) infection at a single institution.

Design/Method: Patients from a single institution that were diagnosed with SARS-CoV-2 between January 2020 and June 2021 while actively receiving cancer treatment, excluding transplant therapies, were retrospectively reviewed. Data collected included age of SARS-CoV-2 diagnosis, cancer diagnosis, gender, race and ethnicity, age-and-gender-adjusted body mass index at time of the SARS-CoV-2 diagnosis, clinical course and severity, symptomatology, and clinical outcome. Active cancer therapies and COVID-19 specific management given during course of infection were recorded.

Results: Of the 33 patients that met inclusion criteria, 14 (42.4%) were asymptomatic during infection course while 19 (57.6%) experienced symptoms, including 3 (9.1%) that developed MIS-C. A majority, 23 (69.7%) patients, required no institutional support while 10 (30.3%) required hospitalization, of which 80.0% required oxygen, 30.0% required intensive care, and 10.0% required intubation. Eighteen (54.5%) patients had at least 1 pre-existing comorbidity, with obesity as the most common. Twenty-two (66.7%) experienced some delay in cancer care due to low immune cell counts and/or inability to administer therapy because of isolation protocols. Ten (30.3%) received COVID-19 directed therapy during the course of the infection. Hospitalization rates (30.3%) and MIS-C development (9.1%) for our cohort were significantly higher than that found in the general, healthy pediatric population, although a lack of or mild symptoms predominated. Obesity was associated with increased odds of hospitalization (OR=25.5; p=0.002) and oxygenation requirements (OR=14.88; p=0.012).

Conclusion: For pediatric patients diagnosed with cancer within our cohort, the overall clinical course was mild, with a majority requiring no institutional support nor presenting with severe symptoms; this is consistent with the course found among healthy children infected with SARS-CoV-2. We do not recommend modifying the intensity or timing of cancer therapies given during course of the infection since modifications were not found to affect clinical severity. Further, we did not find it necessary to preemptively introduce COVID-19-specific treatment to improve clinical course.

Poster # 304

IMPACT OF COVID-19 PANDEMIC ON NEWLY DIAGNOSED PEDIATRIC LEUKEMIA AND LYMPHOMA PATIENTS

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Background: Coronavirus disease 2019 (COVID-19) has affected many aspects of cancer care delivery worldwide. Yet, the major threat for pediatric patients with leukemia and lymphoma continues to be the malignancy itself, with possible delays in diagnosis leading to increased morbidity and mortality. We hypothesized that newly diagnosed pediatric leukemia/lymphoma patients diagnosed during the COVID-19 pandemic presented with increase severity of illness and need for pediatric intensive care (PICU) due to delays in seeking medical care and exposure to SARS-CoV-2 infection.

Objectives: To report an analysis of the clinical characteristics, severity of illness and outcomes among newly diagnosed pediatric leukemia/lymphoma patients admitted to our PICU during the COVID-19 pandemic and compared them to admissions during the two previous years.

Design/Method: A retrospective chart review of newly diagnosed pediatric leukemia/lymphoma patients (≤ 21 years) admitted to our PICU between July 2018-February 2019 (pre-COVID) and March 2020-October 2021 (during COVID). Demographic and clinical characteristics associated with hospitalization and severity of illness were compared among patients.

Results: Out of 106 children with newly diagnosed leukemia/lymphoma, 64 were admitted during COVID and 42 patients pre-COVID, with a median age of 111 (1 - 248) months. The median time from onset of symptoms to hospitalization was 7 (2–120) days with a median PICU length of stay of 4 (2-67) days during COVID vs. 3.5 (1-35) days pre-COVID. The most common reasons for admission were hyperleukocytosis (33 vs. 23 patients) and large mediastinal mass/SVC syndrome (10 vs. 4). Mechanical ventilation and non-invasive ventilation (MV/NIV) were performed for 14 patients (22%) compared to 12 (28.5%) patients pre-COVID. Seven patients (11%) required vasopressors, 6 (9%) hemodialysis vs. 4 (9%) and 4 (9%) patients respectively pre-COVID. The median PRISM scores were not significantly different (4.5 vs. 5). Despite all patients having negative SARS-CoV-2 RT-PCR, history of exposure was present in 4 patients and other 3 had positive antibodies; these patients had longer PICU length of stay (median = 9 days). An increased rate of complications including cardiac arrythmias (6% vs. 2%), pulmonary hemorrhage (5% vs. 2%) and need for pericardial drainage (3% vs. 0%) was observed during the pandemic with no deaths occurring during hospitalization.

Conclusion: These findings demonstrated a higher incidence of complications and a slightly prolonged PICU stay for newly diagnosed leukemia/lymphoma patients during the pandemic. However, there was no statistical difference in severity of illness and need for MV/NIV, vasopressors, hemodialysis in our study population.

Poster # 305

MIS-C IN PEDIATRIC CANCER PATIENTS: RISK FACTORS AND CLINICAL FEATURES

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Background: Children with cancer are at risk of severe COVID-19 infections. Unique from adults, children are susceptible to Multisystem Inflammatory Syndrome in Children (MIS-C). Between 0.01% and 0.06% of children infected with COVID-19 develop MIS-C. However, little is known about MIS-C in children with cancer.

Objectives: Among children with cancer and COVID-19, evaluate the rate of MIS-C along with the clinical and sociodemographic characteristics and clinical course of those who develop MIS-C.

Design/Method: The Pediatric Oncology COVID-19 Case Report (POCC) collects de-identified clinical and sociodemographic data on children with cancer infected with COVID-19 from >100 US institutions. This analysis examines children with cancer (<21y at COVID-19 infection) who developed MIS-C. The following are described: MIS-C prevalence; clinical characteristics (cancer diagnosis, blood or marrow transplantation [BMT] status, disease status [new diagnosis vs. relapsed/refractory], time from last chemotherapy), and sociodemographic characteristics (age, sex, race/ethnicity, insurance); clinical course of COVID-19 (symptoms, level of support, changes in cancer therapy).

Results: Among 1,279 children with cancer and COVID-19, 23 (1.8%) developed MIS-C at a median age of 12 (interquartile range [IQR] 4-17), among whom 12 (52%) were Hispanic and 15 (65%) publicly insured. Nineteen (83%) had hematologic malignancies and 3 (13%) had received a BMT. At the time of infection, children had received chemotherapy a median of 14d (IQR: 4-52) prior, and 7 (31%) patients had an ANC <500. The most common symptoms were: systemic symptoms (n=18, 78%), respiratory (n=13, 57%) and gastrointestinal (n=10, 44%). Eighteen (78%) children were admitted to the hospital, 13 (57%) to the intensive care unit (ICU). Five (22%) required mechanical ventilation, 3 (13%) hemodialysis, and one (4%) extracorporeal membrane oxygenation (ECMO). Fourteen (61%) had their cancer-directed therapy changed. Seven (30%) children with MIS-C died; COVID-19 contributed to the death in five children while two died because of their cancer.

Conclusion: Children with cancer and COVID-19 can develop MIS-C, potentially at higher rates than in the general pediatric population. Additionally, the majority of children with MIS-C and COVID-19 have severe disease as indicated by a high hospitalization rate, and many of these patients require ICU admission and unfortunately die related to complications. More than half also have their cancer therapy changed, which has unknown implications on their long-term cancer outcomes. Pediatric oncologists can consider these risks as they evaluate children with cancer and COVID-19 and as they advise families regarding their risks of COVID-19 and the benefits of vaccination.

Poster # 306

MIS-C CARE PROCESS MODEL; IMPACT OF EVOLVING PEDIATRIC EVALUATION AND PROPHYLACTIC TREATMENT

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Background: A Pediatric subcommittee of the International Society of Thrombosis and Haemostasia (ISTH) published guidelines for the prophylaxis in children at risk for thromboembolic events (TE). Our institution developed two care process models (CPM) with algorithms for multisystem inflammatory syndrome (MIS-C) that aligned with the June 2020 ISTH reccommendations.

Most children with acute COVID-19 have mild disease however coagulopathy has been associated with MIS-C, a post infectious complication. A select population has been identified as high risk for TE and should receive pharmacologic prophylaxis. As our knowledge has grown regarding MIS-C, new risk factors have been identified. In response, our algorithms were evaluated to ensure hosptial wide implementation and to assess if more recent evidence should change our processes.

Objectives: 1. Assess the utilization of our current CPM
2. Appraise CPM in context of risk factors identified in recent literature

Design/Method: Children prescribed anticoagulation therapy require a hematolgy consult. Consults were pulled from our electronic health record (EHR) to identify patients with a history of COVID/MIS-C symptoms July 2020 to Dec 2020. Fifity-three patients met the criteria. EHR were reviewed and compared to our CPG algoithms. Data review included: if the criteria for at risk patients was met, if tier 1 and tier 2 assessments were obtained and if indicated, the initiation of TE prophylaxis. The incidence of TE and the duration of TE prophylaxis was recorded.

Results: Children at our institution, as reported in the literature, are at low risk for the development of TE. Adhererence to our CPG alogrithms neared 100%. Risk factors included older children, obesity, specific ethnicities and those medically complex. When reviewed in context of more recent publications since our July 2020 CPG development, no revisions were necessary.

Conclusion: Management of children with MIS-C continues to evolve. This quality improvement endeavor opened the landscape for further research e.g, TE presence or prophylaxis. The incidence of TE in children is less common than what has been seen in adults. Questions regarding the need for TE prophylaxis at all or the continued use of prophylaxis after discharge in high risk populations is one of the many questions that need further investigation. Additionally, what factors are identified in those children who present with MIS-C and a TE compared to those without a TE. Future research will also need to evaluate risk factorrs associated with the evolving COVID variants to guide clinical practice..

Poster # 307

ADDRESSING COVID-19 VACCINE HESITANCY IN HEMATOLOGY- ONCOLOGY PATIENTS.

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Background: The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic began in December 2019 in China, spreading to the rest of the world causing millions of deaths. No treatment has been proven efficient for this infection, consequently, vaccination is considered the most successful method to counteract the spread of the virus. With the introduction of SARS- COV 2 vaccines, safety was the main concern shown by the general public, especially due to the speed at which they were manufactured, and approved. Although vaccines have been proven safe and effective, vaccination among higher risk populations such as patients with hematologic disorders like sickle cell disease or cancer were suboptimal, triggering a sense of urgency in creation of techniques to improve the immunization rate in order to prevent complications from the infection.

Objectives: Increase immunizations among sickle cell disease, and oncology patients eligible to receive the COVID-19 vaccine by 15-20% in a children's hospital.

Design/Method: Quality and improvement project. Baseline data collection such as age, race, and vaccination status was obtained from randomly selected patients charts. A questionnaire was administered via telephone call, and documentation of their concerns in terms of the vaccine was documented. Phone calls from physicians were made to address the patient's and parental concerns, and a brochure with information was provided during the patient encounters at the clinic, and during hospital admission, or provided via electronic mail. Post intervention vaccination rate was documented.

Results: 60 patients from the hematology oncology unit at Nicklaus Children's Hospital were randomly selected. The baseline vaccination rate of the sickle cell patients was 40%, and for the oncology patient was 60%. All patients included were above the age of 12. The most common concerns were: fear of side effects, lack of information, and mistrust in the vaccine efficacy. After implementing the phone calls and the brochures with information, the vaccination rate among sickle cell patients increased to 73%, and among cancer patients to 70%. 20% was the overall increase in vaccination among all patients.

Conclusion: Vaccination against the novel COVID 19 virus is considered the most effective measure in preventing the spread of the virus and decreasing the complications in vulnerable populations. Most common cause of hesitancy among patients is the fear of side effects and lack of information. After directly addressing the patients concerns among hematology oncology pediatric patients, the increase in vaccination rate was of 20%, reaching an overall vaccination rate of 71%.

Poster # 308

OVERCOMING BARRIERS TO EARLY INTEGRATION OF SPECIALIZED PALLIATIVE CARE: A QUALITATIVE STUDY

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Background: Early integration of specialized Palliative Care (SPC) in children and adolescents with cancer is considered standard of care for high-risk malignancies. Barriers to its early integration are well studied. However, there is a paucity of identified methods to overcome these barriers.

Objectives: The primary objective is to determine the perspective of healthcare providers (HCPs) on barriers to early integration of SPC and methods to overcome these barriers in the pediatric oncology population.

Design/Method: We conducted a pilot qualitative study using semi-structured interviews of Canadian HCPs. An interview guide was prepared following a literature review of barriers to early SPC integration in pediatric oncology. Pediatric oncology and palliative care providers were recruited through convenience sampling to include the diversity of HCPs within the Canadian healthcare system. Interviews via a virtual platform were conducted, recorded, and transcribed. Thematic analysis of the transcriptions was performed to identify barriers and potential solutions.

Results: Eight Canadian HCPs were interviewed including 4 pediatric oncology and 4 palliative care providers (5 staff physicians, 2 nurse practitioners, 1 fellow).

HCP views varied as to whether early SPC integration should be universal, targeted based on standardized criteria, or at the oncologist's discretion. However, there was consensus that early SPC integration should occur in patients with a high risk of mortality or high symptom burden.

The barriers to early SPC integration were categorized into family perception, oncology team-related, palliative care team-related, and process/systemic barriers. The most common barriers were in the family perception and oncology team-related categories – the association of palliative care with death/giving up and the perception that the family is "not ready" to meet SPC, respectively.

Strategies identified to overcome barriers often addressed several categories of identified barriers. Categories of solutions include improving communication with families, enhancing palliative care-oncology team collaboration, and optimizing referral processes. Common strategies identified are (1) familiarizing families with the SPC team and their role, (2) skillfully framing integration to families by pediatric oncologists, and (3) regular discussions amongst the pediatric oncology and SPC teams for specific patient review and broad discussions to optimize collaboration.

Conclusion: This study identified strategies to overcome barriers for early SPC integration for children with cancer. These methods should be considered when improvements in early SPC integration are sought. Future assessment and measuring the effect of these solutions in improving early SPC integration is warranted.

Poster # 309

IMPACT OF ETHNICITY AND LANGUAGE BARRIERS ON END OF LIFE CARE FOR HISPANIC CHILDREN WITH CANCER

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Background: Adult cancer patients from underserved populations receive inferior palliative and end of life (EOL) care, which may or may not be concordant with their goals. The influence of ethnicity and language preferences on palliative and EOL experiences in children with cancer is not well understood.

Objectives: The aim of this study is to explore the impact of ethnicity and language barriers on palliative and EOL care experiences for children with cancer.

Design/Method: English and Spanish speaking families of children with cancers that carry a poor prognosis, as well as bereaved families whose children had died of cancer within the last 5 years were eligible. Parents were invited to participate in semistructured Interviews to explore their experiences with palliative and EOL care. Bereaved parents were recruited through an initial mailed invitation letter followed by phone calls. Upon receiving the primary oncologist's approval, parents of patients with with poor prognosis cancer were contacted during a clinic visit, during a hospital stay, or over the phone to propose the study. Interviews were conducted in the caregivers' primary language to explore families' experiences with palliative and EOL care. Interviews with families are still ongoing.

Results: Twenty families were approached, 10 had at least one parent complete the interview. Six of the families were Hispanic, 5 of which were Spanish-speaking. Our preliminary qualitative analysis has revealed frustrations due to inconsistent use of interpreters for communication with other sub-specialties, challenges with communication despite interpretation, lack of palliative care referral/hospice involvement more often in Spanish-speaking families, and themes of isolation during the COVID pandemic. Spanish speakers described the critical importance of direct communication with medical providers using interpretation. Feelings of isolation were often exacerbated for Spanish-speaking families who experienced communication barriers. COVID visiting restrictions, combined with inconsistent access to telehealth, magnified families' distress by limiting important goals of care discussions to only one parent. Families stressed the importance of visitors and family support during their child's hospitalization, and acknowledged the grief associated with losing access to this support during the pandemic.

Conclusion: Preliminary thematic analysis reveals gaps in our current oncology practice that negatively impact Spanish-speaking patients with poor prognosis cancer, including inconsistent palliative/hospice referral, communication barriers in the setting of telehealth and interpretation, and isolation for grieving families during the pandemic. Further analysis will identify barriers to equitable and goal-concordant EOL care for Spanish-speaking families.

Poster # 310

DESPITE SUPERIOR KNOWLEDGE, ONCOLOGISTS ASSOCIATE PALLIATIVE CARE WITH END OF LIFE SIMILAR TO OTHERS

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Background: Pediatric palliative care (PPC) is a specialty that seeks to improve the quality of life of all children with serious illness through prevention and relief from symptoms and stress. By definition, the majority of pediatric oncology patients qualify for PPC services, so frequent utilization and interaction is expected between these two specialties. Ideally, PPC is to be delivered alongside disease-specific therapy and is best incorporated upon diagnosis of a child's medical condition and continued throughout therapy. Children who are referred to PPC experience improved quality of life with fewer symptoms and less suffering than those not referred; however, many pediatric patients who would benefit from PPC are being referred later in their disease trajectory than recommended or not referred at all.

Objectives: To compare knowledge of, and attitudes towards, pediatric palliative care services between pediatric oncologists and other pediatric specialists.

Design/Method: A REDCap survey was distributed to all pediatric attending physicians at a large, suburban, tertiary care children's hospital which contained both qualitative and quantitative questions. This included a 13-question true/false knowledge assessment of PPC services with confidence scale (score range: -70 to 70) along with open-ended questions. Where appropriate, significance was assessed using independent t-test or Fisher's exact test.

Results: Fifty-four completed surveys and ten incomplete surveys were returned (12 oncologists, 32 non-oncologists). The average confidence weighted score on the knowledge assessment was 58.2 [SD 10.1]. The average oncologists score was significantly higher than the non-oncologists on the knowledge assessment (64.7 [5.6] vs 56.4 [10.4], p=0.01). However, when asked in open ended format "what comes to mind when you think of palliative care," those answering only with themes of end of life and dying were similar in oncologists compared to non-oncologists (33% vs 40%, p=0.75). Sixty-six percent of oncologists indicated the ideal time of referral to PPC was at the time of diagnosis compared to forty percent of non-oncologists, but this difference was not significant (p=0.19). Oncologists more often felt that their knowledge of PPC services affected their referral practices than non-oncologists (92% vs. 50%, p=0.02).

Conclusion: Despite higher scores on objective knowledge assessment, oncologists' ideal referral timeline and association of PPC with only end of life care did not differ significantly from non-oncologists. Broad improvements in palliative care education and exposure would likely benefit oncologists and non-oncologists alike. Further prospective studies correlating pediatric palliative care education with referral patterns and patient centered outcomes are needed.

Poster # 311

COMMUNICATION, PRESENCE, AND PARITY: PROFESSIONALS' VIEWS OF PROMOTING QOL FOR CHILDREN WITH CANCER

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Background: Intensive childhood cancer treatment produces suffering. In addition to physical symptoms, children miss out on life events and experience social isolation. Professionals' attitudes and actions shape children's lives during cancer treatment. Primary palliative care consists of quality of life (QOL)-promoting care enacted by professionals who are not acting within the context of specialty palliative care teams. Despite the rapid growth of specialty pediatric palliative care teams, most children receiving cancer treatment do not receive specialty pediatric palliative care. Yet how professionals conceptualize and enact their primary palliative care roles in the current era remains poorly understood.

Objectives: We sought to understand: (1) professionals' role expectations for themselves and others to relieve suffering and promote joy, meaning, and accomplishment for children in their care; (2) perceived barriers and facilitators to promoting QOL for children in their care; (3) how team dynamics promote or impede QOL for children in their care.

Design/Method: We utilized theoretical sampling and conducted semi-structured interviews of professionals working in a pediatric oncology center. Professionals were invited to participate via email and interviews were conducted face-to-face, by telephone, or via secure video conference by non-clinical members of the research team. Through constant comparative analysis, early interviews informed subsequent data collection. Thematic analysis incorporated the following data sources: audio-recordings, interview transcripts, debriefing discussions with interviewers, and memos.

Results: Fifteen interviews were conducted April-September 2021 with oncologists (MDs/NPs), nurses, social workers, child life specialists, chaplains, and psychologists. Communication to *share information* and *build on each other's ideas* emerged as a central theme. Issues of *presence* and *parity* emerged: physical distancing and restrictive visitation policies due to the COVID-19 pandemic were impediments to promoting QOL. Some respondents perceived less patient isolation and exclusion when "normal life" seemed universally out of reach in the early months of the pandemic. Changes in working patterns induced by COVID-19 were seen as threats to communication, and by extension, to patients' QOL. Within-professions team membership was strengthened by weathering changes wrought be COVID-19. By contrast, efforts to ensure communication across professions were perceived to be asymmetric, leaving some clinicians feeling devalued and at times heightening tensions between professions.

Conclusion: Communication, presence, and parity emerged as preliminary facilitators and barriers to working interprofessionally to promote QOL, particularly in the context of the COVID-19 pandemic. Understanding professionals' attitudes and actions around QOL for children with cancer will inform future interventions to enhance interprofessional primary palliative care.

Poster # 312

IMPACT OF HIRING A FULL-TIME PATIENT NAVIGATOR ON FERTILITY-RELATED CARE AT A PEDIATRIC INSTITUTION

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Background: Fertility impairment is an adverse effect of gonadotoxic cancer treatments and certain non-oncologic conditions like sickle cell disease. It can negatively impact quality of life and psychosocial functioning. However, high quality counseling has been shown to mitigate this distress and improve outcomes. Therefore, fertility counseling is needed for all patients at risk for infertility. Fertility navigators play an important role in providing this counseling, discussing fertility preservation (FP) options, and coordinating care among multidisciplinary teams. Although the importance of patient navigators is well-established, the impact of hiring a full-time navigator at a pediatric institution has not been well-studied.

Objectives: Our primary aim was to examine fertility-related care and FP utilization before and after hiring a full-time fertility navigator.

Design/Method: Retrospective chart review was performed on all fertility consults performed on patients of all ages and diagnoses at a large pediatric institution between 2017 and 2019 (full-time navigator hired July 2018). Patient demographics, diagnostic group (oncology, hematopoietic stem cell transplantation (HSCT), long-term follow up (LTFU), or non-oncologic), consult date, and FP type (if pursued) were collected. Information regarding fertility testing and fertility specialist referrals were also collected for those in LTFU. Descriptive statistics, t-tests, and chi-square analyses were performed.

Results: There were 738 patient encounters; 173 consults were performed pre-navigator and 565 consults post-navigator. Consults for LTFU cancer patients increased from pre-navigator (N = 7) to post-navigator (N = 387). Females had a larger increase in number of consults compared to males ($c^2(3, N = 738) = 8.17$, $p < 0.05$). Of the 738 patients, 26% pursued FP pre-navigator and 28.8% of patients pursued FP post-navigator (p=0.623). The number of fertility tests performed in LTFU patients was not statistically significant pre- versus post- navigator ($c^2(1, N = 394) = 1.149$, $p = 0.250$). More patients were referred to fertility specialists post-navigator (N = 47) compared to pre-navigator (N = 4) ($c^2(1, N = 394) = 12.36$, $p < 0.05$).

Conclusion: After hiring a full-time fertility navigator, there was a significant increase in the number of fertility consults performed. This increase was particularly high among those in LTFU and among females. There was no significant increase in FP utilization or fertility testing post-navigator, though referrals to specialists did increase. Future research should focus on addressing barriers to decisions to pursue FP and patient satisfaction regarding fertility counseling with a dedicated fertility navigator.

Poster # 313

V-SYMPHONY: COLLABORATION TO ENHANCE CAREER DEVELOPMENT FOR PEDIATRIC HEMATOLOGY ONCOLOGY TRAINEES

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Background: A recent survey of Pediatric Hematology Oncology (PHO) providers identified that a majority believe PHO fellows are struggling to find jobs that align with their goals. Career development for PHO trainees has historically been institution specific, which can limit exposure to, and knowledge of, job market options. The "virtual-Symposium of Pediatric Hematology/Oncology of New York" (v-SYMPHONY, https://www.vsymphony.org/), a tri-state (NY/NJ/CT) collaborative educational series, developed a career development series for PHO trainees to better address their needs in the ever-changing job market and increase awareness of the wide variety of career opportunities within PHO.

Objectives: To develop and implement a multi-institutional career development series and evaluate its impact on PHO trainees.

Design/Method: The v-SYMPHONY steering committee organized a virtual career development series with three sessions: (1) PHO Division Chiefs panel on perspectives and expectations for job applicants (2) individual faculty perspectives on different career paths and (3) "nuts and bolts" of job search, CV and cover letter writing, and interview preparation.

Pre-/post-session surveys were administered to all fellow participants. Pre-surveys assessed participant demographics, anticipated career plans, and what they hoped to gain from sessions. Post-surveys evaluated demographics, career plans, job process, and overall satisfaction with series, as well as questions on individual session usefulness, appropriateness, and satisfaction.

Results: Forty-one fellows registered for the career development series and completed a pre-survey. Over half (53.7%) were in their third or greater year of fellowship. Interest in a clinical or clinical research career was the most common desired career path (58.5%). Most pre-survey participants had received career development advice only from providers within their institutions (90.2%) or recent graduates from their institution (68.3%).

Post-surveys were completed by 11/41 PHO fellows (26.8%). Of those respondents, 36.4% were in the process of applying and/or interviewing for positions. Overall, 100% of respondents reported benefiting from the career sessions and would recommend as an annual series. Over 90% felt they learned new information that would help prepare them for the job search. For each individual session, over half of respondents reported feeling that the session was useful to them.

Conclusion: To our knowledge, this is the first regional collaborative targeted at career development for PHO fellows across multiple institutions. PHO fellows overwhelmingly agreed that these sessions were beneficial and useful for preparing them for the job search process. Regional career development sessions are feasible, promote career opportunities, and provide mentorship to early career hematologist/oncologists.

Poster # 314

STRESS AMONGST FELLOWS IN THE PEDIATRIC HEMATOLOGY/ONCOLOGY JOB SEARCH

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Background: The landscape of the Pediatric Hematology/Oncology (PHO) workforce has evolved in recent decades. While fellowship positions nearly doubled for two decades, interest in the subspecialty has waned, with 44% of PHO programs going unfilled in 2020 [1, 2]. A dearth of desirable PHO jobs for graduating fellows could be to blame, but objective evidence is lacking.

Objectives: In this study, we evaluated the perceptions of the current PHO fellows and leaders about the experience of seeking an initial faculty position and its impact on fellow stress and anxiety.

Design/Method: An anonymous electronic survey assessed demographics, job search experiences including facilitators and obstacles, and emotional health outcomes. Following pilot testing, in June 2021 all PHO division chiefs and fellowship program directors were invited to complete the Qualtrics survey and to disseminate the link to their fellows. Descriptive statistics and two-tailed P-values using Fisher's exact test were computed for statistical analysis.

Results: Forty-nine out of 74 programs (66%) responded, and a total of 162 surveys (79 fellows, 83 faculty) were completed. Fellows, more so than faculty, perceived that fellows were struggling to find post-fellowship jobs (87% versus 72% respectively, P=0.0198). However, faculty were more likely than fellows to perceive that fellows are either "extremely stressed" or "stressed" due to the job search process (95% versus 75% respectively, P=0.0003). Almost 50% of fellows reported anxiety on "more than half the days" due to the job search. Over 50% reported difficulty finding jobs that aligned with their ideal goals. By June 2021, 30/44 (68%) candidates had been offered a position, and 24/30 (80%) had accepted a position. Respondents leveraged online listings, program leadership, and word of mouth to identify available jobs. Common barriers in the job search included geographic constraints (N=26, 59%) and partner employment (N=19, 24%). The majority (N=36, 82%) felt that COVID-19 had impacted the job search. Respondents identified unmet educational needs including career development tools (N=46, 58%), early mentorship (N=19, 24%), and centralized job listings (N=16, 20%).

Conclusion: The perception of difficulty and stress regarding the post-fellowship job search is endorsed by most fellow candidates and their program leadership. Interventions to improve the efficacy and subjective experiences of fellows seeking their initial faculty positions are needed. These data highlight unmet educational needs among PHO fellows. Future steps include establishing career development resources to better prepare graduating fellows for the job search.

References:

1. Macy ML et al, Pediatr Research, 2021.
2. NRMP, December 2020.

Poster # 315

AN ADOLESCENT AND YOUNG ADULT (AYA)-FOCUSED TEACHING CURRICULUM

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Background: While overall cancer survival rates have steadily improved, the AYA subgroup has lagged behind. This survival gap is multifactorial, as AYA patients have distinct cancer biology, lower rates of clinical trial enrollment, and complex psychosocial needs. A 2010 AYA position statement highlighted the need for dedicated training related to AYA-specific medical knowledge and care delivery. However, outside of dedicated AYA fellowships, no formal AYA curricula have been published.

Objectives: Our global aim was to design and implement a formal AYA teaching curriculum to increase AYA medical knowledge for both pediatric and medical oncology providers. Our SMART aim was to increase provider confidence in four critical AYA topics.

Design/Method: According to the plan-do-study-act (PDSA) cycle, we developed an AYA curriculum consisting of four 60-minute didactic sessions over a four-month period. The topics included: psychosocial challenges including fertility preservation, treatment updates for acute lymphoblastic leukemia (ALL) and sarcoma, and a military specific topic regarding medical retention versus retirement. We surveyed 23 staff and fellow physicians in two military Graduate Medical Education (GME) training programs using a six-item, five-point Likert Scale online assessment. Surveys were repeated to determine changes in confidence levels after intervention. Two questions were added to the post-intervention survey to assess effectiveness: 1. Success of curriculum in preparing attendees to deliver quality AYA care and 2. Likelihood the curriculum would change clinical practice.

Results: Out of the 23 respondents to the survey, 57% (13/23) were adult oncology providers and 43% (10/23) were pediatric oncology providers. Post-intervention, 100% of respondents indicated the curriculum prepared them to better deliver care to AYA patients and 96% believed they would change their practice based on information learned. We observed improved likelihood of collaboration between adult/pediatric colleagues (35% to 70%), improved confidence in military specific implications of malignancy (37% to 83%), improved knowledge of specific AYA ALL and sarcoma protocols (39% to 57%), and improved confidence of AYA specific psychosocial needs (61% to 91%) and oncofertility (57% to 78%).

Conclusion: This pilot program has shown that a focused AYA curriculum is feasible, well-received, and can boost provider confidence and AYA team collaboration. A formal teaching curriculum delivered to Pediatric and Medical Oncology training programs could serve as the foundation to provide the needed AYA-specific medical knowledge, which, when brought forward

into clinical practice will directly impact AYA care. Future aims of this program include expansion of core topics and expansion to additional GME programs.

Poster # 316

IMPROVING FELLOW INVOLVEMENT IN NEW PATIENT VISITS: A SINGLE CENTER QUALITY IMPROVEMENT INITIATIVE

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Background: Initial management of patients with newly-diagnosed malignancies is a crucial skill that pediatric hematology/oncology (PHO) fellows must acquire during their fellowship training. However, due to complicated logistics, fellows often do not participate in new visits (NVs), missing out on key learning opportunities. A retrospective review at our institution revealed that only 25% of NV appointments included PHO fellow participation, indicating an area for improvement. Based on this data, we initiated a quality improvement (QI) intervention seeking to increase PHO fellow involvement in NVs.

Objectives: To improve PHO fellow participation in all oncology NV appointments within the Department of Pediatrics at Memorial Sloan Kettering Cancer Center (MSKCC).

Design/Method: We assembled an interdisciplinary task force comprised of individuals involved in the PHO fellowship program as well as administrative staff responsible for coordinating NV appointments. Barriers to PHO fellow participation in NVs were identified, which included: conflicting clinical and research responsibilities during appointments scheduled outside of fellows' continuity clinic (CC) hours; lack of fellow knowledge about scheduled NVs; and lack of infrastructure to identify fellows available to participate in NVs. We subsequently developed a workflow for administrative staff to standardize the process of notifying PHO fellows about NVs scheduled on their CC day. Education was provided to PHO fellows, clinic practitioners, and administrative staff. We tracked the NVs that occurred in our five primary oncology disease services and the percentage of NV appointments that included PHO fellow participation based on electronic medical record documentation.

Results: Baseline data (9/1/2020 – 3/3/2021) showed only 25% (31/123) of NV appointments included fellow participation. We introduced our workflow on 7/1/2021 and provided education to all involved parties both before and after introduction. Repeat data collection (8/1/2021 – 12/31/2021) showed improvement in fellow involvement in NV appointments to 49% (68/138). Analysis of a subset of NV appointments (8/1/2021 – 12/9/2021) that did not include fellow participation (n=62) revealed that 32% (20/62) were due to late add-on appointments, 24% (15/62) were due to lack of outreach to fellows informing them of the NV appointment, and another 24% (15/62) were due to lack of fellow availability to join NV appointment.

Conclusion: Using QI methodology, we have increased fellow involvement in NV appointments from 25% to 49%. Future Plan-Do-Study-Act (PDSA) cycles are needed to reinforce our current

workflows, with a specific focus on improving adherence to workflows related to late add-on NV appointments.

Poster # 317

PEDIATRIC OPIOID ANALGESIA SELF-INSTRUCTION SYSTEM (PEDOASIS): AN EFFECTIVE EDUCATION TOOL

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Background: Many children with cancer, survivors of childhood cancer, and patients with sickle cell disease experience pain, yet receive inadequate pain management due to health care provider lack of knowledge and comfort. Pain management using opioids is a required competency for pediatric hematology/oncology (PHO) fellows, yet knowledge gaps persist.

Objectives: Pediatric Opioid Analgesia Self-Instruction System (PedOASIS) is an interactive, case-based education tool for independent learning by post-graduate medical trainees which has undergone pilot testing and validity and reliability testing. The goal of this study was to evaluate its efficacy in increasing PHO fellows' knowledge and comfort with using opioids to manage pain.

Design/Method: PHO fellows were recruited from 74 ACGME-accredited US programs during the 2019-2020 academic year. Participants were randomized to receive access to PedOASIS (intervention) or usual PHO training (control). Participants completed surveys at enrollment, immediately after distribution of the tool, and 6 months later. Surveys assessed subjective comfort with prescribing opioids and objective knowledge, using a version of the questions from the tool.

Results: At baseline, mean scores on the 10-question knowledge assessment did not significantly differ by level of training (first year: 5.05, second year 5.74, third/fourth year: 5.58; $p = 0.410$) or between groups (intervention: 5.38, control: 5.5; $p = 0.795$). Following intervention, mean score was significantly higher in the intervention group (8.91) vs. controls (5.38; $p<0.0001$). Six months later, scores in both groups decreased but remained significantly higher in the intervention group (6.91) compared to baseline ($p=0.0002$) and compared to controls (4.91, $p<0.0001$).
Fellows indicated comfort with selecting opioid and starting dose for an opioid-naive patient at baseline but less with rotating opioids. Intervention group reported significant increases in comfort dosing opioids after exposure to the tool ($p = 0.022$) and in rotating opioids ($p = 0.054$) following the intervention.

Conclusion: Use of PedOASIS was associated with improvement in scores on validated knowledge questions and in comfort using opioids for pain management in PHO fellows exposed to the tool compared to fellows without the tool. These findings suggest that this is a valid, reliable, and effective curricular tool. The use of self-directed learning has been associated with increased knowledge gains when compared to traditional didactic methods. The asynchronous learning structure is useful in the setting of the ongoing SARS-CoV19 pandemic, which has necessitated significant alterations in medical education. Based on these results, we suggest that PedOASIS is

an effective and relevant addition to the PHO fellowship curriculum.

Poster # 318

A PEDIATRIC RESIDENT-FOCUSED HEMATOLOGY/ONCOLOGY CURRICULUM

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Background: Empowering resident physicians with the skills and knowledge to care for ill patients is essential to prevent delays in vital treatment. At the University of Chicago Comer Children's Hospital, the inpatient pediatric hematology-oncology (PHO) service lacked a standardized resident curriculum, making the education provided to pediatric residents variable.

Objectives: To determine the knowledge and confidence gains of learners from a needs assessment-based PHO curriculum for pediatric residents.

Design/Method: To determine baseline competency and knowledge gaps, a needs assessment was distributed to the PHO section, fellows, faculty and advanced practice nurses, and PGY-2/3 residents. This data was used to create a focused 12-webinar curriculum, with topics including oncology, hematology, and stem cell transplant medicine. Webinars are case-based, emphasizing the pathophysiology and management at a resident physician level. As the curriculum was initiated during the COVID-19 pandemic, webinars were given live via a virtual video platform to allow for audience participation.

To measure learner gains, anonymous assessments evaluating pre- and post-webinar confidence or knowledge in the learning goals, were distributed immediately after each live lecture. Respondents used a 5-point Likert scale (5 = Strongly Agree) for each clinical scenario derived from the needs assessment and webinar goals, as well as for evaluating the usefulness of the webinar and whether it accomplished the stated goals.

Results: For the 2020-2021 academic year, the 12 webinars were viewed a total of 304 times. The overall survey completion rate was 58.9% (179/304). Survey responses per webinar ranged from 35 (Introduction to Oncology) to 1 (Introduction to CAR-T Therapy). A paired t-test was used to compare individual pre and post scores. For all knowledge domains within the webinars, there was a statistically significant difference ($p < 0.05$) in the pre and post scores, except for Intro to CAR-T Therapy, which only had one respondent and thus was underpowered. All webinars were found to be beneficial (mean 4.88, standard deviation (SD 0.34) and accomplish the stated goals (mean 4.87, SD 0.33). Rotation evaluations of the inpatient service had improvements in quality of the learning environment and quality of the teaching experience, with means rising from 3.68 (SD 1.0) to 4.07 (SD 0.8) and 3.81 (SD 1.1) to 4.07 (SD 0.8), respectively.

Conclusion: Resident learners found the curriculum beneficial and useful in caring for PHO patients. While knowledge gains were reported in the resident self-assessments, evaluation refinement is needed to better understand if these same gains have contributed to behavioral or practice changes.

Poster # 319

ASSESSMENT OF TRANSFUSION MEDICINE KNOWLEDGE IN PEDIATRIC RESIDENTS: A SINGLE INSTITUTION STUDY

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Background: Adequate transfusion medicine (TM) knowledge is associated with safer patient care. Studies have shown that physicians have gaps in TM knowledge. Inappropriate transfusion practice may expose patients to complications including potentially lethal reactions. Pediatric TM represents a complex part of the TM discipline and pediatric residents (PRs) play a key role in the transfusion process. Despite that, very little is known about TM knowledge amongst PRs.

Objectives: To define gaps in knowledge and areas of improvement within the field of pediatric TM education.

Design/Method: We developed a self-administered electronic survey with the following sections: 1)Demographics; 2)Previous TM experience; 3)Resident's perception of their TM knowledge; 4)Pediatric TM exam; and 5)Impact of the exam on residents' knowledge perception. The exam used in section 4 was developed and validated by pediatric TM experts under the umbrella of the Biomedical Excellence for Safer Transfusion (BEST) Collaborative.
PRs at our institution during the recruitment period were eligible to participate. Pediatric subspeciality trainees and non-PRs were ineligible.

Results: Survey's response rate was 41.4%. Two residents were excluded from analysis: 1 non-PR and 1 pediatric subspeciality fellow. Half of the remaining residents (22) were postgraduate year 2 (PGY-2). Lectures were identified as the method of previous training by all residents, and only 5 had another method.
Overall mean score of the exam component was 40.5% (23.8% - 66.7%). PGY-1 scored the lowest (35.7%) while PGY-2 scored the highest (43.3%). Impact of training level on scores however was not statistically significant (Table1). Residents did better in questions concerning indications and general TM practice compared to those related to complications/reactions (45.9% vs. 33.6%)(Table2). They mostly struggled in correctly diagnosing dyspnea following transfusion. None of the residents correctly answered the massive transfusion question.
Prior to the exam, most residents indicated an average TM knowledge for their level of training. All acknowledged the need for more TM training; with most needing "some training" compared to "a lot of training". After the exam, more residents indicated needing "a lot of training" (Figure 1). The exam has changed residents' knowledge perception as the majority thought they had less than expected knowledge after answering the questions (Figure 2).

Conclusion: PRs have significant gaps in TM knowledge, struggling more with transfusion-related complications/reactions. PRs tend to overestimate their knowledge. A formal TM assessment not only highlights gaps in knowledge but stimulates residents to seek further education. Improved pediatric TM education is needed to raise residents' confidence and ensure patient safety.

Poster # 320

TIMLEY PLACEMENT OF TOPICAL ANESTHETICS PRIOR TO PORT ACCESS

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Background: Topical anesthetics such as EMLA (lidocaine/prilocaine) or LMX (lidocaine) decrease venipuncture/port access pain and decrease stress in pediatric patients. Topicals are frequently used throughout pediatric hematology/oncology practices. These topicals generally take 30-60 minutes to be effective. Timely placement of creams can optimize pain control, decrease rushing access, decrease time to antibiotics and other interventions, decrease time spent in hospital facilities, and improve satisfaction of care. Without proper timing and pain control, patient-healthcare worker relations erode and long-term negative emotional and physical effects can ensue. Furthermore, waiting for topicals to take effect can delay care and subsequently scheduled patients, especially in an outpatient or operative setting.

Objectives: To improve the timely application of EMLA or LMX to skin prior to venipuncture/port access. By achieving our goal, we can decrease pain, stress, delays/wait times, and long-term effects. We can also improve patient safety (by not rushing accesses), patient/family satisfaction, and patient-healthcare worker relationships.

Design/Method: A general Plan-Do-Study-Act format was used for this study. A data collection sheet was made for the clinic and hospital procedure. This sheet included the following information: date, patient initials, date of birth, port access plan, patient/family knowledge on needing access, was a topical anesthetic required, and if topical anesthetic was not placed prior to arrival by patient/family – why not. OR and outpatient staff were educated and data was collected over two months. During this period families were educated on topical anesthetic placement and provided refills. Reminder sheets with plastic protectors, to apply a topical anesthetic prior to leaving for clinic/hospital (English/Spanish) to hang on their front door at home were provided to the families. Baseline data was obtained and data post-intervention is being collected.

Results: Prior to the intervention 224 clinic visits were evaluated: 207 required access, 192 required a topical, and 107 forgot/did not know to place a topical prior to arrival. Fifty-two procedure visits were evaluated: 46 required access, 42 required a topical, and 30 forgot/did not know. Majority of patients/families forgot to place a topical prior to arrival. The rest of patients/families did not know access was needed or they did not have the medication at home. There was a qualitative improvement seen in topical application prior to arrival.

Conclusion: Topical anesthetics have been useful in many pediatric hematology/oncology practices. Topicals can decrease pain and anxiety and improve quality and safety. Family and staff education are needed to optimize timely placement of topical anesthetics.

Poster # 321

DECREASING RELIANCE ON LONG-TERM PICC LINES IN THE PEDIATRIC HEMATOLOGY/ONCOLOGY POPULATION

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Background: Peripherally inserted central catheters (PICCs) are frequently used as an alternative to more long-term central venous catheters in pediatric hematology/oncology patients due to their ease of placement, removal and use. Studies have shown that prolonged use of PICC lines leads to higher rates of complications, including line breakage, occlusions and bloodstream infections. In 2020, American Family Children's Hospital experienced an increase in Central-Line Associated Blood Stream Infections (CLABSI) rate and half of all infections occurred in patients who had PICC lines. As part of our effort to decrease CLABSI rate, we set goals to minimize the number of PICC lines placed and to limit the duration of PICC lines as much as possible.

Objectives: To decrease the number of PICC lines in place for greater than 90 days in pediatric patients with underlying hematologic or oncologic diagnoses at a tertiary children's hospital.

Design/Method: Using data available from the electronic medical record, we determined the number of PICC lines in place for greater than 90 days in all pediatric patients each year 2019-2021. We then performed a chart review to determine which of those patients had an underlying hematologic or oncologic diagnosis. Efforts were made throughout 2021 to encourage pediatric hematologist/oncologists to limit the use of PICC lines in their patients. If a PICC line needed to be placed, physicians were encouraged to consider replacing that line with a tunneled line or a Mediport as soon as medically appropriate.

Results: In 2019, there were 11 pediatric patients with underlying hematologic/oncologic diagnoses who had a PICC line in place for greater than 90 days (range 94-231 days). In 2020, there were eight such pediatric patients (range 103-255 days). In 2021, there were only two such patients (range 95-115 days).

Conclusion: Once an emphasis was placed on the importance of limiting the duration of PICC lines in pediatric patients with underlying hematologic/oncologic diagnoses, we were able to change our group's practice. Coinciding with this change was a decrease in the overall CLABSI rate at our hospital. Though this reduction may be incidental, it is important to eliminate as many risk factors as possible for CLABSI.

Poster # 322

CHARACTERIZATION OF CLABSI IN A PEDIATRIC HEMATOLOGY/ONCOLOGY POPULATION

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Background: Central venous catheters are invaluable tools for pediatric hematology/oncology (PHO) patients but also carry potential risk for the development of central line associated bloodstream infections (CLABSIs). Our children's hospital had an increased CLABSI rate in 2020 and over half of these events occurred in PHO patients.

Objectives: To reduce CLABSI rates, we sought to understand underlying patient- and line-specific factors that may influence the CLABSI rate in children with underlying hematologic or oncologic disorders at our hospital.

Design/Method: We performed a retrospective case-control study of PHO patients at our children's hospital in 2020 who had a CLABSI (n=10) and identified differences with PHO patients who did not have a CLABSI (n=38). These patient charts were analyzed to identify patient- and line-specific factors that might contribute to central line infections.

Results: There is an association between type of central line and CLABSI risk, with all CLABSI events occurring in PHO patients with a PICC or tunneled line and none in patients with ports. Other associated risk factors include younger age, having received ICU care, or having a transplant. Patients with a CLABSI also had admissions that were on average 58.9 days longer in duration.

Conclusion: We describe risk factors that may be associated with increased risk of CLABSI in PHO patients. In terms of infection risk, it may be prudent to maximize the number of PHO patients who can be successfully treated with a port rather than with an external line such as a PICC. Other identified risk factors may be used to focus CLABSI-prevention efforts on the sub-populations at highest risk for developing a CLABSI.

Poster # 323

INCREASING BLOOD PRESSURE COMPETENCY, A SINGLE INSTITUTION QUALITY IMPROVEMENT EFFORT

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Background: Early recognition of abnormal vital signs is crucial to ensure quality patient care and prevent poor clinical outcomes. Though many institutions have implemented a pediatric early warning system (PEWs) to detect risk for clinical deterioration, these algorithms often exclude blood pressure (BP) as hypotension is a late sign of clinical decompensation. However, hypotension and hypertension can have significant implications for pediatric hematology-oncology patients. A root cause analysis following a patient safety event (PSE) identified reliance on early warning system scores led to a lack of recognition and timely notification of abnormal BPs by nursing. Recognizing that continued lack of nursing response to abnormal BPs could lead to further PSEs, a quality improvement project (QI) was initiated.

Objectives: We aim to decrease PSEs related to a lack of recognition of abnormal BP as measured by a decrease in number of BP related PSE reports from 12 to 6 over a six month period and

increase in providers reporting prompt notification of abnormal BP by RNs from 58% to 90%.

Design/Method: An electronic survey was administered in Fall 2021 to physicians and advanced practice providers across the institution. The survey collected data regarding provider concerns about notification of abnormal BP, if abnormal BP led to PSEs, and explored perceived drivers. Utilizing QI methodologies to analyze survey results, key drivers to improve blood pressure competency for RNs and communication to clinical providers were identified. A multidisciplinary team began initiating key interventions in Fall 2021, providers will complete a follow-up survey approximately 4 months after key interventions have started to measure changes in provider perceptions. The electronic PSE reports will be tracked over the same period.

Results: Thirty-nine clinical providers responded to the survey. In the previous 6 months, 74% (n=29) and 76% (n=30) reported delayed notification of hypotension or hypertension, respectively. Forty-two percent (n=16) reported a lack of prompt notification by RNs regarding abnormal BP, with only 58% (n= 23) not needing to follow up with RNs often for abnormal BP. Potential reasons suggested for lack of nursing notification were education/competency of RN, lack of concern for abnormal BP, and lack of RN initiative.

Conclusion: Increased recognition by RNs of abnormal BP with timely communication to clinical providers should decrease PSEs and improve patient outcomes. Using QI methodology, will assess impact of revisions of the vital signs policy and nursing education that highlighted BP abnormalities by age with plans to test BP clinical pathway to augment PEWs.

Poster # 324

MEDICATION ADHERENCE AND HABIT STRENGTH AMONG CHILDREN WITH CANCER OR CHRONIC HEMATOLOGIC CONDITIONS

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Background: Medication non-adherence is a common problem among children with chronic conditions, with only 50% of patients taking medications as recommended. Moreover, poor medication adherence is associated with negative health outcomes, such as increased mortality and impaired health-related quality of life. Nevertheless, few tools to measure medication adherence are valid, reliable, and freely available. One key factor promoting medication adherence is habit formation, and stronger habit strength has been associated with higher adherence levels; however, this relationship is still unclear among children with cancer or chronic hematological conditions.

Objectives: (1) Evaluate adherence to oral medications among children with cancer or chronic hematological conditions and (2) Assess the relationship between adherence and habit strength.

Design/Method: In this cross-sectional study, participants were enrolled from outpatient hematology and oncology clinics and the infusion center. Patients were eligible if they were <26 years-old, English-speaking, and taking an oral medication. Participants completed the PROMIS®

Medication Adherence Scale (PMAS), Adherence to Refills and Medications Scale 7 (ARMS-7), Visual Analogue Scale (VAS), and Self-report Habit Index (SRHI). Spearman's correlations were performed among various adherence measures and in relation to habit strength.

Results: A total of 137 participants completed study assessments, 51 patients (57% male, median age 17 [IQR 7] years old) and 86 parents (85% female, median age 40 [IQR 8.8] years old). Patients' disease conditions were sickle cell disease (37%), hematological malignancy (29%), miscellaneous cancer (15%), miscellaneous hematological condition (11%), and thalassemia (8%). Most prescribed medications included Bactrim (18%), Hydroxyurea (16%), Penicillin (15%), 6-Mercaptopurine (13%), and Jadenu (11%).

Median medication adherence levels were high for the PMAS, ARMS-7 and VAS (44 [IQR 4]; 9 [IQR 4]; 95 [IQR 20], respectively). All medication adherence scores were significantly correlated with one another, including the PMAS and ARMS-7 (r=0.37, $P<0.0001$), PMAS and VAS (r=0.27, $P=0.0014$), and ARMS-7 and VAS (r=0.56, $P<0.0001$) scores, supporting their clinical utility to evaluate adherence behavior.

SRHI score was significantly correlated with all medication adherence measure scores including the PMAS, ARMS-7, and VAS (r=0.30, $P=0.0003$; r=0.33, $P=0.0001$; r=0.18, $P=0.0388$, respectively), suggesting higher adherence levels among those with stronger habit.

Conclusion: Most participants reported high adherence to their oral medications. The PMAS correlated well with validated medication adherence measures. PMAS is a comprehensive, patient-centered assessment of medication adherence rates and barriers. Furthermore, stronger habit of taking oral medication was associated with higher adherence, supporting the need for habit-based interventions to improve medication adherence.

Poster # 325

EMAPALUMAB FOR MACROPHAGE ACTIVATION SYNDROME ASSOCIATED WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

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Background: Macrophage activation syndrome (MAS) is a life-threatening complication of systemic juvenile idiopathic arthritis (sJIA) that is traditionally managed with high-dose glucocorticoids (GCs). However, GCs do not always provide adequate control for all patients, and morbidity and mortality remain high. Preclinical data suggest that interferon gamma (IFNγ) overproduction is pathogenic in MAS.

Objectives: To assess the efficacy and safety of emapalumab, a fully human, anti-IFNγ monoclonal antibody, in patients with sJIA complicated by MAS.

Design/Method: Pilot, open-label, single-arm study (NCT03311854) enrolling patients with sJIA and MAS who had failed high-dose GCs. Emapalumab was initiated at 6 mg/kg and continued at 3 mg/kg every 3 days until Day 15, and twice weekly until Day 28. Study duration was at least 8 weeks. Complete response (CR) was defined as resolution of clinical signs and symptoms of MAS according to the investigator, and normalization of laboratory parameters relevant to MAS. All patients entered a 1-year follow-up study.

Results: Fourteen patients (10 females; median age 11 years, range 2–25) were enrolled (11 in Europe, 3 in the USA). Several patients had previously received cyclosporine A and/or anakinra, in addition to high-dose GCs. Markedly elevated baseline CXCL9 levels were not correlated with total IFNγ levels. Six patients received emapalumab until Day 28. Emapalumab was discontinued early due to MAS remission (investigator's assessment) for 7 patients; 1 patient received treatment up to Day 38. Emapalumab treatment rapidly neutralized IFNγ, as demonstrated by reduced CXCL9 levels. A CR was achieved by 13/14 patients during the study. One patient stopped emapalumab after 3 doses because of investigator's assessment of MAS remission, but lactate dehydrogenase levels remained >1.5× upper limit of normal. At week 8, 11/14 patients had a CR; 2 achieved a CR during the study, but not at Week 8, because of singular laboratory parameter abnormalities in each patient. GCs were tapered in all patients by Week 8 (≥50% reduction, n=12; GC dose ≤1 mg/kg/day, n=8). Emapalumab was well tolerated. No patients discontinued treatment for safety reasons. One serious adverse event was reported (cytomegalovirus reactivation that resolved with antiviral treatment). All patients were alive at the last visit.

Conclusion: Emapalumab administration led to rapid IFNγ neutralization and MAS control in all patients, supporting the pathogenic role of IFNγ in MAS in sJIA. The efficacy and favorable safety profile of emapalumab demonstrates the therapeutic value of IFNγ neutralization in patients with MAS who have failed high-dose GCs. Supported by funding from Sobi.

Poster # 326

INCIDENCE AND RISK FACTORS FOR BROWN ADIPOSE TISSUE UPTAKE IN PET IMAGING IN PEDATRIC PATIENTS

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Background: PET (Positron Emission Tomography) is an imaging modality used in disease evaluation for pediatric oncology patients that uses ^{18}F-fluorodeoxyglucose (FDG) to nonspecifically indicate metabolically active tissues that utilize glucose. Metabolically active brown adipose tissue (BAT) may uptake FDG which can make PET interpretation challenging. Prior studies suggest variables affecting the metabolic activity include age, gender, body mass index (BMI) and outdoor and indoor temperature. Pretreatment with medications, such as propranolol, diazepam, and fentanyl may decrease BAT uptake in PET imaging.

Objectives: This study aims to retrospectively determine our institutional incidence and risk

factors for BAT in pediatric patients in preparation for a future prospective interventional trial.

Design/Method: Records for pediatric and young adult patients who had PET imaging from September 2015-December 2016 at Children's Hospital Colorado were retrospectively reviewed under institutional review board approval. Patients with primary oncology diagnoses (n=86) and non-oncology diagnoses were included (n=68). BAT was retrospectively quantified for each PET scan through consensus review by two pediatric radiologists. The primary outcome was presence of BAT (none, mild, moderate, severe) in each body area (neck, axilla, mediastinum, chest wall, abdomen and pelvis). Potential risk factors that may influence BAT avidity will be assessed using generalized linear mixed modeling with a logit link and a random intercept to account for correlation within subject. A secondary outcome was whether BAT limited PET interpretation, as determined by the radiologist raters.

Results: 154 pediatric and young adult patients, including 285 PET scans, median age 0.3-41.4 years (48.7% male, 51.3% female). BAT was noted in 17% of all PETs, with 14.7% having BAT in more than one body region. Incidence of BAT by body region were: neck 16.5%, axillae 14.4%, mediastinum 5.3%, chest wall 8.8%, abdomen 8.4%, pelvis 0.4%. Moderate or severe BAT was present in 11% of PETs and original radiologic interpretation was limited due to BAT in 5.6%. Pre-medication was used in 5.6% of PETs, with 0.4% having residual BAT. Risk factor analyses, including gender, age, race, ethnicity, BMI, diagnosis, season and glucose prior to PET, are forthcoming.

Conclusion: BAT occurs with moderate frequency in the pediatric population and has the potential to affect interpretation of PET imaging results, although was uncommon in this cohort. Use of medical pretreatment may help decrease BAT, but future research is needed to determine the clinical utility of this practice.

Poster # 327

LIVER DISEASE AND TRANSPLANTATION IN TELOMERE BIOLOGY DISORDERS: INTERNATIONAL CONSORTIUM DATA

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Background: Patients with telomere biology disorders (TBD) are at increased risk of bone marrow failure, pulmonary and hepatic disease, and malignancy. Liver manifestations range from elevated liver enzymes to decompensated cirrhosis. No specific treatment exists for TBD-related liver disease, and the role of liver transplantation (LT) remains controversial due to uncertain peri-transplant considerations and post-transplant outcomes.

Objectives: To describe the clinical characteristics, management, and outcomes in patients with TBD-related liver disease.

Design/Method: We performed a retrospective, multi-center cohort study. Data was obtained from participating centers in the Clinical Care Consortium for Telomere-associated Ailments (CCCTAA) or individual patients using an online registry system, with IRB approval.

Results: Data from 81 patients with TBD and liver disease was collected from 17 centers. Patients were grouped by severity: Group A included 38 patients evaluated for LT, of which 20 underwent LT (Group AT); Group B included 43 patients with less severe liver disease not meeting criteria for transplant evaluation.

At time of liver disease diagnosis, there were no significant differences between Group A and B in age, gender, ethnicity, race, genetic mutation, telomere length, mucocutaneous triad, bone marrow failure, prior androgen use, bone marrow transplant, transaminases, WBC, platelet count, or ultrasound findings. As expected, supplemental oxygen requirement, concern for pulmonary arteriovenous malformation or hepatopulmonary syndrome, higher bilirubin, GGT, and INR were associated with Group A.

Group A patients were declined for LT due to concerns for progressive multisystem disease uncorrected by LT (n=5), liver disease severity not meeting LT listing criteria (n=1), or unclear reasons (n=9). Three patients died on the waitlist. Of 20 LT recipients, three also underwent lung transplantation. Post-LT immune suppression included steroids, tacrolimus and mycophenolate mofetil. Seven (35%) LT recipients had improvements in their supplemental oxygen requirement and/or blood counts. Post-LT malignancy occurred in 1 patient (skin cancer recurrence). Median follow-up from LT was 2.9 years (range 0.6-13.2 years). Median survival post-LT has not yet been reached. Group AT patients had significantly improved survival by age compared to all non-transplant patients (Group B and un-transplanted Group A: median survival in years AT=67, B=40, un-transplanted A=16, log rank test p=0.02).

Conclusion: We report our collective experience with a large cohort of patients with TBD-associated liver disease and who have undergone LT. LT recipients with TBD do not exhibit excessive post-transplant mortality. LT is likely a feasible treatment option for select patients with TBD-related liver disease and should be considered in patients meeting LT evaluation criteria.

Poster # 328

LENTIGLOBIN FOR SCD GENE THERAPY: TREATMENT PROCESS EVOLUTION LEADS TO IMPROVED OUTCOMES

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Background: The ongoing Phase 1/2 HGB-206 study (NCT02140554) of LentiGlobin for sickle cell disease (SCD; bb1111) gene therapy uses a modified human β-globin gene to express an anti-sickling hemoglobin (HbA^{T87Q}). Substantial changes were made to the protocol and manufacturing process in the pivotal (Group C) versus initial cohort (Group A).

Objectives: To assess relationships between biologic outcomes, clinical outcomes, and clonality in Groups A versus C.

Design/Method: The Group A protocol (cell collection and target busulfan dose) and manufacturing process were modified to improve cell dose, transduction efficiency, HbA^{T87Q} expression, and clinical benefit. CD34+ cells (collected by bone marrow harvesting [Group A] and plerixafor mobilization/apheresis [Group C]) were transduced with BB305 lentiviral vector (LVV). LentiGlobin was infused after myeloablative busulfan conditioning. Data are median (min–max) unless otherwise stated; timepoints are post-LentiGlobin infusion.

Results: As of 17 February 2021, Group A (n=7; 26 [18–42] years) and Group C (n=35; 24 [12–38] years) had 61.5 (55.5–66.1) and 17.3 (3.7–37.6) months' follow-up, respectively. Median drug product vector copy number (VCN) and transduction efficiency were greater in Group C (3.7 c/dg; 80.3%) versus Group A (0.6 c/dg; 27.7%). Peripheral blood (PB) VCN stabilized by M6 and was sustained throughout follow-up in both groups; however, M6 median PB VCN and HbA^{T87Q} levels were correspondingly higher in Group C (1.45 c/dg; 5.2 [2.6–8.8] g/dL; n=30/35) versus Group A (0.09 c/dg; 0.5 [0.1–1.8] g/dL). Median number of unique insertion sites was significantly higher in Group C than A ($P<0.001$), consistent with increased polyclonality and complete resolution of severe vaso-occlusive events in Group C. In Group C, treatment-emergent serious adverse events (TESAEs) in >1 patient were abdominal pain, nausea, opioid withdrawal syndrome, and vomiting (n=2; 5.7% each); no malignancy events were reported. One event of sudden death, considered unlikely related to LentiGlobin, occurred >M18 in a patient with significant baseline SCD-related cardiopulmonary disease. In Group A, the most common TESAE was sickle cell anemia with crisis (n=4; 57%); two events of acute myeloid leukemia (AML) were reported at 3.5 and 5.5 years. Both were considered unlikely related to the LVV, had classic AML driver mutations identified post-diagnosis, and resulted in death. Modifications in Group C are anticipated to reduce the risk of AML.

Conclusion: Alterations to the protocol and manufacturing process in HGB-206 resulted in improved cell dose, transduction efficiency, HbA^{T87Q} expression, and clinical outcomes in Group C versus Group A.

bluebird bio sponsored this study.

Poster # 329

REDUCING DURATION OF EMPIRIC ANTIBIOTICS IN CHILDREN UNDERGOING STEM CELL TRANSPLANTATION

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Background: Fever is common in children undergoing allogeneic hematopoietic stem cell transplant (HCT). Broad-spectrum antibiotics are started in febrile children and often empirically continued until neutrophil engraftment. Studies implicate antibiotic usage with altered intestinal microbiota and *Clostridium difficile* infection; therefore, reducing exposure could be beneficial.

Objectives: We instituted a quality improvement (QI) project with the aim of reducing antibiotic usage in low-risk patients undergoing HCT from a median of 20 days in 2020 to a goal median of 10 days.

Design/Method: Patients admitted at our center for first allogeneic HCT between 1/1/2021 and 12/1/2021 were evaluated. The intervention was to limit empiric antibiotics to 7 days after the initial onset of fever (>38°C) in eligible low-risk patients (afebrile for > 24 hours, no diagnosed infection requiring systemic antibiotics, and clinically stable per the treating team). The outcome measure was calendar days of antibiotic use during the hospitalization period from the start of preparative regimen to discharge or 30 days after HCT, whichever occurred first. Balancing measures were occurrence of bloodstream infection (BSI), fever, hemodynamic instability requiring intensive care unit admission within 3 days of intervention. Balancing measures were evaluated in 6-month cycles due to small numbers. IRB approval was obtained for retrospective application of project criteria to patients from calendar year 2020 to construct a historical cohort.

Results: During the QI period, 35 patients underwent initial HCT with 16 eligible for the intervention. For those eligible, median age was 7 years and 44% had an underlying hematologic malignancy. There were no significant differences in age, race, donor source, graft source and onset of fever between eligible patients and the baseline cohort (n=29 patients).

The median calendar days of antibiotic use was 20 (range 9-31) in the baseline cohort and significantly decreased to 12 days (range 4-33) in the intervention eligible cohort ($p < 0.01$). The intervention was adhered to in 12 of the 16 eligible patients. Two patients experienced a balancing measure. One patient had a new fever with a coagulase-negative *Staphylococcus* BSI (not susceptible to the previously stopped antibiotic). The other patient had recrudescence of fever but no infection was identified. There was no difference in BSI incidence during the hospitalization period between the cohorts.

Conclusion: Our preliminary data suggest that it was safe to limit empiric antibiotics to seven days from initial fever in low-risk HCT patients. These results should be validated and include impact on HCT outcomes in a prospective clinical trial.

Poster # 330

CLINICAL IMPACT OF ADENOVIRUS REACTIVATION IN PEDIATRIC ALLOGENEIC TRANSPLANT PATIENTS

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Background: Early adenovirus (AdV) reactivation post-allogeneic hematopoietic stem cell transplantation (allo-HSCT) causes significant morbidity and mortality as cellular immunity is compromised. AdV reactivation typically occurs in the gastrointestinal (GI) tract prior to detection in the blood, suggesting that pathogenesis involves localized tissue inflammation prior to systemic spread. We hypothesized that AdV reactivation triggers adverse events after allo-HSCT, such as graft versus host disease (GvHD) and thrombotic microangiopathy (TMA), and that reactivation and adverse events might be mediated by biomarkers such as interleukin-22 (IL-22), IL-22 binding protein (IL-22BP), and Reg3a.

Objectives: Investigate the clinical impact of early AdV infection post-allo HSCT, by identifying gut biomarkers implicated in the pathogenesis leading to mordbidity.

Design/Method: We performed a retrospective analysis of 108 pediatric allo-HSCT patients transplanted between 2015-2018 at a single institution. AdV positivity was identified by measurable adenoviremia and/or positive GI PCR at least once by day +60. IL-22, IL-22BP, and Reg3a concentrations were measured in plasma at day +30 using ELISA. Secondary outcomes of OS, GI aGvHD and TMA were evaluated using Cox regression analysis to determine hazard ratio (HR).

Results: Twenty-eight of the 108 (26%) patients were AdV+. IL-22 and Reg3a were elevated above their respective medians in the AdV+ cohort,(p= 0.070 and 0.004 respectively) and were modestly positively correlated with each other (r=0.17, p =0.093). IL-22BP was decreased below the median in the AdV+ population, p= 0.013. TMA incidence by day +100 was increased in AdV positive patients 34.7% vs. 20.8%, (HR of 2.10 (1.03 - 4.27, p= 0.04)). Acute GI GvHD was not increased in AdV positive cases (HR 0.95 (0.26-3.54, p=0.950)), but there was a trend towards reduced overall survival (HR 2.16 (0.92 - 5.06, p=0.075)).

Conclusion: Our analysis shows higher IL-22 levels with reciprocal reduction in IL-22BP in association with AdV reactivation. Increased Reg3a supports the presence of intestinal inflammation and is often associated with aGvHD, but our data do not show an association of AdV reactivation with GI aGvHD. This finding is surprising as it might be expected that GI inflammation initiated by AdV reactivation would increase presence of inflammatory T-cells and risk of aGvHD. The observation of increased TMA deserves further study. AdV likely increases local and systemic interferon levels and is a plausible initiator of TMA, as has been show previously with BK virus reactivation.

Poster # 331

SARS-COV-2 IN PEDIATRIC BONE OR MARROW TRANSPLANT PATIENTS IN THE US

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Background: Children with cancer who received an allogeneic blood or bone marrow transplant (BMT) may be at risk of severe COVID-19.

Objectives: We aimed to describe the clinical course of COVID-19 in this population.

Design/Method: The Pediatric Oncology COVID-19 Case (POCC) Report collects de-identified clinical and sociodemographic data on children with cancer infected with COVID-19 from >100 institutions. We examined the COVID-19 clinical course in children (<21 years at diagnosis) with cancer who received an allogenic BMT. We examined symptoms, support required, treatment for COVID-19, and changes in cancer-directed therapy. Additionally, we examined how receiving Graft-vs-Host Disease (GVHD) prophylaxis or treatment at the time of COVID-19 diagnosis affected the clinical course of COVID-19.

Results: Seventy-six POCC patients received an allogenic BMT prior to COVID-19 infection. Median age at COVID-19 diagnosis was 13 (IQR=6-17), 36% were non-Hispanic white, 33% Hispanic, and 26% other race. A majority of patients had a hematologic malignancy (97%); 48% ALL, 22% AML. BMTs were a median of 158 days prior to COVID-19 infection (Range: 14-528). Overall, 76% of patients reported symptoms; the most common being respiratory (59%) and general systemic (43%) symptoms. Forty two percent were hospitalized with 17% admitted to the intensive care unit. Nearly 20% required respiratory support, including oxygen (9%), Bi-Pap (5%), and intubation (5%). Thirty-four percent of patients received COVID-19 directed therapy, including antiviral therapy (16%), immune modulatory therapies (13%), and monoclonal antibodies (11%). Over 20% of patients had changes in their cancer-directed therapy. We compared rates of symptoms, support, therapy, and changes in cancer-directed therapy between those receiving GVHD prophylaxis or treatment at time of COVID-19 diagnosis (GVHD+: n=27, 36%) vs those who did not (GVHD-: n=49, 64%). The GVHD+ group appeared to experience a more severe COVID-19 course, with higher rates of symptoms (82% vs 74%), hospitalizations (56% vs 35%), ICU admissions (22% vs 14%), and respiratory support (30% vs 14%). Additionally, the GVHD+ group had higher rates of COVID-19 directed therapy (41% vs 31%) but similar rates of changes in cancer-directed therapy (22% vs 19%).

Conclusion: Many BMT patients experience severe COVID-19 clinical courses, with 42% hospitalized and 17% admitted to the ICU. Notably, those receiving GVHD prophylaxis or treatment at time of COVID-19 diagnosis had the highest rates of admission (56% hospitalized, 22% ICU). These results can help clinicians counsel their patients about risks of COVID-19 and appropriately monitor COVID-19 positive patients.

Poster # 332

REVACCINATION ADHERENCE FOR PEDIATRIC PATIENTS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT

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Background: Vaccine-preventable diseases are an important source of infectious morbidity among pediatric patients that have undergone allogeneic hematopoietic stem cell transplant (HSCT); full revaccination is standard in the United States. However, significant variability in revaccination initiation and adherence exists among this pediatric population, which may be impacted by transplant-related complications (TRC) and socioeconomic factors.

Objectives: Determine the effect of transplant-related complications, other clinical factors, and socioeconomic factors on revaccination schedule adherence among pediatric post-allogeneic HSCT patients. Determine the utility of a post-transplant vaccine clinic initiated in 2019 for improving revaccination adherence.

Design/Method: We conducted a retrospective chart review of a pediatric patients aged 1 month to 21 years who underwent allogeneic HSCT at Children's Healthcare of Atlanta (CHOA) between January 2010 and August 2020. Patients that died, relapsed, experienced graft failure, or moved out of Georgia prior to reaching 365 days post-transplant were excluded. A post-transplant vaccine clinic was initiated at CHOA in October 2019. Clinical and socioeconomic data were collected from institutional data submitted to the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, the CHOA Epic electronic health record (EHR), and the United States Census data.

Results: Overall, 246/374 (65.7%) of allogeneic transplant patients were eligible. Of eligible patients, 200/246 (81.3%) initiated revaccination and 121/246 (49.2%) completed a three-dose pneumococcal conjugate (PCV13) series. Of patients that initiated revaccination, 20/200 (10%) attended the CHOA post-transplant vaccine clinic. Patients that initiated revaccination had a median delay of 217 days from their transplant and 176 days after discontinuing graft-vs-host disease (GVHD) prophylaxis. Patients with chronic GVHD were more likely to have delayed revaccination (OR 1.2 [1.1-1.4], p=0.008) and a longer delay for initiating revaccination (p = 0.001). Conversely, patient age at transplant, sex, race, ethnicity, insurance status, distance from transplant center, pre-HSCT diagnosis, transplant source, regimen intensity, HLA match, history of acute GVHD, serious infection, or veno-occlusive disease (VOD) had no significant effect on revaccination delay. For PCV13, more patients attending the vaccine clinic completed the three-dose series on time compared to patients receiving vaccines at their primary care provider, though the difference did not reach significance (70% vs 58.9%, OR 1.2 [0.96-1.51], p=0.11).

Conclusion: Initiation of revaccination remains delayed for a significant portion of pediatric patients that have undergone allogeneic HSCT, driven in part by the presence of chronic GVHD. While data is limited, a dedicated post-transplant vaccine clinic shows promise for improving post-HSCT revaccination adherence.

Poster # 333

LONGITUDINAL GONADAL FUNCTION IN FANCONI ANEMIA PATIENTS AFTER HEMATOPOIETIC STEM CELL TRANSPLANT

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Background: Gonadal dysfunction and reduced fertility are common complications described by Fanconi anemia (FA) patients who have undergone hematopoietic stem cell transplantation (HSCT). The effect of HSCT on gonadal function among children with FA is not well described.

Objectives: To evaluate the incidence of premature ovarian insufficiency (POI) and testicular failure among FA patients who underwent HSCT.

Design/Method: We completed a retrospective analysis of FA patients at Cincinnati Children's Hospital Medical Center who had pubertal and hormonal data from their follow-up visits from July 1990 to June 2020. We defined POI in pre-pubertal females as those with undetectable Anti-Mullerian Hormone (AMH; ng/mL) and in pubertal females as those with follicle stimulating hormone (FSH) >20 mIU/L, or undetectable AMH with absent periods. Among pubertal males, testicular failure was defined as FSH >20 mIU/L and/or luteinizing hormone (LH) >10 mIU/L. Inhibin B (pg/mL) levels among male patients were also collected as markers of spermatogenesis and fertility recovery.

Results: We identified 98 female and male FA patients who had data available for analysis. Among 57 transplanted female FA patients, we identified POI among 30 (52.6%) female patients who developed POI at any time point from HSCT. Twenty-four of these patients (80%) developed POI at a median age of 13.82 years (range 5.78-26.86 years) at a median time of 3.81 years (range 0.58-13.99 years) after HSCT. Among 41 male patients, we identified testicular failure in 20 (48.8%) patients, at a median time of 5.2 years (range 0.73-30.4 years) from HSCT. Among all patients with POI, AMH levels negatively correlated with time from transplant ($r^2 = 0.21$, $p = 0.001$). Additionally, FSH levels increased with time from HSCT among POI patients, however was not statistically significant ($r^2=0.01$, $p=0.26$). Serum FSH increased with time from HSCT among male patients ($r^2=0.17$, $p=0.005$). Inhibin B levels also declined among male patients who had testicular failure following HSCT ($r^2=0.14$, $p=0.01$).

Conclusion: The incidence of POI and gonadal insufficiency is prevalent among female and male FA patients who have undergone HSCT. Serum AMH declined among female patients diagnosed with POI after HSCT. Serum AMH may serve as a more precise marker for POI diagnosis among female FA patients who have undergone HSCT. Increasing serum FSH and decreasing inhibin B correlated with time from HSCT among male FA patients. Because of the latency to gonadal dysfunction diagnosis, extended follow-up timepoints may be needed among these patients to monitor gonadal function.

Poster # 334

PILOT STUDY OF BMT ROADMAP 2.0: INCORPORATION OF USER MOBILE APP RATING SCALE TO ASSESS APP QUALITY

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Background: Families and patients undergoing hematopoietic cell transplantation (HCT) are under significant strain given the high-risk for life-threatening complications. Roadmap is a mobile health (mHealth) platform that was developed to support family caregivers during the HCT process. Iterative, user-centered development has led to the integration of resilience-based activities. Currently, a randomized controlled trial of the Roadmap Study is being conducted in family caregiver and patients undergoing HCT (ClinicalTrials.gov NCT04094844; supported by NHLBI R01HL146354).

Objectives: To understand user experiences and perceptions of the Roadmap platform using the uMARS questionnaire.

Design/Method: Between February 2021 and November 2021, a convenience sample of family caregivers and patients post-HCT were approached for pilot study enrollment. Family caregivers had access to the resilience-building activities of the Roadmap platform and patients were provided with access to the "control" version of the platform. The uMARS questionnaire was completed at least one week following enrollment. Descriptive statistics were performed with median calculations. Subscale scores of the uMARS questionnaire for Engagement, Functionality, Aesthetics, Information were calculated. Enrollment is ongoing.

Results: To date, 12 caregiver-patient dyads have enrolled. One dyad withdrew from the pilot study. Patient indications for HCT included: aplastic anemia (N=3), leukemia (N=7), myelodysplastic syndrome (N=1), and sickle cell disease (N=1).

Of the 11 dyads, 7 family caregivers and 8 patients have completed the uMARS survey. Caregiver subscale scores in Functionality and Information were higher for Roadmap compared with those subscale scores of many other mobile health apps (4.25 and 3.50 vs 4.03 and 3.06, respectively).[1] Caregiver and patient subscale score for Aesthetics was also higher (3.50 and 3.67 vs 3.40).[1]

Conclusion: The User Mobile App Rating Scale (uMARS) was successfully incorporated into a pilot study to evaluate the quality of the Roadmap platform. Some caregivers and patient subscale scores Roadmap were higher than other mobile health apps.[1] Based on this pilot evaluation of the uMARS questionnaire, it will be incorporated into future Roadmap studies (https://roadmap.study/), continuing to facilitate iterative improvements in the platform.

[1](Terhorst, Y., et al., PLOS ONE, 2020)

Poster # 335

FEASIBILITY AND ACCEPTABILITY OF EXTENDING VITALS CHECKS TO PROMOTE SLEEP DURING RECOVERY FROM HSCT

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Background: Children and adolescents undergoing hematopoietic stem cell transplant (HSCT) spend several weeks as inpatients, during which time sleep can be disrupted resulting in problems with daytime functioning. Research describing sleep during pediatric HSCT is limited, and few studies have investigated sleep interventions including environmental modifications to improve nighttime sleep. Extending vitals checks to every six hours instead of the standard four hours can potentially increase patient's nighttime sleep.

Objectives: From a randomized controlled study of overnight extended vitals checks to increase nighttime sleep and improve daytime functioning and quality of life, we present patient and parent report of acceptability of the intervention.

Design/Method: Acceptability data were collected from 23 parents and patients (M=13.82 years, SD=3.10, RANGE=8-20) undergoing HSCT at a hospital in the Northeast. Majority (52.2%) of patients were male (N=12); 17 parents (73.9%) were female. Patients were eligible to receive five consecutive nights of extended vitals checks starting on night +5 or night +10 following transplant. Acceptability data was collected on day +15. Items included parent and patient report of challenges to sleep (e.g., symptoms, noise, etc.) and acceptability of extended vitals checks as rated on a 1 (not at all) to 5 (extremely) scale.

Results: Both parents and patients reported that patient sleep disturbances during admission were primarily due to vitals checks, symptoms, and noise. There was high acceptability of receiving extended vitals checks each night the child is eligible (parents: M=4.04, SD=1.31; patients: M=3.60, SD=1.66). Parents and patients reported that vitals checks affect the child's sleep (parents: M=3.08, SD=1.4; patients: M=2.96, SD=1.46). There was low preference for standard vitals checks (parents: M=1.81, SD=0.98; patients: M=1.72, SD=0.70). In considering feasibility of the intervention, approximately 82.61% (n=19) of patients received at least one night of extended vitals and seven patients received all five nights. Fever was the most common reason patients were ineligible for extended vitals checks.

Conclusion: Patients recovering from HSCT may experience sleep disruptions due to the inpatient environment and treatment-related symptoms. In this sample, parents and patients reported high acceptability of overnight extended vitals checks. Most patients received at least one night of extended vitals checks suggesting that patients are generally eligible for this intervention. Future analyses will evaluate whether extended vitals checks improve patient sleep and daytime functioning. Continued assessment of methods to promote high quality sleep during hospital admissions is needed as this may improve daytime functioning and quality of life.

Poster # 336

TISAGENLECLEUCEL LEUKAPHERESIS AND MANUFACTURING OUTCOMES IN PATIENTS <3 YEARS OLD WITH R/R ALL

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Background: Tisagenlecleucel is approved for patients ≤25 years old with relapsed/refractory acute lymphoblastic leukemia (r/r ALL). Patients <3 years old were excluded from tisagenlecleucel trials for r/r ALL.

Objectives: To present US commercial outcomes of leukapheresis and tisagenlecleucel manufacturing for patients <3 years old with r/r ALL.

Design/Method: Patients were <3 years old upon tisagenlecleucel request, and had manufacturing data after the first FDA approval date of tisagenlecleucel. Only patients with US-manufactured (Morris Plains, NJ) and infused tisagenlecleucel were included. Data are stratified by age (<1 year and 1-3 years) and weight (<10 kg and ≥10 kg) and represent an extension of the previous report (Eldjerou, 2019).

Results: At leukapheresis, the median weight of 65 patients was 10.4 kg; median age was 15.6 months; 105 leukaphereses were completed (49 <10 kg and 56 ≥10 kg) with a median of 1 leukapheresis day for adequate cell counts (range, 1-4 <10 kg and 1-6 ≥10 kg). The median total blood volume was 3.5 L for 53 patients. Leukapheresis acceptance criteria (total nucleated cells: $\geq 2.0\times10^9$, CD3+ count: $\geq 1.0\times10^9$, CD3%: ≥3%) were achieved in 59/66 (26 <10 kg and 33 ≥10 kg) leukapheresis products. Median percent cell populations after leukapheresis were T cells 55.1%, B cells 16.9%, natural killer cells 4%, and monocytes 3.9%.

Manufacturing success is achieved by meeting approved specifications in the final products' formulation. Among 66 manufacturing batches (23 batches <1 year old and 43 batches 1-3 years old; 29 batches <10 kg and 37 batches ≥10 kg), 55 (83.3%) succeeded. The median cell dose was 2.3×10^6 CAR+ T cells/kg [range, 0.23-4.6×10^6 (2.5×10^6 <10 kg and 2.1×10^6 ≥10 kg)], median CAR+ expression was 12.0%, and median cell viability was 90.6%. From 2017-2021, the leukapheresis product had the highest CD3+ cell frequency in 2021. In-specification products increased from 69% in 2017 to 100% in 2021, and terminations decreased over time.

Measures for leukapheresis success include allowing >1 day of leukapheresis when feasible, blood priming the instrument, confirming absolute lymphocyte and/or CD3+ counts a day before leukapheresis, preventing hypocalcemia, securing adequate venous access, and sustaining 40% hematocrit. Throughout leukapheresis, monitor for alkalosis, hypocalcemia, hypomagnesemia, and prevent hypothermia.

Conclusion: Tisagenlecleucel leukapheresis and manufacturing in low-weight patients <3 years old with r/r ALL is feasible, with better outcomes over time. Communication between multidisciplinary teams, the institution, and manufacturer is key for advancement. Currently, clinical outcome data are being explored. Supported by Novartis.

Poster # 337

MYELOID CELL PHENOTYPE IN THE SETTING OF CD19-DIRECTED CAR T-CELL THERAPY

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Background: Chimeric antigen receptor T-cell therapy (CAR-T) has revolutionized treatment of relapsed and refractory (R/R) hematologic malignancies. Relapse and severe toxicity after CAR-T remain a problem. Improvements require consideration of other immune cell populations. Myeloid-derived suppressor cells (MDSC), macrophages, and monocytes contribute to the immunosuppressive tumor microenvironment in solid tumors and lymphomas. Knowledge about changes in myeloid cell populations with CAR-T in patients with high-risk hematologic malignancies may provide insight into the risk of relapse or severe toxicity.

Objectives: Our objectives are to determine the myeloid-lineage cell phenotype in patients who receive CAR-T for treatment of R/R B-cell ALL, and to determine if there is a relationship between suppressive or inflammatory myeloid cells, toxicity, and response to therapy.

Design/Method: We will recruit 10 pediatric patients with R/R B-cell ALL who receive CD-19 CAR-T at our institution. This project is ongoing and we have enrolled 5 participants; we expect to reach target recruitment by the time of presentation. Blood samples were collected at 5 key time points. Mononuclear cells were isolated using density centrifugation. Monocyte, macrophage, and MDSC populations were characterized using multi-color flow cytometry panels. Chart review provided information on primary diagnosis and disease course.

Results: Five participants have been enrolled. One participant experienced no toxicity and two experienced grade 1 cytokine release syndrome (CRS). Two participants experienced grade 2 CRS, one of whom also developed grade 2 immune effector cell-associated neurotoxicity syndrome and hemophagocytic lymphohistiocytosis (HLH). No participants have CD19 recovery or relapsed disease. Participants with none or grade 1 CRS demonstrated increased $CD163^{+}CD206^{+}$ tumor-associated macrophages (TAM) prior to CAR-T (pre-chemotherapy and day 0 time point). Participants with grade 2 CRS demonstrated decreased monocytic MDSCs (monoMDSC) prior to CAR-T.

Conclusion: Analysis of myeloid cell subsets prior to and following CAR-T for R/R B-ALL in pediatric patients reveals important trends. Participants with no mild toxicity demonstrated a higher percentage of TAMs, which have significant immunosuppressive potential. This suggests that beyond their ability to suppress the anti-tumor response, TAMs may play a role in mitigating the severe inflammation associated with CRS and HLH. Additionally, participants with more severe toxicity had lower levels of monoMDSCs, which have immunosuppressive capabilities, prior to CAR-T. Absence of monoMDSCs prior to CAR-T may help set the stage for a pro-

inflammatory environment. Taken together, the assessment of TAM and monoMDSC populations prior to CAR-T may help identify patients who are at higher risk of severe toxicity.

Poster # 338

POST-TRANSPLANT CHIMERISM MONITORING IN PATIENTS WITH SICKLE CELL DISEASE: MORE IS NOT ALWAYS BETTER

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Background: Allogeneic hematopoietic stem cell transplantation (AlloHCT) is curative for those with sickle cell disease (SCD). Monitoring of engraftment involves chimerism testing and resolution of SCD symptomatology. Patients may develop mixed donor-recipient chimerism (MC) post-AlloHCT, yet remain asymptomatic. The relationship between MC states and engraftment remains unclear. Similarly, there exists no established guidelines on post-transplant chimerism monitoring.

Objectives:

1. Survey pediatric HCT physicians regarding post-AlloHCT chimerism monitoring practices.
2. Longitudinally examine the stability of whole blood (WB) chimerism levels in patients post-AlloHCT and compare with CD71 (erythroid-specific lineage) chimerism levels.

Design/Method: 14-question survey was sent to 106 pediatric HCT providers and responses were analyzed using Qualtrics™. All pediatric patients who underwent AlloHCT for SCD between 2003 and 2017 at NewYork-Presbyterian Hospital Morgan Stanley Children's Hospital with >1year of and up to 5 years of follow-up were included.

Results: 106 surveys were distributed with a 40% response rate. Frequency of WB chimerism testing varied from weekly to monthly; 75% of providers routinely monitored cellular subset chimerism levels. 48% of participants reported discontinuation of chimerism testing at 5 years, 27% based on chimerism status and 9% indefinite monitoring. 61 patients were included in this retrospective analysis and stratified into 3 groups based on WB donor chimerism levels at 1 year post-AlloHCT: Group 1 - patients with donor chimerism <60% (low level chimerism [LLC],1.6%), group 2- donor chimerism 60-80% (intermediate level chimerism [ILC] 9.8%), and group 3- donor chimerism >80% (high level chimerism [HLC], 88.5%). For each group, mean WB donor chimerism levels remained stable throughout the follow-up period. Most individual chimerism levels remained within the initially assigned range (96.7%). Correlational analysis of WB donor chimerism with CD71 donor chimerism levels showed results to be highly aligned at each time point measured (p-value <0.001). All patients were transfusion independent by 2 years median of 42 days (range: -4 to 432 days post-HCT) with mean Hemoglobin S (HgbS) levels <40%.

Conclusion: Many patients with SCD will develop a MC state post-AlloHCT and practices vary widely among surveyed providers. Our data demonstrates that after one-year post-AlloHCT, WB and CD71chimerism levels remain stable, sustained and highly correlative. In those who are

transfusion independent, total hemoglobin and HgbS levels can also be used as a surrogate marker for monitoring engraftment, suggesting that routine laboratory and clinical assessments may be sufficient in asymptomatic patients which should decrease health care utilization costs. Longer follow-up and larger sample size are necessary to confirm these findings.

Poster # 339

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT FOR SICKLE CELL DISEASE- YALE EXPERIENCE

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Background: Sickle cell disease (SCD) is an inherited blood disorder associated with complex medical issues and decreased life expectancy. Hematopoietic stem cell transplantation (HSCT) is an established path for cure for SCD. The probability of overall survival is >90% at 5 years after human leukocyte antigen (HLA)-matched sibling donor (MSD) HSCT but is limited by donor availability. Donors other than MSD and novel low-intensity conditioning regimens are increasingly being used in HSCT trials with improved outcomes.

Objectives: To evaluate Yale New Haven Hospital's experiences with pediatric SCD HSCT.

Design/Method: A retrospective study of HSCT recipients for SCD was performed after an Institutional Review Board approval. Patients underwent HSCT from matched or one-antigen mismatched related or unrelated donor (UD) graft between 2015-2021.Reduced intensity conditioning (RIC) with alemtuzumab, fludarabine, melphalan +/- thiotepa (NCT00920972) or reduced toxicity regimen with busulfan and fludarabine or non-myeloablative (NMA) regimen with low dose irradiation and alemtuzumab were used. Graft Versus Host Disease (GVHD) prophylaxis included sirolimus (NMA) or tacrolimus, short-course methotrexate. Abatacept was used for all RIC patients.

Results: Fourteen HSCTs in 12 SCD patients (5 male, 7 female) from 2015 to 2021 were performed. Median age at HSCT was 17.5 years (range, 9-25). HSCT indications were stroke/increased transcranial doppler velocity (N=5), acute chest syndrome (N=11), and vaso-occlusive episodes (N=10). Seven and 5 patients received related and UD HSCT respectively; 6 were mismatched at one antigen or allele locus. Graft sources included marrow (10) and peripheral blood (2). Neutrophil engraftment occurred at a median of 13 days (range 10-23). One patient had graft failure (GF) with autologous graft recovery following 1st RIC HSCT and again after 2nd HSCT. This patient was rescued with 3rd HSCT from a haploidentical graft. The remaining 11 patients had >90% whole blood chimerism at day +30. For our 1st HSCT (n=12) recipients, we did not have any acute GVHD and CMV reactivation was 63%. Following a median follow-up of 2.0 years (range 0.3 – 4.7), we observed 100% overall survival (OS). Two patients with UD graft and recipient of 3 HSCT developed chronic GVHD. The rest of our 1-year post HSCT (N=8) patients are back to their normal life.

Conclusion: In our small cohort of high risk SCD patients with HSCT, we observed 100% OS with a low GVHD rate. Our study re-demonstrates the curative and major quality improvement benefit of HSCT for patients with severe SCD.

Poster # 340

TIGHT BP CONTROL DURING HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH SICKLE CELL DISEASE

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Background: Posterior reversible encephalopathy syndrome (PRES) is a serious complication of hematopoietic stem cell transplant (HSCT) characterized by the acute onset of seizures, headache, altered mental status and cortical blindness early post-transplant. It is associated with hypertension (HTN). Children with sickle cell disease (SCD) appear to be especially prone to developing PRES after HSCT with incidences ranging from 21% to 34% observed in major clinical trials of HSCT for SCD.

Objectives: To describe our single institution experience of using tight blood pressure (BP) control in pediatric patients with SCD undergoing HSCT.

Design/Method: At Phoenix Children's Hospital, all patients with SCD underwent a 24-hour ambulatory blood pressure monitoring prior to HSCT and a baseline for each patient was established. All patients identified as hypertensive began treatment, the rest received first-line treatment of either calcium antagonist followed by angiotensin-converting enzyme inhibitor, a diuretic, or both to achieve systolic BP no greater than 10% of their baseline. We conducted a retrospective chart review from 2010 to 2020, identifying 25 patients who underwent a HSCT for SCD, using a Campath/Flu/Mel conditioning regimen. We reviewed several end organ outcomes including cardiac: HTN, left ventricular mass (LVM); renal: eGFR (calculated by Bedside-Schwartz), use of antihypertensives pre/post-transplant; neurological: incidence of PRES, strokes, and MRI findings pre/post-transplant. Analysis performed included paired T test and measuring the frequency of certain outcomes.

Results: The average age at transplant was 11.5 years (range: 2-21 years). Indications for transplant included multiple pain crises, frequent acute chest syndrome and strokes. Preexisting HTN was found in 6 patients, 5/6 achieved good control w/ medications, 4/5 required continued treatment post-transplant. Post-transplant, HTN was diagnosed in 12 patients, 10/12 requiring initiation after Campath and 4/12 being weaned off prior to 1-year post-transplant. Pre-transplant, LVM > 95% for age was present in 7/24 patients; post-transplant, only one individual continued to have high LVM ($p < 0.01$). Pre-transplant, 14/24 patients had hyperfiltration w/ eGFR > 135; post-transplant, 11/24 patients experienced continued hyperfiltration ($p > 0.05$). On pre-transplant MRI, 10/24 patients had evidence of prior stroke; 8/10 eventually needed antihypertensive medications, and 9/10 patients had stable disease post-transplant. None of the 24 individuals who underwent

tight blood pressure control had PRES post HSCT.

Conclusion: Our preliminary results suggest that using tight BP control during HSCT is well tolerated, and no patient had PRES. In addition, patients had improvements or stabilization in cardiac, renal, and neurological function at 1-year post HSCT.

Poster # 341

TIME TO TRANSPLANTATION FOR PEDIATRIC AML IN FIRST COMPLETE REMISSION DOES NOT AFFECT OUTCOMES

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Background: Chemotherapy regimens for pediatric acute myeloid leukemia (AML) generally involve 2 induction courses intended to achieve remission, followed by intensification cycles to sustain it. For high-risk disease, remission is often consolidated with allogeneic hematopoietic stem cell transplantation (allo-HSCT), but the number, intensity and duration of chemotherapy cycles planned prior to allo-HSCT varies and is largely empiric. While additional chemotherapy may deepen the remission, it may also increase toxicity and either preclude or worsen transplant outcomes.

Objectives: To determine whether time to transplant, stratified by MRD status, affects transplant outcomes for pediatric AML patients in CR1 or CR2.

Design/Method: The CIBMTR datasets for secondary analysis from Qayed *et al* ('A validated pediatric disease risk index for allogeneic hematopoietic cell transplantation' in *Blood* in 2020) was utilized. This pediatric dataset from 2008-2017 (n=876) contains time from diagnosis or relapse to transplant (as a surrogate for number of chemotherapy cycles patients received prior to allo-HSCT) and pre-transplant MRD status for AML patients in CR1 and CR2. Comparisons of baseline characteristics by group were performed using two-sample independent t-tests, one way ANOVA, and Chi-square/Fisher's exact tests. Overall survival (OS), disease-free survival (DFS), treatment related mortality (TRM), and relapse were stratified by MRD status and analyzed by CR1 and CR2.

Results: For patients with AML in CR1 (n=651), OS, DFS, TRM, and relapse were not significantly different between time from diagnosis to transplant groups: short (<3.5 months [n=128]), intermediate (3.5-5 months [n=360]), and prolonged (≥5 months [n=163]). For CR2 patients (n=225), there was no difference in relapse, DFS, or TRM between time from relapse to transplant groups: <3.5 months (n=134) and ≥3.5 months (n=91). OS was significantly worse for CR2 patients transplanted ≥3.5 months after relapse (HR 1.7, p=0.0135). There were no significant differences in OS, DFS, TRM or relapse when patients in CR1 or CR2 were further stratified by MRD.

Conclusion: There is no advantage in DFS or OS for pediatric AML patients proceeding to allo-HSCT after a short, intermediate, or prolonged time from diagnosis in CR1. For CR2, earlier allo-

HSCT results in improved survival. This data did not delineate an effect based on MRD status prior to undergoing allo-HSCT, however numbers of patients with MRD status was limited and methods of MRD testing were heterogenous. Further studies are needed to determine optimal number of cycles of chemotherapy and depth of remission that result in the most favorable outcomes for children with AML.

(Qayed *et al*, Blood, 2020)

Poster # 342

CORD BLOOD TRANSPLANT SIGNIFICANTLY OUTPERFORMS IN CLEARING RESIDUAL HOST HEMATO-LYMPHOID TISSUE

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Background: Cord blood (CB) as a donor cell source in Hematopoietic Stem Cell transplant (HCT) has declined in recent years, mirrored by the rise in haplo-identical donor transplant. However, it has retained specific utility in high-risk myeloid malignancy and in those non-malignant conditions where time to transplant is critical and where full donor engraftment is advantageous.

Objectives: We studied whole blood and lineage-specific engraftment patterns in children undergoing allogeneic HCT with CB and other cell sources.

Design/Method: We retrospectively analysed serial donor chimerism of patients aged 0-16 years, treated with allogeneic HCT using CB, bone marrow (BM) or mobilised peripheral blood stem cells (PBSC) at Royal Manchester Children's Hospital for malignant and non-malignant indications between 2010 to 2020. Patients were categorised into CB and non-CB groups, and whole blood and lineage-specific chimerism were compared.

Results: Analysis was restricted to the 445 long-term surviving patients. Serial engraftment patterns were studied in both groups. At engraftment, there was no statistical difference in the mean whole blood donor chimerism between the CB and non-CB groups (98.1% v 98.9%; p=0.6). However similar comparison at 6 and 12 months post-HCT showed cords had a higher percentage of donor chimerism with mean 98.4% vs 93.9% (p=0.03) and 98.9% vs 91.1% (p<0.0001) respectively.

Lineage specific chimerism was analysed at 6 and 12 months. An unpaired two tailed t-test showed that there was significant statistical difference in my eloid (CD15+) chimerism data between the CB and non-CB groups (mean 100% vs 85.3% at 6mths, 99% vs 86.4% at 12months; p=0.003). The CB group also had higher T cell chimerism (Mean CD3: 93.4% vs 69.8% at 6 months; p=<0.0001).

"Last recorded" chimerism values > 2-years post HCT were analysed mean whole blood chimerism was strikingly greater in the CB cohort to the non-CB cohort (Mean 99.3% vs 75.6%, p=<0.0001).

Conclusion: Complete donor chimerism is much higher in CB transplant recipients than those who have received a BM or PBSC allograft. This represents an enhanced "graft versus marrow" effect mediated by CB transplants. This is of utility in difficult-to-cure leukaemia and in these non-malignant conditions where full donor chimerism translates to a clinical benefit, such as in metabolic conditions, including MPSI, since it is associated with superior donor-derived enzyme delivery. CB has higher rates of primary graft failure and procedure-related morbidity compared to these other cell sources but retains significant benefit compared to other cell sources.

Poster # 343

POTENTIAL BIOMARKERS OF ACUTE GVHD IN ALPHA/BETA T-CELL/B-CELL DEPLETED HSCT PEDIATRIC RECIPIENTS

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Background: Despite extensive ex-vivo aßT-cell depletion (aßTCD), grade II-IV acute graf-versus-host disease (aGvHD) still occurs in 25-30% of aßT-cell/CD19 B-cell depleted hematopoietic stem cell transplant (aßhaplo-HSCT) recipients**.** Studies aimed at predicting aGvHD ocurrence in aßhaplo-HSCT specific to children are lacking.

Objectives: To test the hypothesis that highly-polyfunctional aßT-cells adoptively transferred with the graft (<1x10^5/Kg) and recipient serum cytokine signatures early after aß haplo-HSCT (Day 7) predict aGvHD occurrence.

Design/Method: Aliquots of seven aßTCD grafts and twenty-three aßhaplo-HSCT recipients' serum at Days 0, 7, 14, 28, and 100 were collected. Graft-derived single-sorted $CD4^+$ and $CD8^+$ T-cells were stimulated and profiled by single-cell barcode chip assay (IsoPlexis. Brandford, CT) for polyfunctionality (secretion of ≥2 immunomodulatory cytokines from individual T-cells) and polyfunctional strength index (PSI= %polyfunctional T-cells x secreted proteins' mean fluorescence intensity). Furthermore, serum regenerating islet-derived 3a (REG3a) and suppressor of tumorigenesis-2 (ST2) were analyzed by ELISA to calculate the risk of aGvHD, non-relapse mortality (NRM), and steroid-refractory aGvHD (SR-aGvHD) using the previously-validated Mount Sinai Acute GVHD International Consortium (MAGIC) algorithm probability (MAP) (Viracor. Lee's Summit, MO).

Results: Elevated $CD4^+$ and $CD8^+$ T-cell polyfunctionality (up to 4+ cytokines) and PSI with effector and stimulatory dominant functions were observed only on grafts of patients that eventually developed aGvHD (n=4) (Fig1). Average PSI, driven by Granzyme-B, TNF-a, IFN-γ, MIP-1β, IL-2, and IL-8, was higher in both $CD4^+$ and $CD8^+$ T cells from the grafts of patients who developed aGvHD (Fig 2). Combinatorial cytokine secretion analysis showed that T-cells from grafts of patients who did not develop aGvHD (n=3) had unique signatures with $CD4^+$ T cells

predominantly co-secreting IL-2 and TNF-a, and $CD8^+$ T cells co-secreting IL2, IL8, TNF-a; MIP-1β, IL8; and MIP-1β, IFN-γ (Fig2). MAP-score differences between patients with (n=10) or without (n=13) aGvHD were only statistically significant at Day 28 but not at Day 7 as it tends to occur in the T-cell depleted HSCT setting (p=0.007, Fig3).

Conclusion: Increased donor T-cell polyfunctionality and pre-HSCT infusion recipient Th1-dominant serum cytokine signatures may be predictive of an increased risk of aGvHD whereas MAP scores may be more suitable for predicting NRM or SR-aGvHD in aßhaplo-HSCT pediatric recipients. Correlation with ongoing clonotypic analysis of residual graft-derived aßT cells will be crucial to elucidate the cross talking between the donor's immune system and recipient's inflammatory milieu.

Poster # 344

ABATACEPT FOR THE PREVENTION OF GVHD IN PEDIATRIC PATIENTS RECEIVING 7/8 HLA-MISMATCHED TRANSPLANT

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Background: Acute graft-versus-host disease (AGVHD) is a leading cause of transplant related mortality (TRM) following unrelated donor hematopoietic cell transplantation (HCT). The risk of severe AGVHD and resultant transplant related mortality (TRM) is highest after 7/8 HLA mismatched unrelated donor (MMUD) transplant limiting its broader use. Abatacept was recently FDA approved for the prevention of AGVHD in patients receiving an unrelated donor transplant. We sought to investigate the impact of abatacept in children after MMUD transplantation for hematologic malignancies.

Objectives: To determine the real-world impact of abatacept prophylaxis on the development of AGVHD, TRM, and survival in pediatric patients receiving a 7/8 MMUD HCT for hematologic malignancies.

Design/Method: We retrospectively analyzed pediatric patients at two large pediatric centers who received a MMUD HCT for hematologic malignancies and received GVHD prophylaxis with abatacept (days -1, +5, +14, and +28) combined with a calcineurin inhibitor (CNI) and methotrexate (MTX) between January 1st, 2014 and August 1st, 2021. For comparison, we analyzed patients from one center who received an 8/8 HLA matched unrelated donor (MUD) HCT for hematologic malignancies and received CNI/MTX alone for GVHD prophylaxis. Patients were excluded if they received abatacept on a clinical trial, were not in remission at time of HCT, received a prior HCT, or required additional GVHD prophylaxis.

Results: 26 MMUD patients received abatacept at the two centers (MMUD). 29 8/8 MUD patients received standard immunoprophylaxis with CNI/MTX (MUD). Rates of grade II-IV and III-IV AGVHD were 49.2% and 57.5% in the MMUD and MUD groups (p=0.39). Grade III-IV AGVHD

was 4% and 18.1% in the MMUD and MUD groups (p=0.11). Moderate to severe chronic GVHD at 1 year were 60.1% and 23.4% in the MMUD and MUD groups (p=0.04). 1-year TRM was 8.2% and 20.7% in the MMUD and MUD groups (p=0.25). Disease-free survival (DFS) and overall survival (OS) at 1 year were 75.1% and 83.3% in the MMUD group and 65.5% and 69% in the MUD group (p=0.49 and 0.27, respectively). Relapse at 1 year was 16.7% and 13.8% in the MMUD and MUD groups (p=0.82).

Conclusion: Our real-world results show low rates of severe AGVHD and TRM and encouraging DFS and OS in a pediatric cohort receiving abatacept off-study for GVHD prophylaxis after MMUD HCT, even when compared to 8/8 MUD transplants not receiving abatacept. The encouraging survival results occurred even in the presence of higher rates of chronic GVHD in the 7/8 MMUD cohort.

Poster # 345

PROSPECTIVE TRIAL OF IBRUTINIB FOR THE TREATMENT OF PEDIATRIC CHRONIC GRAFT-VERSUS-HOST DISEASE

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Background: Pediatric chronic graft-versus-host disease (cGVHD), a potentially debilitating, life-threatening complication of allogeneic hematopoietic stem cell transplantation, has limited treatment options. Ibrutinib, a once-daily oral Bruton's tyrosine kinase inhibitor, is the first approved therapy in the United States for adults with cGVHD after failure of prior systemic therapy. Ibrutinib treatment has resulted in durable responses and improved quality of life.

Objectives: Primary endpoints included pharmacokinetics (PK) and safety of ibrutinib in children aged ≥1 to <22 years with previously untreated or relapsed/refractory (R/R) moderate/severe cGVHD. Secondary endpoints included overall response rate (ORR) per 2014 NIH criteria, overall survival, duration of response (DOR), and patient-reported outcomes.

Design/Method: In this open-label, multicenter, international phase 1/2 trial (NCT03790332), patients aged <12 years received once-daily ibrutinib starting at 120 mg/m^2 and escalating to 240 mg/m^2 (full adult dose equivalent) after 14 days if no ibrutinib-related grade ≥3 toxicity; patients aged ≥12 years received once-daily ibrutinib 420 mg.

Results: 59 patients (median age 13 years [range 1-19]) were enrolled; 12 were previously untreated (1L) and 47 had received a median of 2 lines of prior therapy [range, 1-12]). Plasma concentration-time profiles for ibrutinib 240 mg/m^2 (recommended pediatric equivalent dose [RPED]) were comparable to those observed in adults with cGVHD at a dose of 420 mg/day. Median time on treatment was 8 months (range 0.1-26). Grade ≥3 treatment-related adverse events (AEs) occurred in 23 patients (39%); 14 patients (24%) experienced an AE leading to ibrutinib

discontinuation. ORR was 78% (46/59): 83% (10/12) in 1L patients and 77% (36/47) in patients with R/R cGVHD. Of 46 responders with a median follow-up of 20 months (range 2-32), 12-month DOR (95% CI) was 60% (25-83%) in 1L patients and 58% (35-75%) in patients with R/R cGVHD; median DOR was not reached. Sustained response rates for ≥20 weeks were 70% (7/10) and 58% (21/36) in 1L and R/R patients, respectively. 14 patients (44%) aged ≥12 years had an improvement (≥7-point decrease) in Lee cGVHD Symptom Scale scores on ≥2 consecutive visits.

Conclusion: In this analysis of children with previously untreated and R/R moderate/severe cGVHD, PK and safety were consistent with the known profiles of ibrutinib and cGVHD. Ibrutinib plasma concentrations at the RPED of 240 mg/m^2 (<12 years) or 420 mg (≥12 years) were generally within the exposure range observed in adults. Response rates were higher than previously observed in adults and were generally durable, demonstrating promising activity of ibrutinib in children with cGVHD.

Poster # 346

TARGETING SOMATIC MOSAIC MUTATIONS IN VASCULAR ANOMALIES WITH ONCOLOGIC MEDICATION

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Background: Vascular anomalies are a heterogeneous group of rare diseases with almost no therapeutics being developed specifically for them. After discovering multiple oncogene mutations as etiologic factors in both vascular malformations and tumors, targeted medications used originally in malignancy have been re-purposed with proven clinical efficacy in the field.

Objectives: Present a case series of our institutional experience.

Design/Method: Chart review of vascular anomalies and/or vascular tumors with identified somatic mutations including *PIK3CA, BRAF, RASA1* and *PDGFRB*. Describe targeted management, side effects and outcomes.

Results: Our case series includes seven patients with *PIK3CA* somatic mosaic mutations treated with alpelisib, one patient with an aggressive vascular tumor characterized by a somatic *BRAF* mutation treated with trametinib, one patient with capillary malformation – arteriovenous malformation caused by *RASA1* mutation treated with trametinib and one patient with metastatic myopericytoma caused by *PDGFRB* mutation treated with imatinib. All the patients consented to targeted medical therapy as there were no surgical or interventional therapies available for their case and they all had progressive disease at the time of initiation. None of the patients included in this case series had a malignancy. Of the seven patients with a *PIK3CA* mutation, five had a clinical diagnosis of CLOVES or M-CM (Congenital Lipomatous Overgrowth with Vascular Malformations, Epidermal Nevus and Skeletal Anomalies/Scoliosis or Macrocephaly-Capillary Malformation). The other two included: *PIK3CA*-related overgrowth syndrome and FAVA (fibroadipose vascular anomaly). There were no greater than grade 2 side effects to alpelisib. The patient that had *PIK3CA*-related overgrowth syndrome

and was treated with alpelisib had stable disease during treatment for two years, but then progressed rapidly and died of disease complications three months after stopping therapy. All the other patients achieved stable and improved clinical status and continue on medication. There was no progression while on therapy and no complete cure. Identification of *PIK3CA/BRAF/RASA1/PDGFRB* mutations via somatic genetic panel analysis allowed initiation of treatment for these patients that had no surgical alternatives. Overall, patients tolerated targeted therapies well with minimum side effects.

Conclusion: Somatic genetic analysis should strongly be considered in progressive, debilitating vascular anomalies. Hematology-oncology can offer targeted medical therapy either as standard of care or by enrollment in a clinical trial for patients with an identified pathogenic variant.

Poster # 347

USE OF THE LEVONORGESTREL INTRAUTERINE SYSTEM IN PATIENTS WITH VASCULAR MALFORMATIONS

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Background: Vascular malformations and their treatment can pose special reproductive concerns. It is important to assess the contraceptive needs of these patients as some may have an increased risk of thrombosis and thus will be limited to progestin only options, others may receive treatment with teratogenic medications and finally a pregnancy may worsen their malformation. Furthermore, some treatments such as anticoagulation may increase menstrual flow.

Objectives: To describe the experiences of treating the reproductive needs of patients with vascular malformations with the levonorgestrel intrauterine system (LNG-IUS), known as an intrauterine device (IUD).

Design/Method: A chart review was performed of all patients who received gynecologic care within a single center's multidisciplinary vascular anomalies clinic from 2018 – present. Data was then gathered on patients who were treated with the LNG-IUS including: indication for use, change in menstrual pattern, continuation rate, complications of the device.

Results: Adolescents and young women seen by Gynecology were offered treatment of their reproductive needs with options, including LNG-IUS when appropriate. Median age was 19 years (Range 12-30). Twelve patients underwent placement of the LNG-IUS. Diagnoses included: venous (5), lymphatic (1), arteriovenous (2), combine include Klippel-Trenaunay (4). Indications for placement included abnormal uterine bleeding, contraception and menstrual associated pain. 3 were placed under general anesthesia. There were no unsuccessful insertions. The only complication was one expulsion which occurred during an episode of heavy menstrual bleeding while the patient was fully anticoagulated. This patient subsequently underwent replacement of the LNG-IUS. All patients reported a reduction in menstrual flow and 9 achieved amenorrhea, defined as no menstruation for 6 months. All patients have continued the device and none have requested removal.

Conclusion: The LNG-IUS appears to be a promising treatment option for patients with vascular malformations with minimal systemic absorption of progesterone.

Poster # 348

PHARMACOKINETICS OF BLEOMYCIN SCLEROTHERAPY IN PATIENTS WITH VASCULAR MALFORMATIONS

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Background: Bleomycin, a chemotherapy agent that inhibits synthesis of DNA, has been increasingly utilized in sclerotherapy for both adults and children with vascular malformations. A serious long-term risk of intravenous bleomycin is dose-dependent interstitial pneumonitis following systemic administration. However, little is known about absorption and circulating levels of bleomycin when used in sclerotherapy for patients with vascular malformations.

Objectives: We hypothesized that bleomycin, when administered as a sclerosant interstitially or intraluminal, will have predictable pharmacokinetics and systemic absorption.

Design/Method: IRB-approved prospective study on patients receiving bleomycin sclerotherapy in the management of vascular malformations. Depending on the type of vascular malformation and mode of intervention, bleomycin was administered either in the lumen or interstitial space of the involved lesion. A bleomycin assay measured serum bleomcyin plasma concentrations vs. time at 7 intervals following treatment. Pharmacokinetic parameters were obtained for each participant and included peak plasma concentration after administration (C_{max}), time to reach peak plasma concentration (T_{max}), volume of distribution (V_d), elimination half-life ($t_{1/2}$), the volume of plasma cleared of the drug per unit time (CL), and total systemic exposure (AUC).

Results: Fifteen patients were enrolled (5 lymphatic, 4 venous, and 6 arteriovenous malformations). Bleomycin was administered interstitially (IS) in 11 patients and intraluminal (IL) in 4. Median age of 13 years (range 2-67). Pharmacokinetic analysis revealed terminal elimination half-life ($t_{1/2\lambda z}$) of 88.51 (± 23.09) and 111.61 (± 37.75) min for the IS and IL groups, respectively. The volume of distribution (Vd) was 4.86 (± 6.74) and 1.55 (± 0.54) L for the IS and IL groups, respectively. The area under the curve (AUC) was 53.9 (± 23.45) and 129.17 (± 93.57) mg*min/L for the IS and IL groups, respectively. There were no statistically significant differences in $t_{1/2\lambda z}$, Vd, or AUC parameters between the IL and IS groups. However, the total volume of distribution (V_d,) for our study was 3.44L.

Conclusion: Bleomycin is absorbed systemically when used as a scleroscant for vascular malformations when injected either interstitially or intraluminal.

Poster # 349

PULMONARY INFANTILE HEMANGIOMA: RARE VASCULAR ANOMALY WITH LIFE-THREATENING OUTCOMES

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Background: Infantile hemangioma (IH) is a common benign vascular tumor that presently shortly after birth. It most commonly affects the skin, although hepatic involvement occurs in some cases and requires specific diagnostic consideration and treatment. Pulmonary IH is rare, and there are limited reports of clinical presentations and outcomes. The natural history of co-occuring pulmonary, cutaneous, and hepatic hemangioma has not been previously reported. We describe the clinical, radiological, and pathological findings of nine patients with pulmonary IH, including five infants with co-occuring hepatic involvement and seven infants with co-occuring cutaneous involvement.

Objectives: To describe the clinical presentation, diagnosis and treatment of nine infants with pulmonary infantile hemangioma

Design/Method: An IRB-approved, retrospective review of patients with a diagnosis of pulmonary IH was conducted. Cases from patients presenting between 1918 to 2021 were identified via the Department of Pathology database at our institution. Histopathologic analysis confirmed pulmonary IH in nine infants, with positive endothelial glucose transporter-1 (GLUT1) immunostaining in eight cases.

Results: All patients presented with respiratory distress, including cyanosis, tachypnea, and hypoxia. The median age at initial presentation was two months (range, birth to 12 months). Five patients had a single pulmonary hemangioma ranging in size from 0.2 to 8.0 cm; four had multiple lesions. Chest radiography demonstrated nonhomogeneous, mass-like consolidative opacities or rounded nodules. The median age at pathologic diagnosis was 6.5 months (range, 5 weeks to 16 months). Treatment was primarily supportive. Four patients received medical therapy with one or more of the following: propranolol (n=2), interferon (n=2), and corticosteroids (n=5). Five patients underwent surgical resection of pulmonary masses and two underwent hepatic embolization. All patients who had surgery or received medical therapy survived. Four patients died; causes of death were sepsis, abdominal hemorrhage, pneumonia, and liver failure.

Conclusion: Although rare, pulmonary IH should be considered in the differential diagnosis of infants with pulmonary masses, especially when accompanied by hepatic IH. While radiography can assist with identification of this rare disorder, biopsy may be necessary to confirm the diagnosis. Early recognition is critical for patients to receive prompt administration of life-saving treatment.

Poster # 350

MENTAL HEALTH EVALUATION IN PATIENTS WITH VASCULAR ANOMALIES

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Background: Patients with vascular anomalies can have significant disfigurement, poor quality of life and chronic pain, all of which can affect their mental well-being. Although most of the multidisciplinary care is focused on the medical and surgical treatment of the vascular anomaly, it is critical to also assess and address the mental health concerns of this population.

Objectives: To evaluate the importance of discussing mental health in patients with vascular anomalies with the involvement of a psychologist.

Design/Method: IRB approved retrospective study of patients with a vascular anomaly attending a single center multidisciplinary clinic between July 2020 to November 2021. All patients who were assessed at least once by the team psychologist were included.

Results: Twenty-six patients were included. Median age was 14 years (range: 3-29). Nineteen female, 7 male. Diagnoses included the following: vascular tumor (1), capillary (2), venous (6), lymphatic (3), arteriovenous (3), combined (5), KTS (6). Thirty-one percent (8 of 26) of patients reported a previous mental health diagnosis. Seven of the 8 were diagnosed with anxiety and/or depression. Only 50% of patients with a mental health diagnosis received mental health treatment. Eleven percent of patients confirmed bullying at school. 96% of patients did not have a family history of mental health issues. Eleven percent of patients reported a history of suicidal ideation. Only 3 of the 26 patients disclosed substance abuse. Forty-two percent of patients complained of chronic pain.

Conclusion: Patients with vascular anomalies may be more susceptible to mental health issues for a variety of reasons. Including a psychologist as an integral part of their multidisciplinary care is, therefore, extremely beneficial to aid patients and families in obtaining mental health therapy.

Poster # 351

MULTIMODAL TREATMENT FOR FIBROADIPOSE VASCULAR ANOMALY: A SINGLE-INSTITUTION EXPERIENCE OF 106 CASES

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Background: Fibroadipose vascular anomaly (FAVA) is a rare, complex vascular malformation characterized clinically by pain, contracture, swelling, and functional limitation of the affected limb. Treatments for FAVA include sclerotherapy, cryoablation, surgical resection, and medical therapy, but limited data exists on the relative use of these therapies and patient response. Outcomes data for FAVA are limited by the rarity of the diagnosis and paucity of large, high-quality studies.

Objectives: To describe the clinical characteristics, treatment approach, and clinical response of patients with fibroadipose vascular anomaly.

Design/Method: A single-institution, IRB-approved retrospective chart review of patients diagnosed with FAVA was performed. All cases had histopathologic confirmation of FAVA. Demographics, presenting features, treatment modalities, and clinical response were evaluated.

Results: A total of 106 patients were evaluated. Female to male ratio was 3:1; median age at symptom onset was 10 years; median time from symptom onset to FAVA diagnosis was 4 years. Presenting symptoms included pain (94%), functional limitation (25%), swelling (13%), and joint contracture (9%). Most FAVA (92%) involved the lower extremities: calf (37%), thigh (31%), ankle (9%), foot (7%), knee (6%), and buttock (3%). Upper extremity involvement included the arm (14%) and hand/wrist (5%). Partial or full surgical resection (88%), sclerotherapy (56%), and cryotherapy (29%) were the most frequent treatment modalities. Twelve patients received medical therapy with an mTOR inhibitor; nine had a partial response. Sixty percent of patients received multimodal treatment; 41% of patients had persistent pain after multimodal therapy. Neural invasion ($p=0.0029$), contracture at presentation ($p=0.014$), and multifocal disease ($p=0.0013$) were associated with persistence of pain after treatment.

Conclusion: A combination of surgical, interventional, and medical therapies are used to treat FAVA. Despite multimodal treatment, many FAVA patients have persistence of pain. Further investigation into the mechanism of disease and exploration of therapeutic targets are needed.

Poster # 401

INCREASED INTRACRANIAL PRESSURE AS THE PRESENTATION OF EVANS SYNDROME IN A 4 YEAR OLD BOY

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Background: Evans syndrome (ES) is a combination of autoimmune cytopenias, most commonly autoimmune hemolytic anemia and immune thrombolytic purpura. Autoimmune lymphoproliferative syndrome (ALPS) is a disorder of disrupted lymphocyte homeostasis that overlaps with ES. Seldom patients with ES/ALPS have been described as having neurological manifestations in the course of their disease.

Objectives: We describe the diagnosis and management of a case of ES presenting as increased intracranial pressure (ICP) in a 4 year old boy.

Design/Method: Authorization for release of health information pursuant to HIPAA was obtained. Chart review done to obtain relevant history, laboratory values, imaging, and pathology.

Results: A 4 year old boy with a history of sickle cell trait failed his vision screening at a well visit: 20/100 oculus dextrus (OD), 20/125 oculus sinister (OS), with bilateral papilledema. In the Emergency Department he was found to be hypertensive. Labwork revealed neutropenia,

thrombocytopenia, and anemia with warm autoantibody IgG (with Direct Coombs IgG 2+, C3 negative, with weak para-agglutination). Brain MRI/MRA/MRV showed only evidence of increased intracranial pressure and MRI spine had enlarged retroperitoneal lymph nodes. Lumbar puncture (LP) was significant for increased opening pressure of 44 cm H_2O and WBC 38 leukocytes/mm^3 .CT abdomen/pelvis had enlarged paraaortic lymph nodes (2.7 cm), without splenomegaly. Bone marrow biopsy/aspirate and biopsy of paraaortic lymph nodes were negative for evidence of malignancy or infection. Subsequently, his neutrophil associated antibody and platelet antibody were positive. ALPS genetic testing was negative; panel had 2 abnormal values [T Cell Receptor (TCR) alpha beta double negative T cells (DNTC) (2.5%) and CD3+CD25+/HLA DR (0.6%)] and 2 normal values [B220+ TCR alpha/beta DNTC (20%) and CD27+ B cells (25%)].

Patient was started on prednisone and topiramate. Repeat abdominal CT, three months from presentation showed reduced paraaortic lymph nodes. Direct Coombs was negative after nine months and antiplatelet antibody was negative after eight months on steroids. His neutrophil antibody remains positive as he is being tapered off his steroids.

Conclusion: The case presented here is unique in that our patient with sickle cell trait presented with poor vision and found to have papilledema as his first sign of ES. Elevated ICP as the driver of neurological symptomatology in ES/ALPS is incredibly uncommon with 5 such pediatric patients previously described, only 2 of which had neurologic manifestations at diagnosis. Additionally, we successfully managed increased ICP with one LP and topiramate in a patient with sickle cell trait.

Poster # 402

RECURRENT CYTOPENIAS IN A CHILD WITH FOCAL SEGMENTAL GLOMERULOSCLEROSIS

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Background: The diagnosis and management of children with cytopenias can be challenging. It can at times be hindered by ongoing concurrent disease and/or immunosuppressive drugs. We present the case of a 3-year-old male with a history of recurrent autoimmune neutropenia and Focal Segmental Glomerulosclerosis (FSGS) now presenting with thrombocytopenia.

Objectives: To review the etiologies and diagnostic approach of cytopenias through a case report.

Design/Method: We present the case of a 3-year-old Hispanic male with a history of autoimmune neutropenia, FSGS controlled on cyclosporine and a potassium voltage-gated channel gene mutation associated with QT prolongation, who was found to have pancytopenia on routine lab work: Hgb: 10.3 g/dL, Hct: 32.0 %, MCV: 73 fL, Retics: 1.46%, WBC: 4.8 10K/uL, ANC:480 10K/uL, and platelets: 26 10K/uL. On exam, the patient presented rhinorrhea and cough. Prior hematologic workup included positive Antineutrophil Antibodies and Normal Hemoglobin electrophoresis with slightly elevated Fetal Hgb at 4.4%. Differential diagnoses for him included

primary or secondary immune-mediated cytopenias or decreased production, such as marrow failure and hematologic malignancies.

Results: Bone marrow examination revealed normal morphology. It showed hypercellularity with all three cell lines well represented and no evidence of malignant cells. M:E ratio was 4:1. Karyotype, FISH ALL Panel, MDS Panel, and NGAMT panels were normal. ALPS panel was significant for increased frequency but a normal absolute count of abTCR+ DNT cells. However, these cells were negative for B220 expression. Moreover, the patient did not present any other criteria for ALPS, such as lymphadenopathy or splenomegaly. Other tests that were negative include Granulocyte antibody, CMV and EBV serologies, and Rheumatologic panel, including ANA. IgGAME was within normal limits except for mildly elevated IgG. Considering his benign bone marrow findings, and that on cyclosporine he could be partially immunosuppressed, we diagnosed his cytopenias to be autoimmune in nature. He was treated with dexamethasone 0.6 mg/kg BID for 7 days. Repeat CBC after treatment resulted as follows: Hgb: 10.3 g/dL, HCT: 31.6 %, MCV: 74 fL, WBC: 9.6 10K/uL, ANC: 2520 10K/uL, Platelets: 490 10K/uL.

Conclusion: Most children with cytopenias have an idiopathic autoimmune disease with no secondary cause. Chronic or multi-lineage disease should prompt testing for decreased production or secondary causes of autoimmune cytopenias, including infectious, SLE, ALPS, and common variable immune deficiency. One should keep in mind that immunosuppressive drugs can influence diagnostic tests, and if possible, should perform diagnostic tests off these agents.

Poster # 403

VARIABLE CLINICAL FEATURES IN A LARGE FAMILY WITH DIAMOND-BLACKFAN ANEMIA

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Background: Diamond-Blackfan Anemia (DBA) is an autosomal dominant ribosomopathy caused predominantly by pathogenic germline variants in ribosomal protein genes. It is characterized by failure of red blood cell production, and common features include congenital malformations and cancer predisposition. Mainstays of treatment are steroids, red blood cell transfusions, and hematologic stem cell transplantation. Despite a better understanding of the genotype of DBA, the biological mechanism resulting in clinical phenotype remains poorly understood, and wide heterogeneity can be seen even within the same family as depicted here.

Objectives: To describe the variable clinical features in a large family with DBA caused by a pathogenic missense mutation in RPS19.

Design/Method: Thirty family members enrolled in the National Cancer Institute inherited bone marrow failure syndromes study were evaluated with detailed medical questionnaires and physical examinations, including 22 in the family bloodline and eight unrelated partners. Eight participants had been previously told they had DBA by clinical criteria. Targeted germline *RPS19* testing was

done on all family members.

Results: A pathogenic heterozygous missense mutation in *RPS19* (p.G185A) was detected in nine family members, including one person previously presumed unaffected. Seven family members presented with macrocytic anemia in infancy, all of whom were responsive to prednisone. Four family members achieved spontaneous remission; however, one individual relapsed after thirty-six years and is now transfusion dependent. One prednisone responsive individual electively discontinued steroid treatment, and lives with severe anemia. One prednisone responsive individual died at age 28 from a stroke. Two family members developed colorectal cancer in their fifties; one had never required treatment for anemia. None had major congenital anomalies, but seven had hypoplastic thenar muscles and six had short stature.

Conclusion: This large family with DBA demonstrates the heterogeneity of phenotypes that can be seen within the same genotype. Most family members presented with steroid-responsive anemia in infancy and subtle congenital malformations, findings consistent with recent genotype-phenotype studies on *RPS* DBA. However, two family members were relatively unaffected, underscoring the importance of further studies to assess modifier genes, epigenetic and/or environmental factors which may result in normal erythropoiesis despite underlying ribosome dysfunction. Additionally, this large family highlights the need for individualized treatment, and the importance of early cancer surveillance even in individuals with clinically mild DBA phenotypes.

Poster # 404

CASE SERIES: DIAMOND-BLACKFAN ANEMIA WITH A DE NOVO RPS19 MUTATION IN A CRITICALLY ILL CHILD

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Background: Diamond-blackfan anemia (DBA), is historically known as the first established ribosomopathy, with a global incidence of five-seven cases per million live births. The hallmark of this disorder is congenital abnormalities, macrocytic anemia with reticulocytopenia and absent or reduced erythroblasts in the bone marrow. Currently, 24 genotypic mutations have been associated with the disorder, the commonest being RPS19. With the widespread use of whole exome sequencing (WES), a multitude of allelic variations have been recognized, leading to the identification of different genotypic-phenotypic presentations straying from what is known as the classical DBA phenotype. Currently, the underlying pathophysiology of how a defect in a ribosomal biogenesis leads to such phenotypic heterogeneity is unknown, however, it's been theorized that dysregulation of apoptotic pathways might play a significant role in the disease manifestation.

Objectives: Two reported cases of DBA harboring a de novo mutation in the RPS19 gene, both presenting in critical illness, aplastic crisis and the latter with Hemophagocytic lymphohistiocytosis (HLH) aswell.

Design/Method: Case series

Results: Case one describes a 6 month old female presenting in status epilepticus and aplastic crisis (Hemoglobin of 3.1g/dl). Bone marrow aspiration reveled markedly decreased erythropoiesis. The diagnosis of DBA was made via WES which identified a de novo mutation in the RPS-19 c.49 G>C gene. Patient was then placed a 6 week course of 2mg/kg of prednisone, her Hemoglobin stabilized at levels >9g/dl without the requirement of any transfusions. Prednisone was then slowly titrated then discontinued, with no relapse in disease. Case two describes a 6 month old female presenting in multisystem organ failure & aplastic crisis (Hemoglobin 1.7g/dl). Diagnostic labs and bone marrow aspirate was consistent with HLH thus the patient was started on dexamethasone and etoposide per the 2004-HLH protocol treatment plan. The diagnosis of DBA was made via WES which identified a de novo mutation in the RPS19 c.357-1G>T gene. The patient was transitioned to a 6 week course of 2mg/kg of prednisolone, her HLH biomarkers continued to normalize, however, Hemoglobin continued to downtrend <9g/dl thus patient was switched to chronic transfusion protocol.

Conclusion: These two cases illustrate two novel genotypic-phenotypic correlation of DBA and further demonstrating variability in treatment response. Moreover, these two cases emphasize the utility of genetic testing in cases of aplastic crisis due to the confounding effects of critical illness that may distort the underlying etiology.

Poster # 405

CASE SERIES: BONE MARROW FAILURE IN TEEN SIBLINGS WITH UNIQUE RPS19 VARIANT

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Background: Upon diagnosis of aplastic anemia, inherited bone marrow failure syndromes and acquired etiologies must be considered. Investigating causality is particularly important when multiple family members are affected. It is also essential to identify novel causative genetic variants of bone marrow failure in order to direct treatment in these patients.

Objectives: To describe the diagnosis and management of two siblings who presented two weeks apart with severe pancytopenia and were ultimately both diagnosed with severe aplastic anemia.

Design/Method: The first patient is a 13-year-old non-binary female who presented from clinic after getting routine labs with severe pancytopenia. Bone marrow biopsy revealed marked hypocellularity (0-10%) with hypoplasia. The second patient is their 16-year-old brother who presented two weeks later with new-onset petechial rash and was found to also have pancytopenia. His bone marrow biopsy demonstrated variable cellularity (10-70%), but after months of transfusion-dependence he met criteria for severe aplastic anemia. Laboratory evaluation for acquired etiologies such as infection was negative. Both patients had briefly taken fluoxetine, but otherwise no potential medical triggers or environmental exposures were identified. Upon genetic evaluation, both patients were found to have a heterozygous variant of unknown significance of *RPS19* (c.-163>T), which substitutes a moderately conserved nucleotide in the noncoding exon 1

in 5' untranslated region of *RPS19*. Although this variant has not been classified as pathogenic, three other variants in the 5' untranslated region of RPS19 have been reported in patients with Diamond Blackfan Anemia (DBA). In contrast to classic DBA, these patients did not present in infancy or early childhood. Likewise, they lacked congenital anomalies or other classic phenotypic characteristics of disease. Given lack of other identified etiologies, however, an inherited bone marrow failure syndrome was presumed.

Results: With suspected genetic predisposition, matched sibling donor transplant was deferred and both patients underwent a matched unrelated donor bone marrow transplant with reduced-intensity conditioning. Our first patient remains well without post-transplant complications and our second patient has recovered from treatment-related peripheral neuropathy and urticarial vasculitis.

Conclusion: With these cases, we aim to share a unique presentation of aplastic anemia that reveals a potentially novel pathogenic variant as well as to provide our approach to medical management in pediatric aplastic anemia in the setting of uncertainty. Identification of other patients with bone marrow failure and this genetic variant will be important to determine its pathogenicity.

Poster # 406

SRP54, A NOVEL SEVERE CONGENITAL NEUTROPENIA AND SHWACHMAN-DIAMOND-LIKE SYNDROME PATHOGENIC VARIANT

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Background: Severe congenital neutropenia (SCN) is a rare disorder, occurring in approximately 1 in 200,000 individuals. Most patients have an identifiable pathogenic variant (PV) in known SCN genes, such as ELANE and SBDS (Shwachman Diamond syndrome). There are many other genes associated with SCN, and new genes are regularly being discovered. SRP54 PVs have been recently described as causative of both SCN and may also cause Shwachman Diamond syndrome (SDS)-like disease, including exocrine pancreatic insufficiency, neuro-developmental delay, and skeletal dysplasia. To date, there are no reports of malignant transformation. Here, we present a patient with SCN and a novel SRP54 pathogenic variant.

Objectives: Expand on the clinical findings and course of disease in SRP54-related SCN.

Design/Method: Chart reviewed patient's demographic information, clinical presentation, disease course, genetic results, and treatment response. Conducted a literature review of SRP54-related SCN.

Results: A two-month-old male initially presented with right middle lobe pneumonia requiring admission to the pediatric intensive care unit (PICU). CBC on presentation showed a WBC of 14.5 K/mcL, hemoglobin of 9.9 g/dL, and a platelet count of 524 K/mcL. The differential was remarkable for an absolute neutrophil count (ANC) of 0 K/mcL and an absolute monocyte count of 8.4 K/mcL (58%). He demonstrated a partial response to granulocyte-colony stimulating factor

(GCSF). After recovery from initial illness and hospital discharge, the patient sustained additional repeated episodes of bacterial infections including perianal abscess. Bone marrow evaluation demonstrated hypocellular trilineage hematopoiesis (60% cellularity) and decreased absolute granulocyte number with left-shifted maturation; no significant dysgranulopoiesis was noted. He underwent an unrevealing, extensive workup, ultimately culminating in pursuing a large germline panel for bone marrow failure. This genetic testing identified a pathogenic variant in SRP54 known as c.349_351del (p.Thr117del). The patient is presently being treated with daily GCSF at 9 mcg/kg, and ANC remains predominantly in or near the normal range (1.2-5.4 K/mcL). The patient does not have clinical or laboratory evidence of SDS to date. Bone marrow surveillance revealed no evidence of clonal evolution or malignant transformation.

Conclusion: SRP54 variants are associated with a novel SCN syndrome and may be associated with extra-hematopoietic features causing SDS-like disease. Due to its rarity, there are no consensus management guidelines for hematologic risks. We report a patient with SRP54-associated SCN but who thus far lacks evidence of additional SDS-like features. Additional reports of similar patients will expand the knowledge of this rare entity and provide further guidance for clinicians and families.

Poster # 407

CHALLENGES IN THE MANAGEMENT OF FACTOR VII DEFICIENCY IN PEDIATRIC PATIENT COMPLICATED BY INHIBITOR

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Background: Among the rare inherited bleeding disorders, factor VII deficiency is the most common. The incidence of a severe homozygous deficiency is 1 in 300,000-500,000 people worldwide. There is wide variability in penetrance and bleeding phenotype, often making management difficult. Current treatments involve replacement therapy with recombinant Factor VII, plasma or FFP, however, these products remain challenging due to the short half-life and availability for home prophylactic regimens.

Objectives: (1) To discuss the management of a severe factor VII deficiency in a growing child given the limitations of current treatments. Recombinant factor VII has a short half-life, complicating prophylactic infusion schedules. (2) To discuss approaches in eradicating inhibitors in patients with factor VII deficiency.

Design/Method: On initial diagnosis, the patient was started on 30 mcg/kg of daily NovoSeven infusions Monday through Friday. She was maintained on this regimen for three months, until she developed a spontaneous intracranial hemorrhage. Her NovoSeven dosing was increased to 90mcg/kg every 12 hours as she was unable to be safely weaned to every 24 hours due to oozing and increasing INR (international normalized ratio). This prophylactic regimen was complicated by multiple central line infections, requiring two central line removals. At 18 months of age, she was incidentally found to have a spontaneous subdural hematoma and a knee joint bleed with good compliance to her twice daily NovoSeven infusions. Mixing studies were obtained and were

indicative of an inhibitor to Factor VII. She was treated with high dose steroids followed by Rituximab and finally cyclophosphamide and IVIG with no improvement in her inhibitor status.

Results: Since the patient has been unable to clear the inhibitor and INR levels continue to be abnormal, she was switched to Sevenfact in place of NovoSeven.

Conclusion: Currently, there are published case studies that share treatment regimens for factor VII prophylaxis, such as the Seven Treatment Evaluation Registry. However, there are currently no published guidelines regarding prophylaxis management for patients with severe bleeding phenotypes. Furthermore, there are also no guidelines that address inhibitor management for factor VII deficiency. Patients, like ours, who develop inhibitors refractory to treatment are at a greater risk of mortality due to life threatening bleeds. Therefore, further research is needed to develop management guidelines for patients with severe factor VII deficiency in need of prophylactic therapy and treatment of inhibitors.

Poster # 408

CASE SERIES OF RECURRENT BILATERAL CENTRAL RETINAL VEIN OCCLUSION IN OTHERWISE HEALTHY ADOLESCENTS

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Background: Central retinal vein occlusion (CRVO) is a rare finding in children associated with local causes, such as compression or inflammation secondary to trauma, and systemic causes, including thrombophilia or hyperviscosity. We describe two cases of recurrent bilateral CRVO.

Objectives: To identify a novel cause related to CRVO in children.

Design/Method: Retrospective case series reviewing records through an electronic medical record.

Results: Case 1: 10-year-old previously healthy male presented with blurry vision of his left eye and was found to have CRVO. Initial workup was normal with a PTT of 29 sec, PT INR of 1.1 sec, fibrinogen of 291 mg/dL, Factor VIII of 174%, Factor IX of 101%, and Factor XI of 112%. Three years later, he developed acute onset headache with blurry vision of his right eye. Exam showed macular edema and CRVO of his right eye. Ophthalmology treated him with aflibercept, with improvement in both macular edema and visual acuity. Daily aspirin was initiated. Work up for an inherited or acquired hypercoagulability, including prothrombin mutation, AT III mutation, hyperhomocysteinemia, protein C & S, and antiphospholipid were negative. Rheumatological and infectious workup were negative. Targeted sequencing for inherited erythrocytosis and polycythemia was normal. Further workup revealed reduced thrombin inhibitor and elevated rates of thrombin formation. Lipoprotein (a) was 168 mg/dL. His mother also had elevated lipoprotein (a) and accelerated thrombin formation. Recently his father was diagnosed with a deep venous thrombosis (DVT), and his grandfather had polycythemia vera. The patient experienced intermittent vision changes and therapy was changed to rivaroxaban. Whole exome sequencing

(WES) for the patient and parents are pending.

Case 2: 14-year-old asymptomatic female with history of amblyopia was diagnosed with CRVO during a follow-up eye examination. Coagulopathy workup was normal with a PTT of 32 sec, INR of 1.0 sec, and fibrinogen of 299 mg/dL. Investigation for an inherited or acquired hypercoagulability including factor V Leiden, prothrombin, and AT III mutations, hyperhomocysteinemia, protein C & S, and antiphospholipid were negative as were rheumatological and infectious workup. Lipoprotein (a) was elevated at 113 mg/dL. Ophthalmology treated with bevacizumab, and she is on prophylactic rivaroxaban. Her macular edema persists with interval worsening of CRVO.

Conclusion: We describe a novel cause of CRVO in adolescent children. Both patients have reduced thrombin inhibition resulting in accelerated thrombin formation and elevated lipoprotein (a) supporting a hypercoagulable state. Perhaps, there is a familial component predisposing recurrent thrombosis.

Poster # 409

DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS SYNDROME ASSOCIATED WITH ENOXAPARIN THERAPY

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Background: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a rare, potentially life-threatening drug hypersensitivity reaction with variable, non-specific characteristics including diffuse skin eruptions, fever, lymphadenopathy, transaminitis, eosinophilia, and atypical lymphocytosis. DRESS develops 2-6 weeks after exposure to inciting medications, commonly antibiotics, antiepileptics, and allopurinol. DRESS syndrome is rarely associated with Vitamin K antagonists and direct oral anticoagulants. In an in-depth examination of existing literature, there are only two reported cases of DRESS syndrome associated with enoxaparin therapy, both in adult patients and no reports of pediatric DRESS syndrome secondary to anticoagulants.

Objectives: Review DRESS syndrome and highlight enoxaparin as a potential cause.

Design/Method: Case Report.

Results: A healthy 11-year-old female was admitted with sepsis secondary to osteomyelitis and periosteal abscess of the left lower extremity with MRSA bacteremia. Clindamycin and vancomycin were initiated for treatment of the infections. A left lower extremity ultrasound with doppler demonstrated an acute deep venous thrombus of the popliteal vein. A heparin drip was started and subsequently transitioned to enoxaparin one week later. Two weeks after the initiation of enoxaparin, she developed facial swelling, a generalized morbilliform rash, and lymphadenopathy on exam and abdominal imaging. Fevers persisted despite multiple washouts, appropriate antimicrobial coverage, and negative blood cultures. Liver enzymes concurrently

increased (AST 362 IU/L (normal 5-60 IU/L), ALT 371IU/L (normal <35 IU/L) at peak). Eosinophilia was not present initially but did subsequently develop (1.1 K/ul at peak). HHV6, CMV, and EBV serologies were negative. Skin biopsy was consistent with a drug eruption. Using the RegiSCAR criteria for DRESS syndrome, labs and symptoms indicated a definite case of DRESS syndrome with a score of 6 (score >5 indicates a definite case). The patient was started on high-dose steroids for treatment. Clindamycin and vancomycin were both discontinued due to their known association with DRESS syndrome, however, no improvement in labs or symptoms was seen over the course of five days. Enoxaparin was then transitioned to apixaban and rash and fevers resolved with improvement in liver enzymes and eosinophilia within a few days.

Conclusion: Diagnosing DRESS syndrome is challenging due to its nonspecific presentation, particularly in pediatric patients where symptoms can overlap with viral syndromes and Kawasaki disease. Prompt recognition and treatment is required to limit morbidity and mortality. In pediatric patients receiving treatment with enoxaparin, DRESS syndrome should be on the differential if they develop persistent fevers, lymphadenopathy, rash, transaminitis and/or eosinophilia, and discontinuation of enoxaparin should be considered.

Poster # 410

A CASE OF A MISSING IVC: ALWAYS ABSENT OR AN ADVERSE EVENT?

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Background: When taking care of the adolescent patient, one must consider pathologies of childhood and adulthood. In this case, a patient had significant thrombosis secondary to extensive venous collateralization. These collateral vessels may represent complications of central catheter placement in childhood or congenital anomaly of the inferior vena cava (IVC). While congenitally absent structures are often expected to show symptoms during childhood, an adult male diagnosed with an absent IVC at age 54 with first deep vein thrombosis (DVT) occurrence has been reported.[1] Congenital absence of the IVC may present with DVT presumably related to abnormal venous flow. Oftentimes it is not well understood whether an absent IVC is an anomaly of fetal development or a complication of central catheterization in infancy.

Objectives: Appreciate the relevance of birth history/congenital anomalies in the care of adolescent/young adult patients

Design/Method: A 16-year-old male was admitted with 1 month of worsening hip and left lower extremity pain with erythema and edema of the left lower extremity (LLE). Past history revealed possible aortic arch abnormality and a reported history of a “kinked” left femoral venous catheter in the NICU. He had no history of immobilization, surgery, DVT, or pulmonary embolism. Exam was significant for non-pitting edema of the LLE to the mid-thigh accompanied by pain with dorsiflexion of the left foot and varicose veins on the left anterior thigh.

Results: LLE ultrasound revealed an extensive and occlusive DVT involving the left femoral, profunda, and common femoral veins extending through the popliteal and posterior tibial veins. CT

venograms of the pelvis revealed no visible IVC and extensive venous collaterals. After lytic catheterization and femoral venoplasty, he was discharged on therapeutic enoxaparin and aspirin with plans for lifelong anticoagulation. It remained unclear if the collateralization was secondary to a congenitally absent IVC or complications of his prior central catheterization.

Conclusion: This is a case of a common presentation of DVT with a rare finding of extensive venous abnormalities of unclear etiology. While multiple embryologic events leading to IVC absence have been proposed, no single event fully explaining agenesis has been identified. Many young patients with IVC thrombosis have had prior catheterization procedures, suggesting the possibility of catheter-induced thrombosis as a cause of eventual agenesis of the IVC.[2] This case demonstrates the importance of considering congenital pathologies and birth history in the care of adolescent and even adult patients.

Javaid Iqbal, Med Case Reports, 2008.
Bass, American Journal of Roentgenology, 1999.

Poster # 411

NEONATAL OCCLUSIVE ABDOMINAL AORTIC THROMBOSIS; A CASE SERIES OF TWO NEONATES

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Background: Neonatal abdominal aortic thrombosis (AAT) is often secondary to arterial catheters and may result in tissue loss secondary to poor perfusion. Literature describing neonatal AAT management is limited.

Objectives: To describe two neonates with AAT treated successfully with different therapeutic regimens.

Design/Method: A retrospective case series of two neonates with AAT treated at Texas Children's Hospital in 2021.

Results: The first case was a nine-day-old full-term girl who presented with severe dehydration. Her bilateral lower extremities (LEs) had poor perfusion, and distal pulses were undetectable by doppler. Doppler-ultrasound revealed an occlusive infrarenal AAT extending to the right common iliac artery (CIA) and the left external iliac artery (EIA) with distal arterial flow via collateral vessels. Therapeutic anticoagulation was initiated with unfractionated heparin (UFH) and transitioned to bivalirudin. Due to worsening of LEs perfusion secondary to sepsis and no change in AAT size, systemic tissue-plasminogen activator (tPA) was started on day five of admission (initially at 0.1 and titrated to 0.6 mg/kg/hr). Systemic tPA was stopped after 43 hours, secondary to no increase in the D-Dimer level and no change in the thrombus size. Following thrombolysis, the patient was transitioned from bivalirudin to low-molecular-weight heparin (LMWH) and completed five weeks of anticoagulation. Doppler-ultrasound demonstrated complete resolution of the infrarenal AAT and residual thrombus in the right CIA at anticoagulation termination. The

second case was an eight-day-old girl with a gestational age of 35+2 weeks delivered via C-section secondary to severe oligohydramnios. Mother had a history of spontaneous miscarriages without a known thrombophilia and was on LMWH during pregnancy. The patient had umbilical arterial and venous lines in the first three days of life. On day eight of life, the patient developed pale bilateral LEs with detectable pulses via doppler. A doppler-ultrasound showed a nearly occlusive mid to distal AAT extending to left CIA and EIA and occlusive thrombus in the right CIA, thought to be secondary to the prior central line. As perfusion was intact with detectable distal pulses, tPA was not initiated. Therapeutic UFH was started and ultimately transitioned to LMWH. The patient completed eight weeks of anticoagulation with doppler-ultrasound showing a reduced thrombotic burden with a residual non-occlusive distal AAT and complete resolution of previous other thromboses.

Conclusion: Neonatal AAT can be treated with anticoagulation with or without thrombolysis. The severity of physiologic compromise secondary to AAT and individual patient bleeding risks must both be taken into account when considering neonatal thrombolysis.

Poster # 412

SUPERFICIAL VENOUS THROMBUS REFRACTORY TO FACTOR XA INHIBITION IN 16-YEAR-OLD MALE WITH CANNABIS USE

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Background: Unprovoked superficial venous thrombosis (SVT) is rare in adolescents. SVT is generally a self-limiting benign condition, with treatment goals of reducing local symptoms and preventing potential thrombotic complications. Risk factors for the development of SVT include varicose veins, venous trauma, elevated estrogen, previous venous thrombosis, malignancy, age, and hypercoagulable states. Treatment for SVT ranges from supportive care to intermediate-dose therapeutic anticoagulation that includes low molecular weight heparin (LMWH), fondaparinux, and rivaroxaban. Treatment decisions are based on estimated risk for extension of the SVT or development of deep vein thrombosis (DVT).

Thromboangiitis obliterans (TAO) consists of segmental thrombi and inflammation of small and large vessels, including SVT in about 19% of cases. The pathophysiology of TAO remains poorly understood. After exclusion of other diagnoses, the Shionoya Criteria are commonly used to clinically diagnose TAO: positive smoking history, onset at less than 50 years old, infrapopliteal arterial occlusions, upper limb involvement or phlebitis migrans, and absence of atherosclerotic risk factors other than smoking. Chronic tobacco use is a critical risk factor. Literature review revealed one previous case of migratory SVT, with biopsy consistent with TAO, in a cannabis user who fully recovered following cessation of cannabis use.

Objectives: Describe a 16-year-old Caucasian male with migratory SVT consistent with TAO.

Design/Method: Case report.

Results: Our patient presented with left inguinal and posterior thigh pain, tenderness, and overlying erythema. His risk factors for thrombus were chronic cannabis use, a remote history of Kawasaki disease, and a family history of limited cutaneous systemic sclerosis. Left greater saphenous thrombus was identified by ultrasound (US). Given the close proximity to the saphenofemoral junction and the risk of progression to DVT he was started on anticoagulation with rivaroxaban, 20 mg once daily. After two months of rivaroxaban, he developed progressive and refractory erythema, pain, and tenderness, with palpable upper and lower extremity superficial thromboses. Repeat US identified progression of SVT. Doppler US did not reveal lower extremity DVT. At this time, anticoagulation therapy was changed to LMWH with symptomatic relief. Extensive thrombophilia, infectious, and autoimmune evaluations were unrevealing.

Conclusion: TAO in adolescence is rare. This case highlights venous involvement of TAO in the setting of chronic cannabis use, and the presence of progressive and refractory disease with factor Xa inhibition. The interaction of smoked cannabis metabolites with the venous vascular endothelium, and SVT progression despite factor Xa inhibition, may provide insight into the pathophysiology of TAO, and may help inform treatment options.

Poster # 413

PEDIATRIC SPONTANEOUS HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS RESULTING IN THROMBOTIC STORM

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Background: The annual incidence of venous thromboembolism in pediatric patients is approximately 6 out of 1000 in the United States. In rare cases, rapid progression of multifocal thrombosis occurs despite therapeutic anticoagulation with heparin or low molecular weight heparin. Heparin-induced thrombocytopenia (HIT) is a pro-thrombotic disorder caused by an IgG-mediated immune response against platelet factor 4 resulting in platelet activation and risk of thrombosis, classically associated with prior exposure to heparin. The literature reports rare cases of adult patients developing HIT and thrombosis (HITT) without prior exposure.

Objectives: Aim to describe a case of spontaneous HITT in a pediatric patient which has not previously been published in the literature.

Design/Method: Single subject case report developed with thorough literature review.

Results: 2-year-old male with no past medical history who presented with 5 days of frontal headaches and irritability. Neuroimaging, including CT, MRI, and MRV demonstrated extensive sinus venous thrombosis requiring initial anticoagulation with heparin. However, within 48 hours of initiation, the patient developed significant thrombocytopenia concerning for HIT. Lab testing was positive for both heparin-induced antibody and serotonin release assay, despite no prior heparin exposure. The remainder of the hypercoagulability workup was negative. Heparin was discontinued and the patient subsequently showed inadequate response to initial treatment with

first-generation1 direct thrombin inhibitor (DTI) (Argatroban). Due to ongoing severe progressive symptomatic thrombocytopenia and thrombosis concerning for HIIT with thrombotic storm, the patient was treated with DTI (Bivalirubin), high dose methylprednisolone, and anti-CD20 therapy (Rituximab). This resulted in an improved clinical, laboratory, and neuroimaging response, and the patient was able to be gradually weaned off steroid therapy, and transitioned to anticoagulation with warfarin, with plans to remain on long-term anticoagulation.

Conclusion: This is the first reported case in the literature of spontaneous HIIT in a pediatric patient. Spontaneous HITT is the primary explanation due to fulminant thrombosis and positive heparin-induced antibody and serotonin release assay with no prior heparin exposure, thrombocytopenia without immediate improvement upon heparin discontinuation, and blood smear showing normal red blood cell and platelet morphology. Spontaneous HIIT is a rare but important differential to consider in patients presenting with thrombosis and thrombocytopenia as the treatment differs from that of classic HIT, requiring heparin discontinuation, alternative anticoagulation, and immunomodulation.

Poster # 414

ENDOVASCULAR RECONSTRUCTION FOLLOWING IVC AND BILATERAL LOWER EXTREMITY THROMBOSIS IN AN ADOLESCENT

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Background: Inferior Vena Cava (IVC) abnormalities are a risk factor for the development of lower extremity deep vein thrombosis (DVT). Abnormalities can be congenital or acquired and include IVC atresia, a rare and lesser known problem for adolescents. Adolescents with IVC atresia are at high risk for DVT's that are often refractory to standard anticoagulation methods, including thrombolysis.

Objectives: The purpose of this report is to highlight a young patient with extensive lower extremity DVT in the setting of underlying IVC atresia and describe the complex care required. The patient is a 16-year-old with a history of venous insufficiency who presented with low back pain and lower extremity swelling. Thrombotic risk factors included factor V Leiden heterozygosity, oral contraceptive use, and recent COVID-19 vaccination. An MRI completed by the orthopedist for back pain was concerning for abnormal signal in the IVC as well as an IVC aneurysm. A contrast enhanced CT was obtained and demonstrated atresia of the suprarenal IVC, subacute thrombosis of the infrarenal IVC along with an IVC aneurysm, and subacute thrombosis of the bilateral iliac veins.

Design/Method: A retrospective chart review of the patient's initial presentation, imaging, and treatments was conducted along with a review of the literature involving similar cases.

Results: Initial treatment was intravenous heparin and t-PA mediated thrombolysis. After overnight thrombolysis, venography revealed significant clot lysis; thus, she was transitioned to subcutaneous enoxaparin and discharged home with therapeutic anti-Xa levels. Follow up imaging

3 days later revealed recurrent thrombosis of the deep veins in both lower extremities. She was readmitted, placed on intravenous heparin, and received catheter directed t-PA thrombolysis. Clot burden was so extensive it was further reduced using Angio jet thrombectomy and balloon angioplasty. Because the recurrent clots were attributed to lack of outflow from the underlying IVC atresia, interventional radiology completed endovascular reconstruction of the IVC. She then transitioned from intravenous heparin to therapeutic enoxaparin, clopidogrel, and aspirin. At three month follow up, imaging was negative for clot and her vasculature was widely patent.

Conclusion: Pediatric patients with bilateral lower extremity DVTs are uncommon and underlying IVC abnormalities should be considered in the evaluation. Optimal treatment strategies are evolving and include aggressive anticoagulation and endovascular reconstruction.

Poster # 415

DEEP VEIN THROMBOSIS AND SADDLE PULMONARY EMBOLISM IN A PATIENT WITH MULTIPLE GENETIC RISK FACTORS

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Background: The prevalence of a heterozygous mutation in either factor V leiden (FVL) or prothrombin G20210A (PT-G20210A) is approximately 5% or 2%, respectively, in the Caucasian population. The prevalence of double-heterozygosity for these mutations is 0.1% in the Caucasian population and may be as high as 5% in patients diagnosed with deep vein thrombosis (DVT). Antiphospholipid syndrome (APS) is a rare autoimmune disorder with estimated prevalence of 20-50 cases per 100,000 persons and most commonly presents in adolescents and young adults. The prevalence of double-heterozygosity for FVL/PT-G20210A and concurrent APS is rare and not well-described.

Objectives: This report aims to describe the diagnosis, treatment, and outcome for the acute presentation of extensive lower extremity DVT and saddle pulmonary embolism (PE) in a previously healthy 17-year-old Caucasian male found to have multiple genetic risk factors for venous thromboembolism.

Design/Method: The patient presented due to new onset chest pain and persistent left leg pain and swelling after a hyperextension injury of the knee 4 days prior forced him to be immobilized. Ultrasound showed extensive DVT of left femoral, popliteal, and tibial veins. CT angiography demonstrated submassive saddle PE.

Results: He was initially started on therapeutic unfractionated heparin IV and oxygen support via nasal cannula. Echocardiogram, BNP, and troponins were normal. May-Thurner syndrome was considered unlikely given the limited proximal extent of the left leg thrombus, and no procedural interventions were indicated. He was transitioned to therapeutic enoxaparin and weaned to room air within 48 hours of presentation. His known trauma, immobilization, and BMI 34 kg/m^2 were considered possible etiologies to provoke the thromboses, and his family history was unremarkable for thrombosis. However, due to the extent of thrombosis, he underwent evaluation for underlying

thrombophilia. Results were significant for heterozygous mutations of both FVL and PT-G20210A, positive anti-beta 2 GPI IgG antibody, and lupus anticoagulant. He was discharged home on therapeutic enoxaparin.

Conclusion: This 17-year-old Caucasian male's presentation of DVT and submassive saddle PE occurred in the setting of trauma, immobilization, obesity, and double-heterozygosity for FVL/PT-G20210A with possible evolving APS. We expect him to continue therapeutic anticoagulation for least 6 months. Patients with double-heterozygosity for FVL/PT-G20210A alone are candidates for lifelong anticoagulation due to recurrence risk. This case highlights the importance of evaluation for thrombophilia in patients in select circumstances with extensive thrombus burden, even in the setting of known risk factors such as trauma and obesity.

Poster # 416

TREATING A LIMB-THREATENING ARTERIAL CLOT IN A NEWBORN WITH CATHETER-DIRECTED THROMBOLYSIS

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Background: Non-catheter related arterial thromboembolism in the pediatric population is rare but carries a significant risk of organ damage and/or limb loss. Thrombolysis, systemic or catheter directed, is reserved for limb/life threatening thrombosis due to risk of bleeding especially in premature infants.

Objectives: Describe a case of a premature newborn with limb-threatening arterial clot treated with catheter-directed thrombolysis.

Design/Method: Case Report

Results: A 1.99kg male newborn was born via emergency c-section at 34 weeks and 4 days gestational age due to maternal abdominal pain, vaginal bleeding, and non-reassuring fetal heart tones in a pregnancy complicated by maternal marijuana use. Following birth, the patient's right upper extremity became dusky and limp with absent distal pulses. Vascular ultrasound demonstrated occlusive arterial thrombus of the distal right subclavian artery and proximal right axillary artery. A decision was made by a multidisciplinary team to have a catheter placed through the umbilical artery due to the increased risk of thrombosis with a femoral artery approach with patient's low birthweight and with no knowledge of what led to the formation of the original thrombus. The catheter was placed with the tip ending in the subclavian artery and catheter-directed tissue plasminogen activator (tPA) was initiated. Systemic anticoagulation with heparin at 5 units/kg/hr was started and titrated to 25 units/kg/hr to reach an anti-Xa level of 0.3-0.5 IU/mL. Antithrombin levels were checked and replaced as needed to maintain a level of 80-120%. The patient was monitored closely for bleeding and clot improvement with frequent physical exams and ultrasounds. Once the clot was decreased in size along with improved perfusion and color of the extremity after 36 hours of treatment, tPA was discontinued. Patient was continued on

anticoagulation until all central lines were removed at which time, he was started on aspirin with plan to continue this until he is two years old. With normal antithrombin levels and no rash or skin necrosis to suggest protein C or S deficiency the cause of the clot remains unknown however, additional hyper-coagulable work-up will be completed as an outpatient.

Conclusion: This is a case of a patient with limb-threatening arterial clot successfully treated with catheter-directed thrombolysis. This is another example of a multidisciplinary team successfully using low-dose thrombolysis to treat an arterial clot with close monitoring for complications[1]. Further investigation is needed to identify the patient population that will benefit from thrombolytic therapy and how to best monitor these patients.

1. Veenstra, J Vasc Surg, 2020

Poster # 417

16 YEAR OLD GIRL WITH CYCLIC NEUTROPENIA, PERIODONTAL DISEASE, AND FIBROUS DYSPLASIA OF THE MAXILLA

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Background: Cyclic neutropenia (CN) and severe congenital neutropenia (SCN) are disorders of neutrophil production. With CN, the absolute neutrophil count (ANC) drops < 200/mm^3 every three weeks with fever, oral ulcers, infections, and/or lymphadenopathy. SCN is a more severe phenotype with ANC consistently < 200/mm^3. CN and SCN involve different heterozygous mutations in the ELAstase-Neutrophil Expressed (ELANE) gene. SCN carries an increased risk of transforming to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) during adolescence/early adulthood.

Objectives: To discuss unique consideration of BMT in a patient with phenotypical CN but gene mutations suggestive of SCN and cherubism.

Design/Method: Case Report.

Results: Since the patient was four months old, she had neutropenia and monthly recurrent infections with tender cervical lymphadenopathy and oral ulcers. Family history includes several unusual deaths: four of her paternal great uncles died before 10 years old and her paternal grandfather's twin died of leukemia at 30 years old. In Ecuador, after negative bone marrow and lymph node biopsies, she was treated with granulocyte colony - stimulating factor (GCSF) and steroids.

At our center, she had repeat negative bone marrow aspirate/biopsy. Biweekly CBCs revealed that her neutropenia occurred in 26 day cycles. CT scan showed fibrous dysplasia of her maxillary bone. Genetic testing, including next generation sequencing panels for inherited neutropenia and primary immunodeficiency, was sent with the following significant finding:

- ELANE, c.722G>A (p.Trp241*): de novo pathogenic/likely pathogenic nonsense mutation associated with CN or SCN;
- CSF3R, c.1325C>T (p.Pro442Leu): CSF3R gene mutations have generally been associated with autosomal recessive SCN and thus do not explain the patient's neutropenia.

Due to her fibrous dysplasia, a work-up for McCune Albright syndrome was initiated by endocrinology and genetics. Clinical criteria were not met, but a paternally inherited VUS in SH3BP2, associated with cherubism, was discovered and may explain this finding.

Dental colleagues performed four quadrants of supra- and subgingival scaling with root planing. The patient is on a Mon/Wed/Fri schedule of 4mcg/kg GCSF to maintain ANC > 500/mm^3.

Conclusion: The patient's clinical phenotype is consistent with CN, which has a low risk for malignant transformation to MDS/AML. Her genotype/phenotype correlations for *ELANE* are still being investigated, as nonsense mutations have been associated with an increased risk. Considering her VUS possibly associated with cherubism, orthopedic specialists are currently evaluating her fibrous dysplasia, as this would need to be addressed before a possible BMT.

Poster # 418

A NOVEL PATHOGENIC VARIANT OF G6PC3 GENE PRESENTING AS CYCLIC NEUTROPENIA IN A PEDIATRIC PATIENT

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Background: Cyclic neutropenia is a rare hematologic disorder affecting neutrophils. It is classified by recurrent neutropenia with associated symptoms including fever and malaise, as well as recurrent mucosal infections and skin infections. Pathogenic variants of ELANE- gene that encodes neutrophil elastase, are thought to cause these findings, however, other pathogenic variants of different genes have also been reported. The estimated frequency of cyclic neutropenia is $1:10^6$ in the general population. It is most commonly diagnosed in children and there is no known increased prevalence in women as compared to men. Whole Exome Sequencing can be used for diagnosis when genetic concerns are present.

Objectives: This case report aims to describe a novel pathogenic variant in a pediatric patient with cyclic neutropenia.

Design/Method: Single subject case report

Results: This is a single case report of a 7-year-old female with past medical history of cyclic neutropenia, anemia, recurrent infections, and learning difficulty. The patient initially presented at age 1 with high fevers and skin infections and was found to have decreased neutrophil counts. Bone marrow aspirate and biopsy performed at 1 and 7 years of age showed decreased neutrophil count with normal maturation and normal cytogenetics. Her peripheral blood for bone marrow

failure evaluation was non-contributory. With her severe persistent neutropenia, normal bone marrow findings, and need for weekly chronic G-CSF administration; whole exome sequencing was evaluated. Results of which showed a novel compound heterozygous pattern for two variant copies of the G6PC3 gene, with our patient inheriting a copy from each parent.

Conclusion: The G6PC3 gene encodes the expressed glucose-6-phosphate enzyme which catalyzes the final step in glycogenolysis. It is hypothesized that this deficiency causes unregulated levels of glucose, resulting in increased stress of the endoplasmic reticulum leading to apoptosis of neutrophils. Pathogenic variants of G6PC3 cause autosomal recessive G6PC3 deficiency and this can be clinically characterized as severe congenital neutropenia. Classic G6PC3 deficiency includes severe congenital neutropenia as well as cardiovascular, urogenital abnormalities, and pulmonary hypertension. This novel pathogenic variant is likely responsible for the cyclic neutropenia observed in our patient. Of note, our patient has learning difficulties, which have been noted in other etiologies of neutropenia. Whole Exome Sequencing is a cost-effective method for diagnosis and a valuable tool in evaluation and management of complex hematological disorders.

Poster # 419

PLATELET FUNCTION DISORDER IN A PATIENT WITH CONGENITAL HEART DISEASE AND MULTIPLE THROMBOTIC EVENTS

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Background: Platelet function disorders are characterized by abnormal adhesion, aggregation, or activation of platelets. These disorders are challenging to diagnose, especially in patients with complex hemostatic profiles. Children with congenital heart disease (CHD) requiring Fontan procedure are typically hypercoagulable following the procedure, often requiring prophylactic anti-thrombotic therapy. Bleeding events are usually attributable to coagulation factor deficiencies from congestive liver dysfunction or acquired platelet dysfunction due to concomitant antiplatelet therapy. The presence of a concurrent inherited platelet function disorder has not been reported.

Objectives: To describe a rare case suggestive of an inherited platelet function disorder in a child post Fontan procedure with concurrent history of chronic thromboses who presented with spontaneous hemarthrosis.

Design/Method: Case report.

Results: A 7-year-old girl with hypoplastic right ventricle and truncus arteriosus, status-post Fontan procedure in 2017, presented for a spontaneous left knee hemarthrosis. Medical history was significant for extensive chronic venous and arterial thrombotic events requiring anticoagulation and antiplatelet therapy with enoxaparin and aspirin. Four weeks prior to presentation, she developed mild-to-moderate bleeding symptoms (epistaxis, easy bruising, vaginal bleeding, hematochezia) prompting discontinuation of aspirin and enoxaparin. No prior bleeding events were

reported. Family history was significant for heavy menstrual bleeding and easy bruising on the maternal side, including a maternal uncle with an "unspecified bleeding disorder" diagnosis.

Laboratory data revealed thrombocytopenia (platelets 102,000/mL) and prolonged prothrombin time and activated partial thromboplastin time (18 and 40 seconds, respectively) which corrected upon mixing with 50% normal plasma. Patient's INR was 1.51. Mild deficiencies-for-age of clotting factors V (39%), VII (54%) and X (58%) were noted but were not felt to be the sole contributors of ongoing bleeding symptoms. Platelet aggregation studies were then performed, revealing decreased aggregation to arachidonic acid, collagen, and high-concentration ristocetin. Platelet function analyses (PFA-100) revealed prolonged response to collagen/epinephrine and collagen/ADP, suggesting an inherited platelet function disorder. Further genetic testing and platelet flow cytometry evaluations are pending.

Conclusion: Thorough hemostatic evaluations are important for patients with CHD following Fontan procedure. Although mild and often subclinical coagulation factor deficiencies have been reported in post-Fontan patients, other defects in primary and secondary hemostasis should be considered when personal and/or family bleeding history is present. History of thrombosis does not preclude a concurrent congenital bleeding disorder. Our patient's evaluation revealed an unexpected platelet dysfunction, presumably contributing to her spontaneous hemarthrosis. To our knowledge, this is the first report suggestive of an inherited thrombocytopathy in a patient with history of Fontan procedure.

Poster # 420

THROMBOCYTOPENIA AS A FETAL PRESENTATION OF SAMD9/SAMD9L MUTATIONS

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Background: *SAMD9/SAMD9L* are two closely related genes located at 7q21.3, involved in endosomal cycling and interferon response. Germline gain of function *SAMD9/SAMD9L* mutations has been identified in congenital bone marrow failure syndromes with somatic genetic rescue events associated with del(7q).

Objectives: Describe the clinical presentation of two newborns with extreme prematurity and thrombocytopenia due to *SAMD9/SAMD9L* mutations.

Design/Method: Case Series.

Results: Patient 1 was born at 26 weeks gestation with prenatal oligohydramnios and severe intrauterine growth retardation (IUGR). Prenatal screen and TORCH workup were negative. On examination, he had microcephaly and ambiguous genitalia with bifid scrotum and hypospadias. The karyotype was 46XY. Endocrine workup revealed undetectable random cortisol level (<0.2) suggesting adrenal insufficiency. Complete blood count showed thrombocytopenia (platelets between 10-50 X 10^9/L). There was no history of thrombosis or bleeding complications. Maternal

platelet count was normal and workup for alloimmune thrombocytopenia was negative. Chromosomal breakage analysis and SNP microarray were normal. A rapid whole-exome sequencing revealed a *de novo* missense mutation in exon 3 of *SAMD9* (c.1457A>C/p.Tyr486Ser). Although this mutation has not been reported previously, his phenotype was consistent with the diagnosis of MIRAGE syndrome (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy). Next-generation sequencing (NGS) hematological malignancy panel was negative for additional mutation(s). He continued to have refractory thrombocytopenia requiring multiple platelet transfusions. He developed Klebsiella sepsis and CMV viremia. Multiple attempts at extubation failed and parents decided to withdraw life-support.

Patient 2 was born at 29 weeks gestation with severe IUGR and severe thrombocytopenia (platelets 5-50 x 10^9/L). Bone marrow biopsy revealed normocellular marrow with megakaryocytic hypoplasia. SNP microarray and chromosomal analysis were normal, whole-exome sequencing showed missense mutation in exon 5 of *SAMD9L* (c.1549 T>C/ p.Trp517Arg). His father, who carried the same mutation, as well as several other family members on the paternal side, had history of thrombocytopenia, but none developed myelodysplasia or leukemia. NGS hematologic malignancy panel was negative for additional mutation(s). He became transfusion independent at four months but was lost to follow-up after eight months.

Conclusion: We describe two neonates with extreme prematurity, displaying severe thrombocytopenia and IUGR with *SAMD9*/*SAMD9L* variants not previously associated with disease. The striking difference was the severity of *SAMD9* mutation presenting as MIRAGE syndrome leading to lethality, whereas *SAMD9L* mutation spontaneously resolved. These cases illustrate the effect of these mutations on fetal hematopoiesis and the importance of considering *SAMD9/SAMD9L*-related disorders in the differential diagnosis of neonates with prematurity and thrombocytopenia.

Poster # 421

SEVERE HEMOLYTIC PHENOTYPE OF HB SS DISEASE WITH CONCURRENT G6PD DEFICIENCY AND SPTA1 MUTATIONS

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Background: Sickle cell disease (SCD) is an inherited blood disorder, wherein patients are prone to hemolysis due to the shape of their red blood cells (RBC). The “hemolytic” phenotype is characterized by lower hemoglobin (Hb), higher reticulocyte count, increased stroke risk, priapism, and leg ulcers. Notably, these patients have less frequent pain is than patients with the “vaso-occlusive” phenotype. Some of the phenotypic variabilities can be explained by co-inheritance of other common causes of hemolytic anemia such as glucose-6-phosphate dehydrogenase (G6PD) deficiency or RBC membranopathies. Studies investigating the potential effects of G6PD deficiency on SCD severity have demonstrated conflicting results. Data on the interaction of SCD with other hereditary hemolytic anemias such as hereditary elliptocytosis (HE) or spherocytosis are

sparse.

Objectives: To describe the evaluation and management of two children with unusually severe SCD who were found to have additional hemolytic anemias.

Design/Method: Case report

Results: Patient A is a 6-year-old male with Hb SS who had intractable dactylitis starting at age 4 months requiring a brief course of chronic transfusions while titrating hydroxyurea (HU), severe baseline anemia (Hb 6 g/dL), and cholelithiasis necessitating cholecystectomy at age 3 years. His HU response was poor with a maximum Hb of 7 g/dL. Next-generation sequencing (NGS) revealed G6PD deficiency (pathogenic variant in *G6PD* associated with the A- genotype), mild HE (pathogenic variant in *SPTA1* associated with the Jendouba genotype); and a variant of uncertain significance (VUS) in *PIEZO1.* Peripheral smear showed sickled RBCs and elliptocytes. Patient B is an 8-year-old male with Hb SS. He experienced severe anemia despite HU (maximum Hb 6.3 g/dL), recurrent acute chest syndrome requiring intensive care, silent cerebral infarctions, conditional transcranial Doppler ultrasound, microalbuminuria, and recurrent priapism, for which chronic transfusion therapy was initiated. NGS revealed G6PD deficiency (A- genotype) and a VUS in SPTA1. This SPTA1 variant has not been characterized as a pathogenic variant, but peripheral smear showed sickled RBCs and abundant elliptocytes. Due to chronic transfusion therapy, RBC osmotic fragility and ektacytometry could not be performed.

Conclusion: Children with disproportionately severe SCD manifestations despite appropriate therapy may have co-inherited RBC enzymopathies or membranopathies that worsen their SCD phenotype and hemolytic anemia. These children may benefit from combination therapy to address Hb S polymerization and treatments that mitigate oxidative damage or improve the glycolytic state of the RBCs. Alternatively, they may be candidates for early consideration of curative hematopoietic stem cell transplant.

Poster # 422

IRON DEFICIENCY ANEMIA REFRACTORY TO IRON SUPPLEMENT; RARE CAUSES FOR A COMMON PROBLEM

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Background: Iron-deficiency anemia (IDA) is one of the most common types of anemia in children. Proper treatment IDA includes treatment of the underlying cause in addition to iron replacement therapy.

Objectives: To highlight two of the rare causes of chronic blood loss leading to refractory IDA and tips for diagnosis.

Design/Method: Case series

Results:

Case1:

A 2-year-old female presented to the ER with severe anemia and hypoxia, intermittent fever up to 102.4 F and cough. Chest X-ray demonstrated bilateral diffuse pulmonary opacities. She was admitted to the hospital for further management. She had been previously hospitalized four months prior and diagnosed with severe IDA with a hemoglobin of 4.0, MCV of 55 and ferritin of 3. She received multiple blood transfusions and iron supplementation with no sustained improvement. Lab work on admission showed a CRP of 3.45, ESR of 21, WBC of 6, and Platelet 361, Hgb 5.3, and MCV of 59, workup for cardiac and infectious etiologies was negative. She developed significant hemoptysis and was transferred to the PICU and intubated due to respiratory failure, Bronchiolar lavage and Lung biopsy were notable for hemosiderin-laden macrophages and negative for infectious causes. The presence of IDA, progressive cough, dyspnea, and infiltrates on CXR were consistent with idiopathic pulmonary hemosiderosis (IPH) which was confirmed by histo-pathology. Patient responded to a burst of steroid with resolution of respiratory failure and anemia.

Case2:

A 16-year-old female presented with weight loss, secondary amenorrhea, and GI distress and iron-deficiency anemia. She was started on iron pills without noticeable improvement.

Few months later, the patient was referred to hematology due to fatigue and pallor, Hgb 8.9 and MCV 67, ferritin of 5, TIBC of 563, stool hemoccult negative. History showed that patient had begun running several miles per day for track competition for the past few months.

The combination of intense physical exercise and refractory IDA without GI blood loss led to consideration of March Hemoglobinuria. Urinalysis was positive for hemoglobin, confirming the diagnosis. Patient was treated with IV iron infusion and recommended to decrease the intensity of her running and to wear low impact running shows. Follow up visit showed gradual increase in Hgb up to 13.8 and normalization of all iron deficiency anemia labs as well as improved fatigue.

Conclusion: Patients can present with persistent iron-deficiency anemia refractory to iron replacement, and it is essential that rare causes of underlying iron deficiency be considered at that time.

Poster # 423

IDIOPATHIC PULMONARY HEMOSIDEROSIS IN TWO YOUNG PRE-MENARCHAL FEMALES WITH IRON-DEFICIENCY ANEMIA

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Background: Idiopathic pulmonary hemosiderosis (IPH) is a rare etiology of recurrent diffuse alveolar hemorrhage (DAH), with the triad of iron-deficiency anemia (IDA), hemoptysis, and radiographic pulmonary infiltrates. Given its variable presentation, IPH remains a diagnostic challenge with a high mortality rate.

Objectives: To describe the unusual presentation of IPH in two young pre-menarchal females with iron-responsive IDA and review existing literature.

Design/Method: Case series

Results: Case 1: An eight-year-old female presented with pallor and fatigue. Workup was notable for hemoglobin 3.4 g/dL, reticulocyte count 2.4%, MCV 71 fL, RDW 17.9%, and iron 11 μg/dL. After blood transfusion, she was discharged with oral iron, demonstrating excellent response on serial hemoglobin monitoring. However, recurrent anemia required re-initiation of iron on multiple occasions. Bone marrow studies confirmed paucity of iron stores. Given intermittent elevated reticulocyte count on oral iron, hemolysis evaluation was obtained, which was negative. There was no evidence of ongoing blood loss, with negative fecal occult blood test, stool calprotectin, urine analysis, and chest x-ray (CXR). She had normal Celiac studies. Subsequently, she required admission for acute hypoxemic respiratory failure. CXR demonstrated diffuse pulmonary infiltrates, with hemoglobin drop from 10.4 to 6.9 g/dL. Bronchoscopy revealed DAH. She had negative rheumatologic, immune-mediated, and infectious workup. She responded to IPH treatment with high dose steroids and hydroxychloroquine. With subsequent relapse, she was found to have Legionella and invasive Aspergillosis, treated with levofloxacin and voriconazole. She was initiated on Rituximab, with stable course at ten months.

Case 2: A seven-year-old female presented with fatigue, pallor, and dizziness. Workup was notable for hemoglobin 5.8 g/dL, reticulocyte count 1.9%, MCV 65 fL, RDW 18.2%, and iron 22 μg/dL. She was transfused and discharged with oral iron. She was followed for two years with intermittent resolution of anemia that returned when off iron. Workup as outlined above was negative, except for mildly elevated Gliadin IgA. Endoscopy and colonoscopy were normal. She subsequently required two blood transfusions and IV iron trial. Despite normal CXR, bronchoscopy surprisingly demonstrated DAH, consistent with IPH. Rheumatologic and immune-mediated workup was negative. She was started on a gluten-free diet for possible Lane-Hamilton syndrome. However, she later re-presented with hemoglobin 5.3 g/dL and thus was initiated on steroids and azathioprine, with stable course at two months.

Conclusion: These cases illustrate the importance of IPH on the differential for recurrent iron-responsive IDA in young pre-menarchal females without respiratory symptoms, screening with CXR and bronchoscopy, and management based on clinical progression.

Poster # 424

PULMONARY CAPILLARITIS IN A PATIENT WITH PERSISTENT IRON DEFICIENCY ANEMIA

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Background: Pulmonary capillaritis is a small vessel vasculitis that presents as diffuse alveolar hemorrhage and anemia. Symptoms can include exercise intolerance and dyspnea. Batwing

appearance of bilateral opacities can be seen on CXR, but high resolution CT is more sensitive and can demonstrate patchy opacities and consolidation secondary to blood in the alveolar sacs. A biopsy confirms the diagnosis, and treatment involves steroids and immunosuppressive medication.

Objectives: To describe a patient who presented with iron deficiency anemia responsive to oral iron supplementation, with a delayed diagnosis of pulmonary capillaritis due to minimal respiratory symptoms and initial normal CXR.

Design/Method: Case Report

Results: The patient presented with severe microcytic anemia in setting of a three-month history of progressive shortness of breath, pallor, and fatigue, and was admitted for diagnostic evaluation and blood transfusion. No history of low iron diet, easy bruising, bleeding or respiratory symptoms. Ferritin was normal, but peripheral blood smear and soluble transferrin receptor were consistent with iron deficiency anemia (IDA). Evaluation for IDA etiology included: oral iron challenge, which demonstrated an expected response; negative CXR; and normal gastroenterology labs (celiac panel, fecal occult, fecal calprotectin, alpha 1 antitrypsin, and stool ova and parasites). He was discharged home with iron supplementation. Iron supplementation was stopped and restarted twice within a 5 month period due to IDA recurrence. Bone marrow evaluation showed erythroid hyperplasia but no evidence of iron metabolism disorders or malignancy. Given persistent IDA ~ 10 months from initial diagnosis, a CXR was repeated, showing bilateral pulmonary infiltrates. High resolution CT chest confirmed extensive ground glass opacities. Patient then endorsed that he had experienced a few months of intermittent hemoptysis but had not mentioned it to the doctors. He was referred urgently to pulmonology. Flexible bronchoscopy with bronchoalveolar lavage demonstrated numerous hemosiderin-laden macrophages. Lung biopsy was consistent with pulmonary capillaritis, and treatment was initiated with corticosteroids and rituximab. IDA has not recurred thus far, currently stable one month after discontinuation of iron supplementation.

Conclusion: Patients with diffuse alveolar hemorrhage can present with a protracted course if subtle or absent respiratory symptoms. In individuals with unclear etiology of IDA even with no respiratory symptoms and initial negative respiratory workup, reassessment of a pulmonary source is warranted.

Poster # 425

HEAD LICE INFESTATION - AN UNUSUAL CAUSE OF IRON DEFICIENCY ANEMIA IN A 13-YEAR-OLD FEMALE

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Background: Pediculosis is a parasitic infestation of the human head and body by *Pediculus humanus.* This is a benign condition commonly seen in children and manifests with severe pruritus. The parasite thrives on human blood and in some cases, the volume of blood loss

over time could be large enough to precipitate anemic symptoms. The standard of care uses topical pediculicides to eliminate ectoparasites. We present a case of chronic lice infestation leading to severe Iron Deficiency Anemia (IDA), requiring blood transfusions, and the use of oral Ivermectin for treatment.

Objectives: To emphasize the importance of having a holistic approach to the investigation and management of IDA in children.

Design/Method: This is a case report with a literature review.

Results: A 13-year-old female presented with shortness of breath on exertion and easy fatigability. She had balanced meals with adequate consumption of iron-rich foods and no history of menorrhagia. Physical examination showed severe palpebral pallor, scratch marks on the body, and the presence of lice all over the hair with visible nits. Initial labs showed a hemoglobin of 5.3g/dl with a mean cell volume of 71. Total Iron Binding Capacity was 521, ferritin – 2.6, and a serum iron level of 464ug/dl, although she had taken an iron tablet some hours prior to presentation. Blood lead level was less than 1mcg/dl, hemoglobin electrophoresis ruled out hemoglobinopathies like sickle cell disease and thalassemia, peripheral blood smear showed microcytic and hypochromic cells with no schistocytes, teardrops, or target cells. Stool assay was negative for Giardia and Cryptosporidium antigens, as well as *Helicobacter pylori* antigen. Evaluation for rheumatologic disorders yielded negative results for antinuclear antibodies. Ectoparasites chronically sucking blood from this child was the most likely source of anemia.

Treatment was initiated with topical permethrin, however, due to the heavy lice burden and previous treatment failures, she was also treated with oral Ivermectin. She received 3 units of packed red blood cells over the course of her 3-day admission. At discharge, she had a hemoglobin of 9.8g/dl and was placed on oral ferrous sulfate at 6mg/kg/day.

Conclusion: This case highlights the importance of having a thorough approach to the management of anemia in pediatric patients. Severe IDA secondary to *Pediculosis capitis* should be a diagnosis of exclusion. Having ruled out possible red blood cell production and consumption pathologies, we were left with blood loss secondary to lice infestation as the only potential cause of anemia in this child.

Poster # 426

Non-immune Hemolytic Anemia in an adolescent with vitamin C deficiency

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Background: While scurvy is often thought of as a disease of the 18th century, it is still seen today in malnourished individuals. In the developed world, scurvy may be underrecognized in individuals with severely restricted eating patterns. Anemia can be seen in up to 80% of patients with scurvy, caused by various mechanisms including gastrointestinal bleeding, impaired erythropoiesis, concurrent folate deficiency, and intravascular or extravascular hemolysis.

Objectives: Present a case of hemolytic anemia in the context of scurvy and discuss prior research and possible etiology.

Design/Method: Case report.

Results: A 14-year-old male with autism spectrum disorder presented with 3 weeks of worsening bilateral leg pain, inability to bear weight, and bruising. History revealed a restrictive diet consisting primarily of quesadillas and pancakes. On exam, vital signs were notable for tachycardia at 130 bpm. He was pale with bruising and non-pitting edema of the bilateral lower legs and had pain with extension of bilateral knees. Labs showed anemia with hemoglobin of 5.8g/dL, MCV of 73fL, RDW of 16.4%, reticulocyte count of 6% and leukopenia (WBC 3.8). Direct antiglobulin test (Coombs) was negative; total and indirect bilirubin were elevated at 1.53 mg/dL and 1.14 mg/dL, respectively. LDH, haptoglobin, uric acid, and CK were normal. Rheumatologic workup, including anti-dsDNA and anti-Smith antibodies, ANA titer, and CH50, was negative. Coagulation studies were normal. The patient's leukopenia prompted a bone marrow biopsy which showed erythroid hyperplasia with decreased myelopoiesis. Plasma free hemoglobin and red cell enzymes including G6PD**,** 6-PGD**,** pyruvate kinase**,** and hexokinase were elevated. Given the patient's restricted diet, nutritional markers were collected: serum ascorbic acid was undetectable, confirming scurvy. Two units of pRBCs were administered with subsequent hemoglobin improvement to 9.1 g/dL. Repeat labs after vitamin C supplementation showed hemoglobin of 11.9 g/dL.

Conclusion: Previous cases of hemolytic anemia in patients with scurvy have been reported, possibly caused by reduced RBC survival. Merskey et al. demonstrated decreased survival time of transfused RBCs in patients with scurvy. Another study of mouse RBCs demonstrated that low serum ascorbic acid both decreased synthesis of beta-spectrin and increased osmotic fragility. Previous cases have also demonstrated Coombs negative hemolytic anemia, decreasing the likelihood of an immunologic component.

Our case is another example suggesting non-immune hemolysis as an etiology of anemia in scurvy, supported by increased plasma free hemoglobin, increased serum red cell enzymes, and reticulocytosis as well as negative autoimmune workup

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Poster # 427

A NOVEL METHOD FOR DIAGNOSIS OF HEREDITARY HEMOLYTIC ANEMIA- CASE SERIES AND LITERATURE REVIEW

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Background: Hemolytic anemia is the premature destruction of red blood cells due to erythrocytes' membrane or enzymatic defect, or globin gene variation. These anomalies can be inherited or acquired. Diverse diagnostic evaluations have been used throughout the years. However, as science is evolving there have been less invasive and more informative tests available

that can diagnose complex and unclear presentations. Next gene sequencing has simplified our practice to evaluate and diagnose these patients.

Objectives: This case series aims to describe four interesting cases with hemolytic anemia that required Next gene sequencing for diagnosis

Design/Method: Use of Next gene sequencing for diagnosis of refractory hemolytic anemia

Results: First case is a 16-month-old infant with refractory anemia in whom, comprehensive hemolytic work-up was done and next gene sequencing revealed two heterozygous missense alterations in the alpha spectrin gene (SPTA1), as well as a common phenotype modifying polymorphism alpha-LELY and diagnosed with Hereditary Pyropoikilocytosis.
Second case is a full-term newborn found to have severe normocytic anemia and Coombs positive requiring NICU admission for management and comprehensive hematology workup. Next gene sequencing revealed that he was heterozygous for a pathogenic variant of ANK1 and diagnosed with autosomal dominant Hereditary Spherocytosis.
Third case is a 17-year-old adopted male with unknown biological family history that presented with severe symptomatic hemolytic anemia and splenomegaly that was refractory to treatments. Next gene sequencing was obtained and showed a common SPTA1 gene variant in alpha-LELY polymorphism and a segmental variation in beta spectrin gene which is seen in Hereditary Spherocytosis.
Fourth case is a 10-year-old female from Jamaica that presented with splenomegaly and symptomatic hemolytic anemia. Next gene sequencing to assess the cause of her hemolytic anemia, revealed a pathologic variant of Spectrin Alexandria in the alpha spectrin gene (SPTA-1) supportive of red blood cell membrane disorder often seen with Hereditary elliptocytosis/ pyropoikilocytosis.

Conclusion: All these patients had similar but complex medical presentations; however, on gene analysis three were noted to have missense mutations of the SPTA1 gene, while one was found to have pathogenic alterations of ANK1. Patients presenting with refractory hemolytic anemia, those requiring several transfusions, or those in need of splenectomy might benefit from next gene sequencing as a diagnostic test for more specific and definitive management.

Poster # 428

SPHEROCYTOSIS IN NEWBORN SECONDARY TO NOVEL HETEROZYGOUS MUTATION IN SPTB GENE

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Background: Hemolytic anemia (HA) is attributable to the erythrocyte's intrinsic characteristics or extrinsic processes affecting the erythrocyte. Serology is significant for reticulocytosis, hyperbilirubinemia, anemia, and abnormal peripheral blood smear. Pallor and jaundice are indicative of an intrinsic cause. Further information is necessary to elucidate the specific etiology, including family history, MCHC, direct antiglobulin, enzyme function, and genetic testing.

Hereditary spherocytosis is caused by genetic variations in proteins that disrupt the erythrocyte membrane and cytoskeleton, such as spectrin, ankyrin, band 3, and band 4.2.

Objectives: To describe a novel mutation of the SPTB gene as a potential pathogenic cause of spherocytosis in a newborn with HA.

Design/Method: Single subject case report.

Results: The patient is a 3-week-old male born full-term via NSVD with a history of an 8-day NICU stay due to significant hyperbilirubinemia requiring phototherapy for 5 days. His labs were significant for anemia, reticulocytosis, negative Coombs test, and no ABO or Rh incompatibility. Peripheral smear was significant for polychromasia with microcytes, normocytes, and burr cells in the absence of nucleated cells. G6PD and Pyruvate Kinase levels were within normal limits. Both parents are of African American heritage, and family history was negative for hemoglobinopathies and HA. Initial HA screening panel on day 6 revealed increased osmotic fragility, decreased Eosin 5-Maleimide binding, and decreased Protein band 3, which suggests hereditary HA. His persistent symptomatic anemia with reticulocytosis and elevated MCHC initiated evaluation of next-generation sequencing (NGS). Hereditary Hemolytic Anemia Panel revealed a heterozygous out-of-frame deletion in Exon 2-3 of the SPTB gene, resulting in an abnormal and non-functioning protein product. Loss-of-function mutations of the SPTB gene are known to cause abnormally shaped erythrocytes. However, the specific deletion present in this patient has not been reported in literature and is thus potentially pathogenic.

Conclusion: Spherocytosis commonly presents in the neonatal period with jaundice secondary to HA. This case presents an example of spherocytosisin the setting of a heterozygous SPTB loss-of-function mutation not previously reported in the literature. Evaluation of the patient's clinical course and treatment strategies can elucidate future management recommendations to treat patients with this mutation. Parental blood NGS is pending to discover if this is a de novo or inherited mutation.

Poster # 429

MEDICAL HISTORY: FRIEND OR FOE? A CASE OF TWO TYPES OF ANEMIA IN THE SAME PATIENT

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Background: Anemia is one of the most common laboratory diagnoses in the pediatric population. It is a collection of disorders that affect red blood cells (RBCs) either through decreased production, increased loss, or premature breakdown.

Objectives: Two congenital causes of anemia in the same patient is rare, but possible.

Design/Method: A 4 y.o. M with a medical history of hereditary spherocytosis (HS) diagnosed at birth due to family history presented to an outside hospital with a one-day history of LUQ pain,

pallor, jaundice, and fatigue. He denied any recent illnesses. Since 3.5 y.o., he had more frequent ED visits for worsening jaundice, thought to be due to HS.
Workup showed mild leukocytosis (WBC 16.5), severe normocytic anemia (hgb 5.8 g/dL, MCV 85 fL), and normal platelets (237x10^3/mm^2). Severe reticulocytosis and a positive Coombs test with warm autoantibodies were discovered. He was diagnosed with warm autoimmune hemolytic anemia (AIHA) in addition to HS. High dose IV solumedrol was initiated for 72 hours and then transitioned to oral prednisone. After completion, his AIHA resolved with labs showing negative Coomb's test, hgb 10 g/dL, and reticulocyte count 16%.
Due to his unusual presentation, further workup included genetic confirmation of his HS. The genetic panel revealed he was heterozygous for cytotoxic T lymphocyte antigen 4 (CTLA4) haploinsufficiency. He was treated with sirolimus and started on monthly IVIG therapy. His hemoglobin remains stable. His mom and sister were also found to be positive for the same mutation.

Results: Due to overlapping lab values and similar findings on peripheral smears, the diagnosis of anemia is not always clear. HS is traditionally diagnosed by spherocytes on a peripheral smear and a positive family history of the disease. However, AIHA can also have spherocytes. Therefore, using a peripheral smear and family history alone can lead to an incorrect or incomplete diagnosis. To diagnose warm AIHA, a positive Coomb's test displays IgG bound to RBC membranes.
An accurate diagnosis can have implications for treatment. Often, splenectomy is recommended in patients with HS. However, splenectomy is not recommended in patients with CTLA 4 haploinsufficiency due to risk of infection post-splenectomy.

Conclusion: Pediatric anemia is a common problem. However, there are subtleties among the different types that can make it difficult to diagnose. This case emphasizes the importance for clinicians to have a high index of suspicion for a secondary process if a patient's symptoms evolve over time and no longer fit with the initial diagnosis.

Poster # 430

IRON OVERLOAD ASSOCIATED WITH INTRAUTERINE TRANSFUSIONS IN INFANTS WITH RH ALLOIMMUNIZATION

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Background: Hemolytic disease of the fetus and newborn (HDFN) results from maternal rhesus (Rh) isoimmunization. Multiple intrauterine transfusions (IUTs) for the treatment of HDFN have been used to prevent fatal outcomes, but were described to lead to iron overload. No guidelines currently exist for the management of neonatal iron overload, but reports suggest infants respond well to aggressive chelation therapy.

Objectives: Report a case of severe iron overload requiring chelation therapy in a newborn with HDFN and review of the literature for management recommendations.

Design/Method: Case Report and Review of the literature

Results: A male infant was born at 36 weeks of gestation to a G4P0222 mother with Rh alloimmunization. At 24 weeks, the fetal hemoglobin was 3.4 g/dL. Fetal blood type was O, Rh-positive, with positive fetal direct antibody test (DAT). Maternal blood type was O negative, and her indirect antibody screen was positive. A total of five IUTs were administered between weeks 24 and 33. At delivery, the infant was noted to have petechiae and a platelet count of 59. He was hypoxemic requiring high flow nasal cannula. The total bilirubin was 11.4 mg/dL. The direct bilirubin was 8.7 mg/dL. Hypoglycemia, thrombocytopenia, and coagulopathy were also present suggesting liver dysfunction. The ferritin was 9,889 ng/ml suggesting iron overload. The hemoglobin was 14.2 g/dL. The absolute reticulocyte count was 20,000. DAT was negative. MRI demonstrated hepatomegaly with diffusely decreased signal of T2, in-phase and out-of-phase images with associated decreased T2* relaxation times most consistent with liver iron deposition. Marked splenomegaly (7.6 cm) and iron deposition in the spleen were also present. Liver biopsy was not performed. Deferoxamine was initiated on day 2 of life at a dose of 25 mg/kg given intravenously over eight hours. On day 10 of life, the dose was increased to 40 mg/kg given over 12 hours. Erythropoietin (EPO) was started to promote red blood cell production and iron utilization. The hyperferritinemia, coagulopathy, and hyperbilirubinemia subsequently improved. Exome sequencing detected a de novo, likely pathogenic missense mutation in *PIEZO1,* which is associated with dehydrated hereditary stomatocytosis.

Conclusion: Infants who received intrauterine transfusions should be monitored for iron overload, which can present as reversible cholestasis and coagulopathy in the neonatal period. Iron chelation and EPO are safe and effective therapeutic options. Genetic testing may identify additional risk factors for iron overload.

Poster # 431

SPONTANEOUS CALVARIAL INFARCTION IN A TEENAGER WITH SICKLE CELL SS DISEASE AND G6PD DEFICIENCY

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Background: Sequelae of sickle cell disease (SCD) are often the result of vaso-occlusion (VOC) resulting from the dysmorphic shape of sickled red blood cells (RBC). Bone infarction occurs commonly in patients with sickle cell, most notably in long bones and axial skeleton. Infarct occurs much less frequently in the bones of the skull. Calvarial bone infarct results in MRI findings of T2 hyperintensity in areas of bone marrow edema with associated hemorrhage. Headaches in children with SCD are more likely to be due to severe underlying cerebral pathologies than in those children without SCD. When evaluating a child with SCD presenting with headache, consideration should be given to bony infarct.

Objectives: The purpose of this case study is to discuss an uncommon sequela of SCD in a pediatric patient.

Design/Method: This is a single subject case study.

Results: A 15-year-old male with a history of sickle cell disease (type SS) and G6PD deficiency presented with headache and swelling over the left parietal region for two days with associated left sided visual disturbance. He denied head trauma or seizure-like activity. Upon presentation, he was febrile with tachycardia and a normal neurological exam. CT scan of his head was significant for a left subgaleal hemorrhage and bilateral epidural midline and left parietal fluid collections consistent with bone marrow infarcts and associated subacute epidural hematomas, without evidence of brain parenchymal injury or sinus venous thrombosis. A follow up MRI obtained during hospitalization indicated that the left subgaleal hematoma remained stable with breakdown of subgaleal blood products. The patient was treated primarily with supportive care including hydration, packed red blood cell transfusions and pain management. He did not require neurosurgical intervention. His hospital course was complicated by additional VOCs, sickle cell hepatopathy and acute chest syndrome.

Conclusion: Rarely, calvarial VOC has resulted in epidural hematoma. In this case, calvarial infarct with unilateral headache, acute vision loss and acute cranial swelling resulted in subgaleal hemorrhage. This clinically significant finding results from bleeding between the periosteum and scalp galea aponeurosis, which may lead to hypovolemic shock. Calvarial infarcts should be considered on the differential in sickle cell disease patients presenting with a headache as prompt diagnosis can improve morbidity outcomes.

Poster # 432

TREATMENT OF CHRONIC PAIN IN AN ADOLESCENT WITH SICKLE CELL USING AN INPATIENT REHABILITATION MODEL

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Background: Chronic pain syndrome (CPS), defined as ongoing pain (>15 days per month) lasting for at least 6 months, affects more than a quarter of pediatric patients with sickle cell disease (SCD) by adulthood. CPS is associated with an increase in depressive symptoms, decreased quality of life, frequent school absences and frequent hospital admissions. CPS is typically managed at specialized inpatient rehabilitation centers or by anesthesia trained pain specialists, though experience with patients with SCD is limited. Multidisciplinary pediatric hospitals have both scarce and varying approaches to address chronic pain in patients with SCD.

Objectives: To describe the success of a piloted, individualized inpatient chronic pain rehabilitation program in a patient with SCD. The goal of this approach was to decrease opioid dependence and increase functional capacity.

Design/Method: Single subject case report

Results: A 16-year-old female with HbSS disease on chronic red cell exchange presented with multiple ER visits and hospitalizations for pain crises. After six prolonged admissions for pain (>2 weeks) in one year despite maintaining HbS <30%, a multidisciplinary, chronic pain rehabilitation approach was initiated. A regimented inpatient schedule that included daily psychology, physical and occupational therapy, art therapy, palliative care, chaplain services and sleep hygiene was implemented. Continuous opioid infusion was weaned off after three weeks, and daily scheduled opioids were weaned off after 4.5 weeks. She was discharged home on buprenorphine, amitriptyline and pregabalin. Multidisciplinary team meetings occurred weekly to coordinate care. On discharge, bi-weekly phone calls and weekly multidisciplinary meetings continued to troubleshoot outpatient care, which were gradually stopped as the patient's family gained outpatient skills and independence. Despite presenting to the emergency department and clinic four times since discharge for breakthrough pain, the patient has remained out of the hospital for over three months since completing the chronic pain rehabilitation program.

Conclusion: Despite a high prevalence of CPS in pediatric patients with SCD, there is a paucity of standardized management tools and a scarcity of resources to address chronic pain in the SCD population, especially at centers lacking dedicated pain specialists. Few inpatient pediatric chronic pain programs exist across the country, and it is not feasible to relocate families to these rehabilitation programs. Furthermore, many of these chronic pain centers lack experience with patients with SCD. We describe the successful implementation of a multidisciplinary chronic pain management program that has decreased opioid use, increased functional capacity, and drastically reduced hospitalizations in an adolescent patient with SCD and chronic pain.

Poster # 433

TRANEXAMIC ACID FOR MANAGEMENT OF RENAL PAPILLARY NECROSIS AND HEMATURIA IN SICKLE CELL DISEASE

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Background: Tranexamic acid (TXA) is an antifibrinolytic drug used as a hemostatic agent in the management of hereditary or acquired bleeding disorders. Sickle cell disease (SCD) can cause hematuria secondary to renal papillary necrosis and altered hemodynamics. TXA for treatment of hematuria in patients with SCD has been proposed. TXA may mitigate hyperfibrinolysis in the setting of renal papillary necrosis due to RBC sickling.

Objectives: In this report, we summarize the outcomes of two adolescents with SCD treated with TXA for persistent gross hematuria.

Design/Method: A retrospective review was performed on two patients treated at St. Louis Children's Hospital.

Results: Patient A, a 16-year-old female with Hgb SC on no disease-modifying therapy, presented with gross hematuria after physical assault. Her hemoglobin dropped from 12.5 to 6.1 g/dl, necessitating red cell transfusion. Urinalysis had >50 RBCs/hpf. Ultrasound and computed tomography showed no mass, hematoma, hydronephrosis, or disruption of the renal capsule. Cystoscopy confirmed blood exiting the right ureter. She received intravenous hydration, pain management, and intravenous iron infusions. Gross hematuria and anemia persisted for eight weeks, and vascular interventions such as embolization were deemed too risky without likely benefit. TXA 650 mg thrice daily was initiated, with resolution of hematuria within one day. Over the next year, she had two recurrences of gross hematuria that resolved rapidly with TXA; she had no signs of urinary tract obstruction. Her creatinine remained at her baseline.

Patient B, a 15-year-old male with Hgb SS disease receiving chronic red cell exchange transfusions, was admitted with 24 hours of painless hematuria. Hemoglobin, reticulocyte count, and creatinine were at his baseline. Urinalysis showed >50 RBCs/hpf. Renal ultrasound showed no masses or hydronephrosis, and hematuria was presumed due to renal papillary necrosis. After 48 hours of conservative management with bedrest and intravenous hydration, hematuria was unchanged. Based on our prior experience with patient A, oral TXA 650 mg thrice daily was started, with resolution of gross hematuria 8 hours after the first dose. Urinalysis repeated the following day had 0 RBCs/hpf. He completed a 5-day course of TXA and has not had recurrence of hematuria.

Conclusion: This report describes the successful treatment of refractory hematuria in two SCD patients with TXA. Importantly, neither patient experienced urinary tract obstruction after TXA treatment. Our experience suggests that this agent may be considered as a therapeutic option for persistent gross hematuria.

Poster # 434

ANTIBODY-NEGATIVE DELAYED HEMOLYTIC REACTION IN A YOUNG ADULT WITH SICKLE CELL DISEASE

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Background: Delayed hemolytic transfusion reaction (DHTR) is a rare and life-threatening complication of red cell transfusion that may occur between 3 and 25 days post-transfusion in previously alloimmunized patients. Patients with sickle cell disease (SCD) are often at risk due to the high likelihood of alloimmunization, the lifetime burden of transfusion, and the need for urgent transfusions for life-threatening complications or while in an inflammatory state. In older SCD patients, DHTR may account for up to 11% of mortality, although this is believed to be under-reported. Diagnosis of DHTRs may be delayed in SCD patients due to similarities in presentation with a vaso-occlusive crisis (VOC) and lack of consensus on diagnostic criteria.

Objectives: We describe our management of a complex SCD patient requiring emergent transfusion complicated by clinical DHTR and review literature on this under-reported complication.

Design/Method: Descriptive report of complicated transfusion reaction in SCD patient.

Results: We report a 19-year old male with hemoglobin SS disease and cerebral vasculopathy status post chronic transfusions for 15 years complicated by transfusional iron overload and remote history of anti-JsA alloantibodies, who presented to our emergency department for vaso-occlusive crisis, hepatomegaly, transaminitis and hyperbilirubinemia consistent with intrahepatic cholestasis and sequestration. After conservative management with parenteral narcotics and hydration, he was transfused 2 red cell units on day 7 for worsening hepatopathy with preceding immunosuppression using intravenous immunoglobulin and high dose corticosteroids. He showed immediate clinical improvement following transfusion with appropriate hemoglobin response. His indirect and Coombs antibody tests were negative before transfusion with negative antibody screen on crossmatch before transfusion. On day 9 he developed acute worsening abdominal pain with new oxygen requirement, dropping hemoglobin and rising lactate dehydrogenase concerning for hemolytic reaction despite immunosuppression. His red cell antibody screens remained negative throughout his stay. He received 4 additional courses of immunoglobulin and 2 doses of Rituximab between days 9 and 16. He also received 6 courses of plasmapheresis from days 9 through 18 with eventual improvement in hemolysis and stable hemoglobin by day 21. He was discharged after 22 days with a prolonged steroid taper.

Conclusion: Our patient presented with alloantibody-negative DHTR onset within 48 hours of transfusion. The literature suggests classic alloantibody-mediated DHTR occurs in a third of patients. Nearly 40% of patients may be allo-antibody negative with complement-mediated hemolysis, while the rest may have an additional auto-antibody response. A high index of suspicion is important to decrease morbidity with this challenging complication

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Poster # 435

A Rare Presentation of Acute Sternal Osteomyelitis in a Pediatric Patient with Sickle Cell Disease

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Background: Patients with sickle cell disease (SCD) are noted to have several complications resulting from vaso-occlusion (VOC) due to the dysmorphic shape of sickled red blood cells, for which they undergo close follow up and frequent images/studies. Given frequent episodes of bone infarction, osteomyelitis is one of the most common infections that they present with, usually involving the long bones and rarely affecting the flat bones. In the general population, Staphylococcus aureus is the most common organism; however, in patients with SCD encapsulated organisms such as Salmonella are the most common causative agent.

Objectives: This case report aims to describe the case of a 2 year old male with SCD who developed acute methicillin sensitive Staphylococcus aureus (MSSA) sternal osteomyelitis, beyond those previously identified

Design/Method: Single subject case report- developed by literature search of previous cases of osteomyelitis in pediatric patients with SCD and includes the references as noted below.

Results: This is a 2 year old male with SCD and non-adherence with prophylactic antibiotics who presented with fever and diffuse abdominal pain. Patient was positive for Rhinovirus and Adenovirus and blood cultures grew MSSA. Fever curve improved after initiation of parenteral antibiotics; however, the patient developed sternal soft tissue swelling with mild discomfort only on deep palpation. Initial superficial ultrasound was consistent with cellulitis. Given worsening of swelling, chest MRI was obtained and revealed acute sternal osteomyelitis. PICC line was placed for a prolonged course of Cefazolin. The patient continues to follow closely with hematology, cardiothoracic surgery, and Infectious disease specialists.

Conclusion: Osteomyelitis is an uncommon complication in children with SCD. Encapsulated organisms are usually the causative organisms and patients often have a history of prior vaso occlusive crises. These patients often present with fever and vaso occlusive crisis. This case describes the presentation of a rare complication of SCD given the site of infection, the causative organism, and absence of history of vaso occlusive crisis in this patient.

Poster # 436

PULMONARY HYPERTENSION AND REFACTORY CYTOPENIAS IN BETA THALASSEMIA MAJOR

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Background: Beta thalassemia major (BTM) is a severe hemolytic anemia that results in multisystem complications from anemia and iron overload. Transfusions mitigate the risks of chronic anemia but an inadequate regimen can lead to ongoing hemolysis and pulmonary hypertension. Iron deposition from chronic transfusions can be exacerbated by increased intestinal absorption when ineffective hematopoiesis occurs. While aggressive transfusion and chelation are the mainstays of therapy, geographical variation in resources can result in uncharacteristic and acutely life-threatening manifestations.

Objectives: We describe a 20-year-old female from Afghanistan with known BTM who presented during a humanitarian crisis with acute onset seizures, refractory cytopenias, pulmonary hypertension, and chronic kidney disease.

Design/Method: Case report.

Results: A 20-year-old Afghan female with known BTM and prior splenectomy had received red blood cell (PRBC) transfusions about every 21 days since 2-years-old. She had also received triple chelation therapy with deferiprone, desferal, and desferoxamine for the past decade. Her last transfusion was 3 weeks prior to presentation. Information was limited to the medications on hand and extended family member recollection. During evacuation she suffered a generalized tonic-clonic seizure. Laboratory values showed hyponatremia (sodium 125mmol/L), anemia

(hemoglobin 3.5g/dL), and thrombocytopenia (platelets 77 x10^3/mL). After 4 units of PRBCs (30mL/kg), she was transferred to our tertiary hospital. Hemoglobin was 7.2g/dL and reticulocytes 1.9%. Additional PRBC transfusions every 72 hours resulted in short-lived rises to hemoglobin 9.9g/dL and reticulocytes 0.7%, with no evidence of antibodies. Sodium was 125mmmol/L, potassium 6.6mmol/L, urea nitrogen 65mg/dl, and creatinine 1.1mg/dL. Physical examination showed short stature, 4/6 systolic murmur, hepatomegaly, ascites, and extremity muscular atrophy. Echocardiogram showed severe tricuspid regurgitation and pulmonary artery systolic pressure estimated at 128mmHg consistent with very severe pulmonary hypertension. The patient was treated with sildenalfil, macitentan, and spironolactone with notable improvement in her murmur, hepatomegaly, ascites, and electrolytes. Her platelets rose to 171x10^3/mL, and her transfusion requirements were reduced to 1 PRBC unit every 2 weeks, to maintain hemoglobin>10.5g/dL. Despite multiple endocrinopathies, to include insulin-dependent diabetes mellitus, short stature, and central hypogonadism, her ferritin was 516ng/mL. T2* magnetic resonance imaging revealed normal liver and cardiac iron, but pituitary imaging demonstrated iron deposition.

Conclusion: Global migration has increased the need for recognition of uncharacteristic presentations of thalassemic complications, including pulmonary hypertension with microangiopathic anemia and thrombocytopenia, and life-threatening electrolyte derangements. Optimal management of PRBC transfusions and pulmonary hypertension is imperative. Despite maximal chelation, the pituitary may remain susceptible to iron deposition and secondary endocrine dysfunction.

Poster # 437

HEMOGLOBIN SWITCHING IN LARGE β-GLOBIN GENE CLUSTER DELETIONS-A NOVEL εGγAγ DELETION WITH INTACT LCR

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Background: The εγδβ thalassemias (EGDBT) are infrequently occurring deletions of the β-globin gene cluster on chromosome 11. They are categorized into two groups, both with loss of the five DNaseI hypersensitivity sites upstream of the β-gene (HBB) called the locus control region (LCR). Large deletions not involving the LCR but remove the embryonic (*HBE*) and fetal genes (*HBG2/HBG1*) [LCR($\varepsilon^G\gamma^A\gamma$)$^0\delta\beta$] have not been previously reported.

Objectives: To evaluate the clinical impact of large deletions in the β-globin gene cluster and the implications on hemoglobin switching.

Design/Method: Four individuals with an LCR($\varepsilon^G\gamma^A\gamma$)$^0\delta\beta$ deletion have been evaluated. These include monochorionic, diamniotic twin girls whose newborn screen (NBS) both returned significant for HbA percentage greater than HbF. Pregnancy was uncomplicated without twin-to-twin transfusion or anemia and bilirubin levels in the low to low-intermediate risk zones were reported. At 20-months of age, hemoglobin electrophoresis showed borderline HbA2 and no HbF

in both twins. Ferritin levels were low-normal in Twin A (14 μg/L) and low in Twin B (9 μg/L). Multiplex Ligation-dependent Probe Amplification (MLPA) was then used to evaluate the infants, their 25-year-old healthy mother and an unrelated 40-year-old female with mild anemia and borderline HbA2.

Results: All individuals returned positive for a heterozygous large deletion affecting *HBE, HBG2, HBG1,* and *HBBP1* loci by MLPA. MLPA deletion/duplication testing on the α-genes was negative. No β-globin variants were identified by DNA sequencing. All cases showed the same MLPA pattern. Long-read sequencing performed on one case confirmed a single contiguous 32,599 bp deletion that matched the MLPA data (g.5262276-5294875).

Conclusion: The newly detected deletion differs from EGDBT mutations in that the LCR is intact therefore this mutation is expected to display different phenotypic features than classic EGDBT. *HBD* and *HBB* are not deleted therefore adequate transcription of HbA2 and HbA are expected without imbalance of α/β chains after the neonatal period. This can explain the decreased Hb F levels in the NBS. The HbA2 increase results from this deletion and does not indicate β-thalassemia. The heterozygous absence of *HBE* and *HBG2/HBG1* may result in upregulation of *HBD* and *HBB* expression through loss of FKLF and FKLF-2 binding. Additionally, *HBB*-EKLF binding results in less competition as the *gamma* promoter elements were heterozygously deleted. Compared to classic EGDBTs this novel LCR($\varepsilon^{G}\gamma^{A}\gamma)^{0}\delta\beta$ deletion was associated with normal CBC values with an absence of severe neonatal anemia, inverted HbF/HbA percentages at birth and borderline HbA2 levels.

Poster # 438

REVIEW OF HEMOGLOBIN VARIANTS WITH ABNORMAL PULSE OXIMETRY READINGS.

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Background: Abnormal oxygen saturation by pulse oximeter (SpO2) in children may result from acute or chronic respiratory, cardiovascular, or hematologic conditions. We report on three unrelated children found to have different rare congenital hemoglobinopathies due to structural hemoglobin (Hb) variants presenting with an abnormal SpO2.

Objectives: To report on three children with low SpO2 who received extensive interventions and had normal cardiopulmonary evaluations (chest x-ray, ECHO, EKG, venous/arterial blood gas) as inpatients. To compare the clinical and laboratory findings of three Hb variants: Hb Lansing, Hb Koln and Hb Santa Ana.

Design/Method: We conducted a retrospective chart review of three pediatric patients who were found to have rare Hb variants associated with abnormal SpO2. A literature review of these hemoglobin variants was also performed.

Results: Three children presented to an emergency room without any apparent respiratory distress and were found to have low SpO2 readings. Despite considerable interventions including albuterol nebulizers, IV corticosteroids, IM epinephrine, and supplemental oxygen, these patient's SpO2 readings remained low. All patients had a normal echocardiogram, EKG, chest x-ray, and venous/arterial blood gas. The first patient had a mild normocytic normochromic anemia with a normal Hb electrophoresis. Outpatient genetic testing revealed Hb Lansing due to a heterozygous mutation in the HBA2 gene (c.266C>G, p.His88Gln). Oxygen affinity testing was normal. The second patient had a mild macrocytic hypochromic anemia with reticulocytosis. Hb electrophoresis revealed an abnormal Hb variant. Outpatient genetic testing confirmed Hb Koln caused by a heterozygous mutation in the HBB gene (c.295G>A, p.Val99Met). Oxygen affinity was decreased. The third patient presented with jaundice, dark urine, and splenomegaly. He was found to have a macrocytic normochromic anemia with reticulocytosis. Hb electrophoresis revealed an abnormally elevated Hgb F and outpatient genetic testing confirmed Hb Santa Ana, the result of a heterozygous mutation in the HBB gene (c.266T>C, p.Leu89Pro). Oxygen affinity was increased.

Conclusion: The limitations of pulse oximetry should be recognized by clinicians when confronted with a child without apparent respiratory distress who may have an undiagnosed structural Hb variant. Normal Hb electrophoresis as part of the evaluation of discrepant pulse oximetry readings dose not disprove a Hb variant. Knowledge of the unique natural histories of these rare Hb variants will help medical personnel provide appropriate and non-invasive care to affected individuals.

Poster # 439

KIKUCHI FUJIMOTO DISEASE MIMICKING LYMPHOMA IN AN ADOLESCENT FEMALE

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Background: Kikuchi-Fujimoto disease (KFD) is a rare disease that has a predilection for younger individuals of Japanese and East Asian descent. KFD symptoms include lymphadenopathy, fever, and sweating, making it difficult to distinguish it from malignancies, especially lymphoma.

Objectives: 1- To raise awareness of clinical practinior to this rare disease.
2- To show the benifit of using PET scan to identify viable lymph node for biopsy

Design/Method: Case report

Results: A 13-year-old African-American female presents to the Emergency Department with a 10-day history of fever, rash and right large supraclavicular lymphadenopathy. CT neck, chest, abdomen and pelvis showed extensive cervical adenopathy, worse on the right. Labs showed anemia, leukopenia with neutropenia, and elevated Interleukin-2. Due to the persistent fever, lymphadenopathy, rash, cytopenia, and high ferritin (2370) and IL-2 (2100) levels, the differential diagnosis included lymphoma on the top of the list, with associated secondary Hemophagocytic Lympho-Histiocytosis (HLH). A lymph node biopsy as well as bone marrow aspirate and biopsy were done. Bone marrow showed significant hemophagocytosis without malignant infiltration, but

lymph node biopsy was inconclusive, as the node was completely necrotic; thus, lymphoma could not be ruled out. Due to the worsening systemic symptoms of HLH, etiology of the patient's symptoms had to be quickly determined. However, there was concern that another lymph node biopsy might not yield viable tissue. Therefore, a PET-CT scan to identify potentially viable lymph nodes was done. Another biopsy targeting the node with the highest SUV PET positivity was done. It
showed partial necrosis without neutrophilic infiltration, characteristic of KFD. Genetic workup for familial HLH was negative, so the diagnosis of KFD with secondary HLH was confirmed. The patient was started on dexamethasone, which promptly resolved her symptoms, including lymphadenopathy.

Conclusion: KFD, while rare, it is important to be included in the differential for lymphoma. KFD is especially challenging to diagnose because viable tissue must be obtained from a lymph node biopsy to confirm the diagnosis. We highlight the benefit of using a PET scan in such time-sensitive cases where attaining viable lymph nodes may be difficult due to widespread lymph node necrosis –which is a common finding in this rare disease–

Poster # 440

WHEN BONE PAIN AND BLEEDING MEAN MORE THAN LEUKEMIA - THE CASE OF NUTRITIONAL DEFICIENCIES

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Background: In resource-rich countries, severe vitamin C and D deficiencies in children are mostly rare and often associated with very restricted diets secondary to developmental or psychiatric issues. Both deficiencies can cause significant bone changes and pain, which may mimic other diseases, including leukemia. Treatment with supplementation is known to improve pain within a short period of time.

Objectives: To report two cases that presented with bone pain and bleeding that were found to be secondary to severe nutritional deficiencies.

Design/Method: Case series

Results: CASE 1: A 3 year old female with a history of developmental delay presented with a four week history of worsening bilateral lower extremity pain and refusal to bear weight. Initial x-ray imaging showed lumbosacral spinal dysraphism, but no other findings. An MRI of the spine was suggestive of an infiltrating marrow process targeting metaphyses. The complete blood cell count (CBC) and a bone marrow biopsy and aspirate were normal. Given patient had facial dysmorphisms, Genetics sent for chromosomal microarray testing, which also resulted normal. Endocrinology sent for a complete vitamin and mineral level workup, which showed a low level of vitamin D, 1-25-dihydroxy. A bone survey showed changes consistent with scurvy in the lower extremities. Patient was started on ergocalciferol and vitamin C with significant improvement in mobility and pain. CASE 2: A 4 year old female with history of developmental delay presented

with a three week history of worsening bilateral lower extremity pain and decreased mobility with edema and bruising on her left ankle. Patient was also taking amoxicillin for a presumed dental infection. Bilateral hip and knee x-rays showed linear metaphyseal lucencies in the proximal femurs, distal femurs and proximal tibias with cortical erosion concerning for leukemia. A CBC informed hypochromic microcytic anemia. Inflammatory markers, ESR and CRP, were elevated. The bone marrow biopsy was normal. On further history, patient was deemed to have a very restrictive diet of almond milk and mashed potatoes. Low 25-hydroxy vitamin D led to a bone survey which showed long bones with metaphyseal radiolucencies to varying degrees, concerning for scurvy. Patient was started on vitamin C supplementation with dramatic response.

Conclusion: Vitamin deficiencies may present with bleeding, bone pain, and x-ray findings that could be confused with findings seen in leukemia. In addition to ruling out critical diseases, these cases highlight the importance of a thorough dietary evaluation in young children presenting with debilitating sub-acute bone pain and/or bleeding.

Poster # 441

MISDIAGNOSIS OF KIKUCHI-FUJIMOTO DISEASE: THE IMPORTANCE OF TIMELY HISTOPATHOLOGY IN LYMPHADENITIS

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Background: Febrile lymphadenopathy not responding to first line antibiotics in a patient hailing from or with a history of travel to tuberculosis endemic countries is often primarily diagnosed as extra-pulmonary tuberculosis. However, histiocytic necrotizing lymphadenitis or Kikuchi-Fujimoto Disease(KFD) presents with similar clinical features. Etiological theories of KFD include viral agents, autoimmunity, and physicochemical factors such as leaking implants. Although KFD has classically been described in young Asian females, recent studies show men and women can be equally affected, with cases increasingly being reported from the USA and Europe as well. Availability bias amongst physicians can lead to misdiagnoses, especially in patients from tuberculosis endemic countries.

Objectives: To describe a case of misdiagnosis of KFD in an adolescent.

Design/Method: Case report

Results: A 16-year-old male from a tuberculosis endemic country, with a history of asthma, eczema and excision of omental infarct, presented with sub-occipital lymphadenopathy which resolved with antibiotics. Six months later, he complained of tender left cervical lymphadenopathy, associated with fever and fatigue, which lasted for a month. Two courses of antibiotics failed to decrease symptoms. Based on his clinical history, he was started on empirical anti-tubercular medications despite negative tests for tuberculosis. However, his symptoms began to worsen after three weeks of this treatment, and he developed high evening rise of temperature associated with chills, night sweats, frontal headache, pedal edema and generalized pruritic maculopapular rash.

Laboratory workups revealed leukopenia (WBC:3830/µL); elevated Erythrocyte sedimentation rate (29 mm/h), C-reactive protein (68.6 mg/dL), Aspartate Aminotransferase(95 U/L) and Alanine Aminotransferase(61 U/L). Rapid antigen test for SARS-CoV2 was negative, and no appreciable levels of SARS-CoV-2 IgG antibodies were detected. Investigations for Tuberculosis, EBV, CMV, Dengue, Malaria, Typhoid, Leptospirosis and Scrub typhus were all negative. Chest X-ray and abdomen ultrasound scan were normal.

Histopathological analysis of the excised cervical lymph nodes demonstrated crescentic histiocytes and karyorrhexis in a background of coagulative necrosis. Neutrophils, granulomas and acid-fast bacilli were absent. Immunohistochemistry was positive for CD3, CD20, CD68; and negative for CD15, CD30 and PAX-5.

A diagnosis of KFD was made, and patient was given supportive treatment only. His symptoms rapidly resolved within 48 hours, with complete resolution by three months.

Conclusion: It is important to raise awareness of KFD, a benign and self-limiting condition with good prognosis, which has many clinical symptoms mimicking grave conditions like extra-pulmonary tuberculosis, SLE and lymphomas. Timely histopathological analysis can help avoid anxiety surrounding a misdiagnosis and adverse reactions due to unnecessary toxic treatments.

Poster # 442

COVID-19 INFECTION OR UNDIAGNOSED LEUKEMIA AS A CAUSE OF PANCYTOPENIA; A PHYSICIAN DILEMMA!

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Background: COVID 19 infection frequently presents with respiratory tract infection although it is well described as being a systemic disease including the hematopoietic system. In fact, lymphopenia is a cardinal laboratory finding, with negative prognostic significance. In addition to lymphopenia, Covid 19 infection can also cause thrombocytopenia, anemia, and coagulopathy. Pancytopenia can be secondary to numerous viral infections, as well as other causes like leukemia. The co-existence of leukemia and viral infections can present as a diagnostic challenge.

Objectives: We describe a case report of a patient with Covid 19 infection concurrently with Leukemia.

Design/Method: Case Report

Results: The patient is a 6-year-old previously healthy female who presents with fever and upper respiratory symptoms. Labs revealed pancytopenia with a white blood cell count of 1500, absolute neutrophil count of 270, hemoglobin of 3.8 gm%, platelets 78000, reticulocyte count of 3.2%. Her respiratory pathogen panel was positive for Covid 19 and Rhinovirus/Enterovirus. She received supportive care including intravenous antibiotics and blood transfusions. To rule out leukemia,

peripheral blood smears and flow cytometry were reviewed, which were normal except for a few reactive lymphocytes. She was clinically stable and subsequently monitored as an outpatient. She ultimately underwent a bone marrow evaluation 16 days after discharging due to persistent pancytopenia. Her CBC at that point showed WBC 1500, ANC 40, Hemoglobin 9.2, Platelets 69000. Bone marrow morphology and flow cytometry revealed B cell ALL.

Conclusion: COVID 19 presents with a wide variety of symptoms including lymphopenia, anemia, and thrombocytopenia. Bone marrow suppression can also be the clinical manifestation of other viruses. Despite well-described myelosuppression that can be caused by a viral infection, a broad differential diagnosis should still be considered as less common causes of pancytopenia can still occur. In the present case, the co-existing viral infections lead to a dilemma in differentiating viral myelosuppression from leukemia. Close monitoring of this patient allowed for a rapid diagnosis to be made without ill effect on the patient. This case demonstrates the importance of keeping a broad differential diagnosis. Another important lesson from this case is the accuracy of bone marrow versus peripheral flow cytometry.

Poster # 443

NOVEL USE OF IMATINIB IN NOONAN SYNDROME THAT PRESENTED AS MANDIBULAR FIBRO-OSSEOUS DYSPLASIA

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Background: Fibro-osseous dysplasia of the mandible and maxilla, more commonly known as cherubism, begins during toddler years and culminates with involution during puberty. Cherubism classically is associated with *SH3BP2* mutations, but similar lesions can be observed in Noonan syndrome, Fragile X syndrome, and neurofibromatosis type I. In addition to physical disfigurement, these maxillary and mandibular lesions can cause difficulty with mastication, pain, and airway compromise. While intralesional corticosteroids, calcitonin, and alpha-interferon have been used, both response time and overall efficacy vary depending on the cohort studied. Imatinib also successfully has reversed cherubism in a small case series of patients with *SH3BP2*-positive disease.

Objectives: This case report highlights treatment of *SH3BP2*-negative cherubism with imatinib in a 10-year-old male with short stature who presented with conductive hearing loss, difficulty with mastication, burdensome activity restrictions, and frequent exposure to bullying due to marked mandibular hyperplasia.

Design/Method: Integrative clinical sequencing, including matched tumor/normal DNA and tumor RNA sequencing was performed following a mandible biopsy.

Results: Germline sequencing revealed an activating *PTPN11* p.156V mutation pathogenic for Noonan syndrome. The patient had a normal echocardiogram and had no history of developmental delay, highlighting an atypical presentation of Noonan syndrome solely with fibro-osseous dysplasia and short stature. As Noonan syndrome features MAP kinase pathway activation, use of

imatinib over additional agents studied in cherubism is attractive mechanistically since imatinib is known to inhibit downstream activity of the MAP kinase pathway through inhibition of cKIT. The patient was treated with imatinib at 300 mg/m2 daily selected by rounding the conventional 340 mg/m2/day dose to the nearest whole tablet.
The patient and his family noted regression of the bilateral mandibular hyperplasia within two months, and full resolution was appreciated both clinically and on computed tomography following one year of treatment. Therapy was well tolerated with nausea managed with ondansetron. The patient's conductive hearing loss resolved, and he is able to participate fully in sports. He also notes cessation of bullying from his peers and improved self-esteem.

Conclusion: Imatinib therapy was successful in treating fibro-osseous dysplasia due to underlying Noonan syndrome and should be considered over other therapies given its well documented safety profile and ability for home oral administration.

Poster # 444

HYPERCALCEMIA AND ELEVATED PTHRP WITHOUT EVIDENCE OF UNDERLYING MALIGNANCY IN PEDIATRIC PATIENTS

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Background: Although malignancy-associated hypercalcemia (MAH) occurs in as many as 30% of adult patients with cancer, the incidence of malignancy-associated hypercalcemia (MAH) in childhood is very rare only occurring in 0.4 – 1.3% of patients. Approximately half of children present at diagnosis with hypercalcemia particularly in patients with hematologic malignancies; while patients with solid tumors more commonly present with hypercalcemia during therapy or at time of relapse. The most common cause of MAH is a paraneoplastic syndrome, in which the tumor produces an ectopic hormone, parathyroid hormone-related peptide (PTHrP) that causes increased osteoclastic bone resorption, increased renal resorption of calcium, and increased renal phosphate loss. Hypercalcemia associated with the secretion of PTHrP is a relatively common occurrence in adult patients with cancer. In the pediatric population, however, the significance of hypercalcemia secondary to elevated PTHrP and risk of malignancy is not well understood.

Objectives: The purpose of this abstract was to systematically identify a small series of cases of hypercalcemia with elevated PTHrP without clear etiology in pediatric patients, that prompted extensive work up for underlying malignancy.

Design/Method: This was a hospital-based, retrospective case series that identified pediatric subjects with persistent hypercalcemia and elevated PTHrP in the absence of an underlying malignant process. We considered hypercalcemia serum calcium above 9.8 mg/dL, ionized calcium above 1.45 mmol/L. There was no available standardized level of PTHrP in serum.

Results: 4 children presented at mean age of 10.5 months with FTT, hypotonia, oral aversion, and severe hypercalcemia ranging from 13.6-16mg/dL (ionized Ca ranging from 1.57-2.24mmol/L). Workup for hypercalcemia was only significant for PTHRP elevated (12.9 to

21mmol/L) with suppressed PTH. All children underwent extensive workup for malignancy including PET scan, whole body MRI and bone marrow aspirate/biopsy with no evidence of malignancy. All patients received bisphosphonate therapy with prompt improvement in calcium and symptoms and were followed closely. At a mean follow up time of 2 years, all children remained clinically well with no recurrent hypercalcemia nor development of cancer diagnosis.

Conclusion: The presence of PTHrP-mediated hypercalcemia in the adult population is ubiquitously associated with a paraneoplastic syndrome related to an underlying malignancy. In this small retrospective case series of 4 children with PTHrP-mediated hypercalcemia, hypercalcemia was self-limited and none of the children were found to have underlying malignancy. This suggests that PTHRP mediated hypercalcemia is less associated with malignancy in children than in adults.

Poster # 445

SEVERE IMMUNE CHECKPOINT INHIBITOR ASSOCIATED HEPATITIS SUCCESSFULLY TREATED WITH BASILIXIMAB

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Background: Immune checkpoint inhibitors (ICIs) targeting programmed cell death 1 (PD-1) and its corresponding ligand PD-L1 are being increasingly used for a wide variety of cancers, including refractory sarcomas. Autoimmune hepatitis is a known side effect of ICIs, typically occurring 8-12 weeks after initiation. It is seen in 5-15% of patients using a single agent ICI, but only 1-3% experience Grade 3-4 hepatotoxicity. First line therapy remains discontinuation of the ICI and initiation of steroids, with some literature supporting T-cell-specific immunomodulators such as mycophenolate, tacrolimus, or azathioprine as second line agents. No current recommendations exist for patients with ICI induced hepatitis resistant to these first- and second-line agents.

Objectives: We describe a case of severe ICI associated hepatitis successfully treated with the anti-CD25 monoclonal antibody basiliximab, to specifically deplete activated T-cells.

Design/Method: Case Report

Results: A 22-year-old female with recurrent metastatic osteosarcoma of her right proximal tibia began treatment with the anti-PD-1 monoclonal antibody nivolumab for refractory disease. Nivolumab was discontinued after three months given new onset hepatitis indicated by isolated rising liver function tests (LFTs). She initially was treated with oral steroids, but with continued rise in her LFTs was admitted for an IV steroid pulse in conjunction with mycophenolate and IVIG. An infectious workup was negative for any infectious etiology explaining her hepatitis, and a biopsy showed scattered apoptotic hepatocytes with lobular T-cell infiltrates (CD3, CD4, and CD8+), but no steatosis or fibrosis. Given continued elevation in her LFTs, further treatments included everolimus, rabbit ATG, and tacrolimus, none of which were successful in persistently decreasing her LFTs, which peaked at greater than 20 times normal, indicating a Grade 4 adverse event. While immunosuppressed secondary to treatment, she experienced acute hypoxic respiratory

failure requiring intubation and vasopressors due to ESBL E coli sepsis. Given persistently rising LFTs with minimal response with the above therapies, basiliximab was initiated while continuing tacrolimus, mycophenolate, and steroids. She received a total of 6 doses of basiliximab, the initial two during the first week for a loading dose effect, then weekly for an additional four weeks. Her steroids have been able to be weaned to physiologic doses and mycophenolate and tacrolimus are being weaned with normalization of her LFTs and no major side effects secondary to basiliximab.

Conclusion: Basiliximab may be an effective therapy for steroid-resistant severe ICI associated hepatitis.

Poster # 446

ASPARAGINASE ASSOCIATED INTRA-CARDIAC THROMBUS PRESENTING AS SEPSIS IN AN ADOLESCENT ALL PATIENT

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Background: The incidence of pegaspargase induced thrombotic complications in pediatric patients with acute lymphoblastic leukemia (ALL) is 5.2%, with the majority of thromboses induced by asparaginase occurring in the venous system. Drug-induced intracardiac thrombosis is very rare and, if noted, usually develops within the right atrium in relation to central lines.

Objectives: To report a unique case of pegaspargase associated left ventricular thrombosis (LVT) with severe acute mitral valve regurgitation, initially diagnosed as septic shock.

Design/Method: A chart review was performed for this case.

Results: A 14-year-old female was diagnosed with B-cell ALL. At the time of diagnosis, her echocardiogram revealed a mild congenital dysplastic mitral valve with underdevelopment of the posterior leaflet, but cardiac function was not affected. The patient was started on a 4-drug induction and received 2 doses of pegaspargase. She was readmitted to the hospital on induction day 25 with diffuse body aches, generalized weakness, mildly elevated lipase, hyperbilirubinemia, pancytopenia, and severe hypo-albuminemia (1.6 gm/dl). Her direct bilirubin measured 1.7 mg/dL and amylase measured 289 U/L. On induction day 38, the patient developed a fever of 39.2°C. She became very ill looking and pale, but was oriented and alert. She stated that breathing was harder than earlier that morning. A chest x-ray was ordered to assess increasing O_2 requirement and bilateral opacities were found at the base of the lungs. Her heart rate was 130 bpm and blood pressure was 100/77 mmHg. After being transferred to intensive care, a stat echocardiogram was ordered due to suspected sepsis-induced cardiogenic shock. However, upon examination, the echocardiogram demonstrated an echo bright mass along the lateral wall of the left ventricle (LV), consistent with an LVT. The thrombus extended to the mitral valve causing severe acute mitral regurgitation leading to cardiogenic shock requiring pressors and inotropic support. The patient was initially started on heparin infusion to treat the LVT due to contraindications for surgical intervention including thrombocytopenia, neutropenia, and active cytomegalovirus infection. She later underwent LV thrombectomy and mitral valvuloplasty. She improved significantly after

surgery and was transferred to the rehabilitation unit.

Conclusion: This patient demonstrated a unique presentation to pegaspargase associated thrombus formation. Given the rareness of cardiogenic shock secondary to intra-cardiac thrombosis during pediatric ALL therapy, the clinical picture can be mistaken with septic shock. Having a high index of suspicion may prompt early evaluation with an echocardiogram, which can make an immense difference in the management and outcome of a patient.

Poster # 447

MIXED PHENOTYPE ACUTE LEUKEMIA/LYMPHOMA IN AN INFANT WITH CONSTITUTIONAL MISMATCH REPAIR-DEFICIENCY

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Background: Constitutional mismatch repair-deficiency (CMMRD) is a rare inherited cancer predisposition syndrome associated with malignant brain tumors, gastrointestinal and hematologic malignancies. Patients may develop multiple synchronous or metachronous cancers and prognosis is poor. CMMRD is caused by biallelic germline mutations in DNA mismatch repair genes MSH2, MLH1, MSH6, and PMS2. Approximately one-third of patients develop a hematologic malignancy, with a median age of 6 years. Only one case diagnosed in infancy has been described in the medical literature.

Objectives: Here we report an infant with a biallelic PMS2 mutation and mixed phenotype acute leukemia/lymphoma.

Design/Method: Case report

Results: An 8-month-old male with past history of infantile hemangioma, juvenile xanthogranuloma, café-au-lait macules and intracranial venous anomalies presented with pancytopenia, leukocytosis with circulating blasts, and an anterior mediastinal mass with a pleural effusion.

Flow cytometry revealed minimally differentiated AML from peripheral blood and T-cell lymphoblastic lymphoma (T-LL) from pleural fluid, meeting criteria for bilineal mixed phenotype acute leukemia, T/Myeloid (MPAL). The AML and T-LL clones appeared cytogenetically distinct: AML abnormalities included somatic trisomy 21 and pathogenic mutations in GATA1, WT1 and KRAS, while the T-LL clone featured losses within 7q and 14q and mutations in NF1, PTPN11, BCOR and FBXW7. Whole exome sequencing identified compound heterozygous pathogenic mutations in the PMS2 gene and tumor immunohistochemistry was negative for PMS2, consistent with CMMRD. There was no significant family history.

He received induction chemotherapy per AAML0531 with gemtuzumab and achieved negative minimal residual disease (MRD) for AML, but remained deep-sequencing MRD-positive for T-

LL with residual hypermetabolic mediastinal mass. He then received re-induction per AALL1231, with significant decrease in the mediastinal mass but progressive marrow disease with MRD positivity for both AML (1.6%) and T-LL (0.06%). This was followed by Topotecan, Vinorelbine, Thiotepa, Clofarabine (TVTC), then three additional salvage regimens including Nelarabine, Venetoclax/Navitoclax and Daratumumab. After each attempt he had persistent MRD for T-LL (remaining negative for AML), and variable response of his mediastinal mass. There were no unexpected toxicities. He died 9 months after diagnosis due to progressive disease with superior vena cava syndrome.

Conclusion: This is the first documented case of bilineal MPAL diagnosed in an infant with CMMRD. It is possible that AML and T-LL actually represented two distinct synchronous malignancies. CMMRD is a challenging disease and chemotherapy resistance is common. The diagnosis must be considered in children with features such as café-au-lait macules and hematologic or other associated malignancies.

Poster # 448

EXPANDING THE PHENOTYPE OF RTEL1-ASSOCIATED TELOMERE BIOLOGY DISORDERS TO INCLUDE BURKITT LYMPHOMA

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Background: Telomere Biology Disorders (TBD) can affect various organ systems. Multiple genes have been identified as causative for TBDs, including *RTEL1*. Hematologic manifestations of TBDs are typically bone marrow failure and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML). Although rare, Non-Hodgkin lymphoma has been reported previously in TBDs, and to our knowledge Burkitt lymphoma has never been reported in the setting of a TBD.

Objectives: Expansion of phenotype associated with *RTEL1* pathogenic variants.

Design/Method: Medical chart review of patient's demographic information, clinical presentation, disease course, genetic results, and treatment response. We also conducted a literature review of *RTEL1* and TBDs.

Results: A 13-year-old male initially presented with abdominal pain requiring diagnostic work-up, including ultrasound and X-ray, the ultrasound was suspicious for intussusception. The patient underwent laparoscopy, which identified an ileocecal mass prompting resection of the terminal ileum and cecum with primary anastomosis. Pathology was consistent with Burkitt lymphoma. A bone marrow aspirate and biopsy was performed which demonstrated normocellular marrow (70%) with trilineage hematopoiesis and no evidence of involvement by Burkitt lymphoma. PET/CT scan was consistent with Stage II Burkitt's lymphoma. The patient was treated per Children's Oncology Group protocol ANHL1131, group B and has been in remission for over 1 year. During his course he was found to have a significant family history of cancer, with his father diagnosed with Burkitt lymphoma of the jaw at age 9 and early greying at age 19. The patient was referred for genetic counseling and underwent extensive testing with a large hematology and hereditary cancer panel

which identified a likely pathogenic variant in *RTEL1* (c.3182-2A>C). Because of this result, a 6-panel assay telomere length measurement test was performed which found all measured telomeres at less than the 10th percentile. Cascade testing identified the same *RTEL1* variant in the patient's father.

Conclusion: Due to the identification of a TBD in this family, we are now able to offer surveillance for additional manifestations seen in TBDs, including pulmonary fibrosis and liver cirrhosis. This result also informs us of the family's additional risks for other hematologic malignancies and prompts regular surveillance with blood counts and bone marrow biopsies. Additional hematologic malignancies may be associated with TBDs beyond classic BMF and MDS/AML, though evidence of other patient data is needed to solidify this association.

Poster # 449

HODGKIN LYMPHOMA AND FUSION-POSITIVE RHABDOMYOSARCOMA ASSOCIATED WITH GERMLINE MSH6 MUTATION.

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Background: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, however it is rare in adulthood with very poor survival. Embryonal-RMS (ERMS) is associated with a range of somatic alterations described (TP53, RAS pathway, LOH 11p15.5), whereas Fusion positive Alveolar RMS (FP-ARMS) is notable for low tumor mutational burden (TMB). In fact, in a large study to characterize underlying genetic etiologies in RMS, 10% of ERMS patients had an underlying cancer predisposition syndrome (CPS), whereas none were seen in FP-ARMS patients.

Objectives: We hereby describe a young adult patient presenting with two lifetime primary malignancies that led to a search for an underlying CPS; a novel association was found.

Design/Method: A 29-year-old female with a history of recurrent Hodgkin Lymphoma (HL) presented with a right neck and ethmoid mass. Her initial HL was treated 10 years prior to presentation with ABVD. She relapsed 5 years later and received ICE followed by BEAM and an autologous stem cell transplant. Tissue biopsy confirmed FP-ARMS. She subsequently received 6 cycles of VAC/VI which was discontinued due to chemotherapy intolerance. She remains in remission 12 months since her initial diagnosis. Family history was significant for breast cancer in her mother and prostate cancer in her maternal uncle, both diagnosed after age 60.

Results: Immunohistochemistry of the right ethmoid and cervical lymph node showed tumor cells positive for desmin, CD56, actins, myoD1 and myogenin. FISH confirmed FOX01 gene rearrangement. RNA sequencing confirmed FOXO1-PAX3 fusion protein, in addition to a pathologic variant in NRAS in Exon 3 (c.181C>A) with a 37% variant frequency. Overall tumor had stable microsatellite instability, absent PD-L1 expression, and low TMB. Germline testing revealed a heterozygous MSH6 mutation (c.1618_1620del (p.Leu540del)), which is diagnostic for Lynch Syndrome (LS).

Conclusion: LS is an autosomal dominant cancer predisposition syndrome caused by germline mutation of mismatch repair (MMR) genes, most frequently associated with colorectal and endometrial sarcomas starting in the 4th decade. This is very rarely associated with sarcomas, with only 3 patients described with RMS. Lymphomas are overall rare but have been described more frequently in LS pedigrees. This is the first description of a patient with LS harboring a FP-ARMS. Interestingly, this patient's tumor has a stable MSI profile and absent PD-L1 expression. These findings are discordant from MMR deficient tumors. Further genomic studies are planned to delineate this patient's unique genomic profile to inform future treatment decisions in this challenging patient.

Poster # 450

INTRACRANIAL DESMOID-FIBROMATOSIS AFTER RADIATION THERAPY FOR PINEOBLASTOMA IN A PATIENT WITH FAP

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Background: Familial adenomatous polyposis syndrome (FAP) is known to be associated with astrocytic tumors and medulloblastoma. To date, pineoblastoma is not a common brain tumor type for patients with FAP, although 2 case reports have been published of adult women with pineoblastoma and APC gene mutations. In addition, studies suggest FAP syndrome does not carry increased risk for radiation toxicity. However, little knowledge exists about the risk of radiation-associated secondary malignancies in the setting of FAP syndrome.

Objectives: We present a case of a 6 yo boy with FAP syndrome who developed a pineoblastoma. He subsequently developed intracranial desmoid-type fibromatosis within his radiation treatment field, which has partially responded to standard sorafenib therapy.

Design/Method: Case Report. An extensive literature review was performed to review known tumor pathology with FAP syndrome and associated radiation-toxicity risk.

Results: Our patient presented at 4 years-old with pineoblastoma with metastatic ventricular disease. The patient's family had a history of clinically diagnosed FAP syndrome without genetic confirmation; therefore, we pursued full APC gene testing, which identified a pathogenic variant consistent with FAP syndrome (c. 3183_3187delACAAA). The patient's pineoblastoma was treated with multi-agent chemotherapy followed by craniospinal radiation, with complete response.

On disease surveillance about one-year post-therapy, new contrast-enhanced lesions were identified in the right frontal and parasagittal durae. These lesions progressed after short-interval active surveillance. Resection of the largest lesion was obtained, and pathology was consistent with desmoid-type fibromatosis. The lesion quickly re-grew and therefore given their high-risk location, the patient began treatment with the oral multi-kinase inhibitor Sorafenib, which he continues to

date. After approximately 3 months of therapy, the patient's desmoid tumors have shown partial response.

Conclusion: Our patient, with FAP syndrome, developed pineoblastoma- a rare but reported tumor type for his cancer predisposition syndrome. While 2 reports have been published of adults with Turcot syndrome and pineoblastoma with APC gene mutations, no reports have been published describing a similar phenomenon in younger patients.

This same patient subsequently developed desmoid-type fibromatosis with intracranial desmoid tumors. While studies suggest FAP syndrome does not carry predisposition for increased radiation toxicity, we suspect the patient's cranial radiation may have predisposed to development of in-field desmoid fibromatosis. Thus far, the patient's desmoid tumors have partially responded to standard therapy. More information about the role of radiation toxicity in FAP patients is needed.

Poster # 451

EBV+ HODGKIN LYMPHOMA IN A PEDIATRIC PATIENT WITH ATAXIA TELANGIECTASIA

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Background: Ataxia telangiectasia (AT) is a rare, inherited autosomal recessive disease due to mutations in the ataxia-telangiectasia mutated (ATM) gene. Mutations in ATM alter cellular abilities to detect and repair DNA damage. This genetic instability leads to a markedly elevated lifetime risk of developing cancer, especially leukemia and lymphoma. Patients with AT are highly sensitive to radiation therapy as well as chemotherapy. Given these unique challenges, the optimal treatment approach in AT patients has not been clearly established.

Objectives: We describe a pediatric AT patient with Stage IVB EBV-positive classical Hodgkin lymphoma who was treated successfully with a hybrid chemotherapy approach.

Design/Method: Patient presented with symptoms concerning for pulmonary embolism, but was found to have significant lymphadenopathy with tracheal compression on chest CT. Biopsy of right supraclavicular node revealed Reed-Sternberg cells staining positive for CD30, PAX5, CD15 and EBER; negative for CD20 and CD45. Final Ann Arbor classification was Stage IVB with large mediastinal adenopathy. Induction therapy with prednisone and brentuximab vedotin (BV) was initiated based on the report by Meister et al. A modified, dose-reduced COPP regimen (cyclophosphamide, vincristine/vinblastine, dacarbazine, prednisone) + BV was utilized for consolidation therapy. Dacarbazine was substituted for procarbazine due to antidepressant drug interactions. Vincristine and vinblastine were alternated within cycles in an effort to reduce the risk and severity of neuropathies. Dose-reduction in cyclophosphamide was decided given concerns for potential telangiectasias in the bladder. Rituximab was not utilized given CD20-negative status at diagnosis.

Results: Response assessment after seven cycles of induction therapy demonstrated significant partial volumetric and metabolic response. Our patient experienced complications during consolidation including neuropathies, pain, osteonecrosis and multiple infections which warranted further dose reductions. PET/CT after Cycle 5 consolidation demonstrated complete remission. In a joint decision, our patient did not complete the 6th planned cycle of consolidation given the morbidity and negative PET results. Our patient remained disease free for 13 months off-therapy before expiring from acute hypoxemic respiratory failure of unknown etiology.

Conclusion: Similar to the previously described case by Meister et al, we achieved remission for our patient with AT and Stage IVB Hodgkin Lymphoma following a modified, dose-reduced Brentuximab + COPP regimen. There is a paucity of data for AT patients with Hodgkin Lymphoma given the rarity of this disease compared to leukemia. Additionally, choosing a therapeutic regimen suitable for curing the disease with limited side effects is difficult given how sensitive these patients are to chemotherapy. (Meister, Pediatric Blood & Cancer, 2015)

Poster # 452

WHEN A DICER1 MUTATION OF UNCERTAIN SIGNIFICANCE IS ACTUALLY SIGNIFICANT

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Background: DICER1 is a cancer predisposition syndrome caused by mutations within the DICER1 gene on chromosome 14. DICER is an enzyme that cleaves RNA into microRNA and is integral in inhibiting unregulated cell growth and protein expression. We report a case of a young girl with two DICER1-associated tumors, who was found to have a variant of uncertain significance (VUS) in the DICER1 gene. Immediate family members also demonstrated the mutation, with two of three exhibiting DICER1-associated diagnoses. While DICER1 is typically inherited in an autosomal dominant fashion and manifests with low penetrance, this report illustrates high penetrance with this mutation, suggesting re-designation of the VUS to pathogenic.

Objectives: 1. Recognize potentially late presentation in DICER1 syndrome
2. Understand that a VUS can be pathogenic and may warrant re-designation
3. Understand the importance of testing patients presenting with DICER1-typical tumors

Design/Method: Case Report and Literature Review

Results: A 9-year-old female with past medical history significant for cerebral palsy and right ovarian torsion with oophorectomy at 6 years of age presented with a 2 week history of abdominal pain, distention, and decreased appetite. Imaging revealed a large 24 x 21 x 5.5 cm solid, cystic mass, with concern of origin from the left ovary. Alpha-fetoprotein and Inhibin A were within normal limits. CA-125 was elevated to 377 u/mL. Pathology showed poorly differentiated retiform Sertoli-Leydig Cell Tumor (SLCT) with rhabdomyosarcoma components after removal. Due to a strong family history of tumors associated with DICER1 syndrome, DICER1 testing was initiated. A heterozygous missense mutation in c.2408G>A (p.Gly803Glu) was detected and classified as a

VUS. Subsequently, her mother and two sisters underwent testing and possess the same germline mutation. Almost one year off-therapy from 4 cycles of Cisplatin, Ifosfamide, and Etoposide for her primary tumor, she developed a second abdominal malignancy, with pathology revealing Spindle Cell Sarcoma/Embryonal Rhabdomyosarcoma.

Conclusion: DICER1 syndrome is a rare genetic disorder, with development of DICER1-associated tumors occurring even less commonly. Our patient's VUS has not yet been designated a pathogenic variant for DICER1 syndrome. However, re-designation may be warranted due to the presence of multiple DICER1-associated tumors in the proband, as well as discovery of the same variant in her mother and sisters. This case exemplifies the importance of DICER1 testing in response to typical tumors associated with this mutation, as well as testing of family members. This will ideally lead to initiation of surveillance strategies with hopes of early diagnosis of potentially ominous malignancies.

Poster # 453

REMISSION OF AML IN A PATIENT WITH GERMLINE TP53 MUTATION AFTER DECITABINE MONOTHERAPY

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Background: Li-Fraumeni syndrome (LFS) is an autosomal dominant cancer predisposition syndrome due to germline mutations in the TP53 tumor suppressor gene. About 40% of individuals with LFS will be diagnosed with cancer by the age of 18. The incidence of hematologic malignancies in all patients with LFS is only 4%, and most often presents as a therapy-associated malignancy. We describe a pediatric patient with LFS who developed acute myeloid leukemia (AML) as a primary malignancy.

Objectives: To describe the use of decitabine in germline TP53-mutated AML.

Design/Method: The patient is a seven-year-old male who was diagnosed with AML, enrolled on study AAML1831, and received chemotherapy per Induction I with cytarabine, daunorubicin, and gemtuzumab ozogamicin. Bone marrow evaluation after the completion of the first block of chemotherapy showed primary induction failure with blasts comprising 50% of marrow cellularity on biopsy. In addition, our patient experienced numerous complications, including a retropharyngeal abscess, right internal jugular venous thrombosis, subdural empyema requiring hemicraniectomy, appendicitis, and typhlitis. To balance treatment of his numerous toxicities with his high disease burden, we started a hypomethylating agent, decitabine, to provide disease control while allowing time for recovery, with the plan to return to conventional cytotoxic chemotherapy to try to achieve remission prior to transplant.

Results: After three 28-day cycles of decitabine 20 mg/m^2 daily for 10 days, our patient had no morphologic or immunophenotypic evidence of leukemia. He underwent a 9/10 partially matched unrelated bone marrow transplant, with myeloablative fludarabine/busulfan conditioning. His

course was complicated by expected mucositis, pancytopenia, need for nutritional support, and hypertension. He had neutrophil engraftment on day +22 and slow platelet engraftment. He remains early post-transplant; however, bone marrow evaluation on day +30 showed no evidence of residual disease.

Conclusion: Primary myeloid malignancies related to LFS are rare. Our pediatric patient with LFS and AML was able to achieve complete morphologic and immunophenotypic remission after initial induction failure of AML with decitabine monotherapy. This allowed recovery from his previous chemotherapy-related complications, enabling the delivery of consolidative and hopefully curative therapy with stem cell transplantation. Decitabine has been shown to decrease variant allele frequency in TP53-mutated myelodysplastic syndrome or AML in adults. Patients with TP53-mutated AML have a poorer prognosis than those with non-TP53 mutated AML. Decitabine or other hypomethylating agents may be beneficial in patients who have germline TP53 mutations and AML.

Poster # 454

HEPATOSPLENIC T-CELL LYMPHOMA IN AN ADOLESCENT WITH PREVIOUSLY UNDIAGNOSED UNC13D-MUTATED FHL TYPE 3

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Background: Familial hemophagocytic lymphohistiocytosis Type 3 (FHL3) is an autosomal recessive immunoregulatory disorder caused by mutations in the UNC13D gene. UNC13D mutations have also been associated with the development of malignancies including lymphoma.

Objectives: We report a case of a previously-healthy adolescent male simultaneously diagnosed with FHL3 and gamma-delta hepatosplenic T-Cell lymphoma (HSTCL).

Design/Method: Case Report

Results: A 15-year old previously-healthy male was admitted for fever, pancytopenia and hyponatremia. He was discharged later with a presumptive diagnosis of viral marrow suppression. Six weeks later he was readmitted with similar findings but noted to have hepatosplenomegaly on ultrasound. Bone marrow aspirate/biopsy showed hypocellular marrow with histiocytosis. Soluble IL-2R was elevated at 9942 U/ml and ferritin 10,182 ng/mL. To confirm the diagnosis of HLH, whole exome sequencing (WES) was ordered and results showed compound heterozygous UNC13D pathogenic variants, consistent with FHL3. Lymphocyte immunophenotyping identified an abnormal T-cell population (50% of T cells) expressing gamma/delta T-cell receptor, positive for CD3, CD7, CD2, negative for CD4, CD8, CD5, CD56, CD26. T-cell receptor clonality testing by PCR indicated monoclonal gamma gene rearrangement. Repeat bone marrow biopsy was consistent with HSTCL.

Chemotherapy with ifosfamide/carboplatin/etoposide (1st line therapy for HSTCL per NCCN guidelines) was given without response. He was subsequently treated with pulse solumedrol for

persistent fever and rising HLH markers and 2nd line therapy with EPOCH (etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin). He had an excellent response to EPOCH and underwent allogeneic matched unrelated donor hematopoietic stem cell transplant following preparation with cyclophosphamide, ATG and TBI. He remains in remission from his HSTCL eight months post-transplant without signs of HLH.

Conclusion: Individuals with UNC13D mutations have a predisposition to HLH, lymphomas and leukemias. HSTCL is a rare, often fatal lymphoma typically affecting young adult males; sometimes in a setting of long-term immunosuppression. HSTCL can present with clinical findings of HLH in healthy males. However, our patient is the first to our knowledge found to have HSTCL associated with primary HLH due to mutations in UNC13D. Patients presenting with rare hematologic malignancies such as HSTCL should be evaluated for inborn errors of immunity such as HLH, given the ever-expanding spectrum of these disorders.

Poster # 455

CONCURRENT RHABDOMYOSARCOMA AND NEUROBLASTOMA IN A PATIENT WITH COSTELLO SYNDROME

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Background: Costello Syndrome (CS) is a rare pediatric overgrowth disorder characterized by a coarse facial appearance, intellectual disability, cardiac anomalies, musculoskeletal anomalies, failure to thrive, developmental delay, and cancer predisposition. CS is a RASopathy with a tumor incidence of approximately 15% by 20 years of age in individuals with an identified HRAS mutation. The most common tumors that occur in CS are embryonal rhabdomyosarcoma, neuroblastoma, and transitional cell carcinoma of the bladder.

Objectives: To describe the clinical course of a patient with CS and a known HRAS mutation who developed concurrent rhabdomyosarcoma and neuroblastoma.

Design/Method: Case Report

Results: The patient was transferred from Saipan at 2 weeks of age to our NICU for management of cardiac arrhythmia and developed complications of pulmonary hypertension, tracheomalacia, subglottic stenosis, hyperinsulinism, somatic overgrowth, and G-tube dependence. She was diagnosed with Costello Syndrome on whole genome sequencing which revealed a heterozygous c.34G>A variant in HRAS. At 2 months of age, oncology was consulted to evaluate right calf swelling, which showed FOXO1-negative alveolar rhabdomyosarcoma on biopsy. Staging work-up showed extensive inguinal, pelvic, and abdominal lymphadenopathy consistent with stage 3, group 3 rhabdomyosarcoma. Due to significant swelling and rapid mass enlargement, she began chemotherapy per intermediate risk COG D9803 protocol. She underwent disease response evaluation following week 13 of chemotherapy that demonstrated a decrease in size of right lower extremity mass and inguinal and pelvic lymphadenopathy. However, imaging revealed a left adrenal mass that in retrospect, was present on diagnostic imaging. Urine HVA and VMA were

elevated at 55.2 mg/g creatinine and 54.7 mg/g creatinine respectively. Biopsy of the adrenal mass showed a composite tumor with both neuroblastoma and rhabdomyosarcoma components. While recovering from the biopsy, the patient was readmitted due to recurrent right lower extremity swelling and pain. Despite receiving an additional cycle of chemotherapy, imaging showed worsening tumor burden in her right lower extremity and new lung nodules consistent with metastatic disease. Due to progressive disease, the patient transitioned to palliative care without further chemotherapy and died at 8 months of age.

Conclusion: Patients with CS require frequent cancer surveillance, and a tumor screening protocol has previously been proposed. This is a novel case of a patient with CS and a G>A HRAS mutation who developed two concurrent malignancies before one year of age. While G>A HRAS mutations are less common in CS, these individuals are at the highest risk of cancer and require more vigilant monitoring.

Poster # 456

VERY HIGH-RISK PRE-B ALL IN A 5-YEAR-OLD PATIENT WITH LYNCH SYNDROME: A CASE REPORT

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Background: Lynch syndrome (LS) is due to a heterozygous pathogenic variant in either MLH1, MSH2, MSH6, PMS2, or the EPCAM, leading to an increased risk of colon, endometrial, ovarian, brain, and skin cancer. Bi-allelic or compound heterozygous pathogenic variants of these genes define constitutional mismatch repair deficiency syndrome (CMMRD), which manifests as aggressive, early-onset childhood cancer, most commonly leukemia or brain tumors. The youngest patient described in the literature to date with an LS-related cancer was a 13-year-old with colorectal cancer.

Objectives: To report the youngest oncologic presentation of a patient with Lynch syndrome diagnosed with very high-risk pre-B cell Acute Lymphoblastic Leukemia (ALL).

Design/Method: Case report conducted via chart review.

Results: A 5-year-old previously healthy girl presented with 2-3 weeks of bruising and epistaxis alone. She was initially diagnosed as standard risk pre-B cell ALL. Cytogenetic analysis revealed a t(1;19) translocation. Fluorescence in situ hybridization (FISH) was negative for the KMT2A, ETV6/RUNX1, BCR/ABL1, and CRLF2 gene rearrangements. She underwent standard induction therapy as per Children's Oncology Group (COG) protocol AALL0932. Minimal residual disease (MRD) was 0.038% at the end of induction, therefore she was escalated to very high-risk therapy as per COG AALL1131. She achieved an MRD-negative remission at the end of consolidation. Her treatment course was complicated by PEG-asparaginase related pancreatitis which precluded further asparaginase therapy. The patient had an isolated bone marrow relapse 14 months from remission and underwent re-induction therapy on COG AALL1331, with continued M3 status at the end of re-induction. She subsequently received Inotuzomab on study COG AALL1731

followed by CD19 directed CAR-T therapy. She achieved MRD negative remission. After three months she recurred with CD19 negative CD22 positive ALL. She received chemotherapy with Fludarabine, Cytarabine and Idarubicin (IDA-FLAG), CD22 directed CAR-T therapy, and allogeneic bone marrow transplant. The patient died of progressive disease 28.5 months from her initial diagnosis. During her treatment course, the cancer genetics service was consulted due to her history of multiple chemotherapy-related toxicities and refractory disease, and she was found to have a germline pathogenic variant in MSH6 and a variant of uncertain significance in NRAS. She was diagnosed with Lynch syndrome. Her mother tested negative for the variants, and her father did not pursue germline testing.

Conclusion: This is the youngest reported patient with Lynch syndrome and an aggressive, early-onset childhood cancer. Emerging evidence is linking heterozygous germline pathogenic variants in the mismatch repair genes with the development of childhood leukemia.

Poster # 457

VHL SYNDROME IN ADOLESCENT PRESENTING WITH NEW-ONSET DIABETES AND HYPERTENSION

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Background: Von Hippel-Lindau syndrome (VHL) is a rare genetic disorder involving a mutation in the *VHL* gene, which normally acts as a tumor suppressor. Patients can develop tumors in the brain, spinal cord, adrenal glands, pelvic tissues, eyes, and pancreas.

Objectives: Herein we discuss our patient who presented with severe hypertension (HTN), new onset hyperglycemia and abnormal uterine bleeding (AUB). Detailed family history and initial work up for a suspected pheochromocytoma (PCC) /paraganglioma led to new diagnosis of a familial cancer syndrome.

Design/Method: A 15-year-old female with AUB and ovarian cysts presented to an outside ER for systolics of 170 and hyperglycemia discovered during a GYN clinic visit. Her BP on arrival was 147/96 with A1c of 12.5% and exam notable for acanthosis but no lymphadenopathy. Ultrasound incidentally revealed a solid adnexal mass. Abdominal and pelvic MRI afterwards showed masses in the pancreas, liver, ovary, and adrenal gland. A cancer syndrome was suspected. Family history included a teenage sister with an ovarian mass, mother who died of a pancreatic neuroendocrine tumor (NET). Biopsy of the pancreas and liver revealed unspecified NET and focal nodule hyperplasia, respectively. MIBG and octreotide scans suggested right-sided adrenal PCC. After the PCC was resected, her glucoses stabilized, and no insulin or anti-hypertensives were required. The left ovarian mass and right ovarian cyst were resected; the solid mass was found to be a steroid cell tumor.

Results: Plasma normetanephrine level 5.84 nmol/L (normal: 0-0.89 nmol/L), urine 24-hour metanephrine level 32 ug/d (normal: 40-209 ug/d), urine 24-hour normetanephrine level 1920 ug/d

(normal: 65–406 ug/d) and chromogranin A level was 189 ng/mL (normal: 0-103 ng/mL). A Prevention Genetics panel confirmed a heterozygous VHL sequence variant c.499C>T (p.Arg167Trp), shown to cause PCC and VHL Type 2B.

Conclusion: Given the wide array of effects of VHL, including the diverse symptoms possible with PCC, high clinical suspicion and careful family history contributed greatly to diagnosis.

Poster # 458

TWO HIT HYPOTHESIS IN PRACTICE: MONOZYGOTIC TWINS WITH SIMULTANEOUS ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: It has been shown that for monozygotic twins who both develop leukemia in early childhood, their leukemia arose from a common clone shared in utero. While *KMT2A* rearranged infantile leukemias have a nearly 100% concordance, leukemias diagnosed after infancy have a much lower concordance as postnatal secondary genetic "hits" are required for leukemogenesis. There is a known association between hyperdiploid b cell acute lymphoblastic leukemia (B-ALL) and RAS mutations, with hyperdiploidy believed to be a prenatal event followed by a postnatal RAS mutation.

Objectives: To present twenty-three-month-old monozygotic twins simultaneously diagnosed with ALL, whose genetics provide an example of hyperdiploidy as a prenatal event and secondary RAS mutations acquired as a postnatal event.

Design/Method: Case report developed from patients' electronic medical record, parental interview, and review of current literature.

Results: Twenty-three-month-old monozygotic twins were diagnosed with B-ALL within a two-week span. Notably, twin B was not identified due to screening after twin A's diagnosis, but rather because he became symptomatic. Consistent with a shared prenatal hyperdiploid clone, cytogenetic analysis revealed hyperdiploid ALL with identical chromosome gains (53, XY, +X, +6, +14, +17, +18, +21, +21; guthrie cards unavailable for evaluation). They were also noted to have identical germline mutations in CD36 and CDH1. Consistent with a postnatal "second hit" leading to the development of ALL, genomic testing identified different somatic mutations related to the RAS/MAPK pathway for each twin. Twin A was found to have a KRAS G12D mutation and ERBB2 amplification, whereas twin B had KRAS A146T, NRAS G12D and G12A (subclonal), and PTPN11 mutations.

While the timing of diagnosis was possibly coincidence, the identical time course to presentation raises the question as to if their RAS mutations were acquired at the same time due to a shared exposure. Potential exposures were discussed with the family. There was no exposure to tobacco smoke and parents could not remember a shared viral infection, however radon gas had been identified in the family's basement when the twins were 6 months of age.

Conclusion: These monozygotic twins that developed simultaneous B-ALL provide further evidence that for leukemogenesis in hyperdiploid B-ALL, hyperdiploidy is an in-utero event with RAS mutations being acquired postnatally. As they were diagnosed within two weeks of each other, this raises the possibility of a shared postnatal exposure leading to the simultaneous acquisition of different RAS mutations.

Poster # 459

RESIDUAL INVERSION 16 IN CD117+ BUT NOT CD34+ CELLS IN AN ADOLESCENT WITH ACUTE MYELOID LEUKEMIA

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Background: Inversion 16 (inv16) is a type of core-binding factor mutation found in acute myeloid leukemia. Core-binding factor mutations, notably t(8;21), may exist in cancer stem cells and long-lived non-proliferating myeloid cells. Non-zero minimal residual disease during chemotherapy cycles has important implications for treatment and should be further investigated. Fluorescence-activated cell sorting-fluorescence in situ hybridization (FACS-sorted FISH) may be used to select different cellular compartments, such as CD34+CD38-, for testing of a specific pathogenic mutation.

Objectives: To report a case of inversion 16 acute myeloid leukemia with residual PCR in mast cells but not stem cells.

Design/Method: Case report.

Results: A 19-year old Hispanic female with no past medical history presented with fatigue, pallor, easy bruising, and a diffuse hyperpigmented rash. She was diagnosed with inversion 16 (CBFB-MYH11, inv(16)/t(16;16)(p13;q22) acute myeloid leukemia. She was enrolled on the AML16 clinical trial and had negative minimal residual disease after Induction I, ultimately completing a total of four cycles of intensive chemotherapy. Eleven months off therapy, she demonstrated 1.2% residual AML in the bone marrow. She underwent re-induction as per AAML1421, and after cycle 1, she had positive residual inversion 16 by polymerase chain reaction (PCR) with negative minimal residual disease by flow cytometry. Three weeks later after count recovery, repeat bone marrow examination with FACS-sorted FISH testing revealed inv16 in the CD117+ (mast cell) compartment but negative inv16 in the CD34+ compartment. Flow cytometry for minimal residual disease was again negative. After these results, she did not receive additional chemotherapy and proceeded to alpha-beta depleted haploidentical stem cell transplant. After transplant, her inv16 PCR declined to zero. She is currently eight months post-transplant, only has intermittent grade 1 cutaneous graft-versus-host disease, has no evidence of residual disease, and is otherwise doing well.

Conclusion: With the advent of mutation specific PCR testing for acute myeloid leukemia, the results may be confounded by long-lived non-proliferating cells harboring the same

mutation. FACS-sorted FISH testing can resolve the discrepancy between flow cytometry and PCR, and in this scenario, abrogated the need for additional chemotherapy prior to stem cell transplant.

Poster # 460

KAT6A-EP300 MUTATION IN CONGENITAL MYELOID SARCOMA YET ANOTHER MARKER FOR SPONTANEOUS REMISSION?

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Background: Congenital myeloid sarcoma of the skin has a variable clinical course, ranging from spontaneous remission to rapidly progressive disease with systemic involvement based on the underlying molecular defect. Molecular subtypes with higher chances of spontaneous remission have been described with t (8, 16) [KAT6A-CREBBP fusion]. Only one known case report of an infant with t (8, 22) [KAT6A-EP300 fusion] undergoing spontaneous remission has been reported from Japan.

Objectives: We report a case of congenital leukemia cutis with KAT6A-EP300 mutation with sustained spontaneous remission for over a year.

Design/Method: Case report

Results: A one-month-old male infant presented with a slow-growing, bluish-purple firm nodule on his left cheek. This lesion was not present at birth but was noticed at 2 weeks of age. He was otherwise in good health and meeting age-appropriate growth and developmental milestones. Antenatal and postnatal history were unremarkable. At 6 weeks of age, a new similar nodule was noted on the scalp. Broad differential diagnosis considered included a vascular neoplasm such as tufted angioma, cutaneous neuroblastoma, Langerhans cell histiocytosis, and rhabdomyosarcoma. Biopsy of the scalp nodule was performed and the histopathology revealed dense infiltration of the dermis and subcutaneous fat by blastic mitotically active neoplastic cells. Immunohistochemistry was uniformly positive for CD4, CD68, and lysozyme and variably positive for myeloperoxidase, suggestive of myeloid sarcoma with monocytic features. Further workup for systemic involvement by acute myeloid leukemia (AML) was performed. Bone marrow aspiration and biopsy were negative for leukemic involvement. Positron Emission Tomography–Computed Tomography (PET-CT) showed no abnormal uptake. Fluorescence in situ hybridization (FISH) from the skin biopsy specimen was negative for MLL, inv 16, t (8, 21) and, t (8, 16). Foundation one testing showed a t (8, 22) with a resultant KAT6A-EP300 fusion, which has been associated with spontaneous remission. Given the identified mutation along with the patient age and risks of systemic therapy, the decision for observation was agreed on with the family, and he has been in remission for 13 months.

Conclusion: This is the second known reported case with KAT6A/EP300 fusion undergoing spontaneous remission. Congenital AML with skin involvement with this mutation has the potential for spontaneous remission.

Poster # 461

DETECTION OF A NOVEL CBFA2T3-GLIS3 FUSION IN AN INFANT WITH AML REFRACTORY TO CHEMOTHERAPY

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Background: Infants with non-Down syndrome M7 acute myeloid leukemia (AML) were initially found to harbor cytogenetically cryptic *CBFA2T3-GLIS2* fusions on RNASeq. More recently, *CBFA2T3-GLIS2* fusions have been found in other AML subtypes, most commonly in cytogenetically normal (CN)-AML. Across all subtypes, *CBFA2T3-GLIS2* fusions have been associated with poor outcomes and a lack of response to conventional chemotherapy. Patients with these fusions are now considered high-risk and are stratified to receive stem cell transplantation on AAML1831.

Objectives: To describe the clinical course, next-generation sequencing (NGS) results, and patient derived xenograft (PDX) findings from an infant who presented with CN-AML and was found to have a novel *CBFA2T3-GLIS3* fusion.

Design/Method: Case report.

Results: A 12-month-old female presented for diffuse bruising with initial labs notable for a white blood cell count of 369K and a physical exam consistent with leukemia cutis. Flow cytometry was diagnostic of AML but not consistent with a RAM phenotype. Cytogenetics and an AML FISH panel were normal. She was initially treated per AAML0531, Arm B with gemtuzumab. Following the first induction course, however, her marrow demonstrated minimal residual disease (MRD) of 4.8%. Her MRD reached 0% following a cycle of mitoxantrone, cytarabine and gemtuzumab. While awaiting donor availability she was bridged with cytarabine and etoposide but unfortunately had an MRD of 0.3% at the completion of this cycle. Despite salvage therapy with CPX-351, her MRD remained positive at 0.15%. She was treated with 5 additional salvage regimens including two phase 1 clinical trials but progressed after each cycle. She passed away 12 months after her diagnosis.

RNASeq from a relapse sample revealed in-frame *GLIS3-CBFA2T3* and *CBFA2T3-GLIS3* fusions. Analogous to *GLIS2* overexpression seen in the more common *CBFA2T3-GLIS2* fusion, Tukey's outlier analysis demonstrated that *GLIS3* was overexpressed by 32x from the median in this patient compared to other leukemia samples and 7x from normal controls.

A PDX from relapse was serially passaged with all mice succumbing to leukemia within 3-4 weeks from injection.

Conclusion: This report describes the first case of AML with a *CBFA2T3-GLIS3* fusion and highlights the need for unbiased NGS testing including RNASeq at diagnosis, as patients with *CBFA2T3-GLIS3* fusions should be considered for transplant. Clinical-grade panel testing, including the assay used on AAML1831, cannot detect novel fusions including *CBFA2T3-GLIS3*. A PDX generated from this patient has a short latency period and represents a strategy to test novel agents that may be effective in this aggressive subtype of AML.

Poster # 462

PROLONGED SURVIVAL USING OUTPATIENT PALLIATIVE CHEMOTHERAPY IN TWO CHILDREN WITH REFRACTORY AML

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Background: Nearly 60% of children diagnosed with Acute Myelogenous Leukemia (AML) will become long-term survivors, however, therapy options in relapsed/refractory disease are limited. Palliative chemotherapy in these settings have been explored in adult patients, but little evidence exists in children.

Objectives: Describe the clinical course of two pediatric patients with refractory AML who experienced significant therapy-related complications and transitioned to outpatient palliative chemotherapy with disease control and good quality of life each for over a year.

Design/Method: Pt 1 presented age 2 years with lethargy and leukocytosis to >600k: a diagnosis of AML. She underwent induction I with Cytarabine, Daunorubicin and Etoposide (ADE) with refractory disease on count recovery. She received three subsequent cycles of chemotherapy, with multiple complications and 15-20% blasts on marrow re-evaluation. An outpatient regimen of decitabine and vorinostat was provided.
Pt 2 presented age 16 years with a new diagnosis of AML. He underwent induction I with ADE. Recovery marrow demonstrated residual disease. He underwent induction II with Mitoxantrone and Cytarabine. This course was complicated by multi-organ failure secondary to multiple infections including Klebsiella pneumonia and radiographically identified pulmonary fungal disease. On recovery marrow showed no evidence of disease but the patient preferred to pursue a palliative regimen. Azacitidine and lenalidomide were provided.

Results: Pt 1 tolerated the regimen for approximately 13 months requiring weekly blood products but only one hospitalization for a central-line infection. Her blast count then increased precipitously. The disease progressed, and she was admitted to the hospital for end-of-life care.
Pt 2 tolerated 14 months of his regimen with only one hospitalization for hydration for post-lumbar puncture headache. He was then found to have 0.02% MRD on marrow flow analysis. Given his improved health and reassessment of goals, he elected to pursue bone marrow transplant. He was transplanted with 7/8 HLA-matched unrelated donor cells after conditioning of busulfan and cyclophosphamide and is now day +63. To date his course has been complicated by febrile

neutropenia and hemorrhagic urinary obstruction.

Conclusion: Less intensive, outpatient chemotherapy regimens are regularly considered for older patients with AML who are ineligible for more intensive therapy. We describe two pediatric patients with relapsed/refractory AML who achieved disease control and acceptable quality of life with minimal side effects utilizing outpatient palliative chemotherapy for over 12 months each. These regimens should be considered for disease control in patients who either no longer desire cytotoxic chemotherapy or are ineligible for further aggressive approaches.

Poster # 463

THERAPEUTIC LEUKAPHERESIS WITH REGIONAL CITRATE ANTICOAGULATION FOR AML IN AN INFANT

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Background: Infantile leukemia is associated with increased morbidity and mortality. Leukapheresis helps prevent cardiovascular and pulmonary complications secondary to the hyperviscosity caused by hyperleukocytosis and leukostasis. Leukapheresis in infants is logistically complex due to the need for a large-bore catheter, the risk of electrolyte derangement during apheresis, and the potential for hemodynamic instability due to the large extracorporeal volume required by the apheresis circuit.

Objectives: Describe the management of a 6-week-old male with a history of Pompe disease who presented with respiratory distress due to medically refractory hyperleukocytosis and leukostasis secondary to acute myeloid leukemia (AML).

Design/Method: Chart and literature review.

Results: A 6-week-old (4.6 Kg) late preterm male with a history of late-onset Pompe disease presented to the emergency department with acute respiratory distress. He had one episode of hematochezia one week prior to presentation and progressively worsening feeding intolerance for 3 days. Routine evaluation one month prior to admission showed normal CBC, EKG, and echocardiogram with normal biventricular function and without hypertrophy.

On physical exam, he was found to have lethargy, central cyanosis (SatO2 at 70%), tachycardia, and tachypnea with subcostal retractions. There was no hepatosplenomegaly.

Laboratory workup revealed WBC 624 000/uL, differential with 82% blasts, hemoglobin 5 g/dL, platelet count 42 000/uL, LDH 6 343 IU/L, Uric acid 5.7 mg/dL, and BNP 772 pg/mL. Flow cytometry showed blasts with myeloid markers including CD33+. AML FISH panel and PML/RARA PCR were negative. EKG and echocardiogram were normal.

The patient was placed on HFNC and transfused platelets and packed RBCs in small aliquots due to concerns for hyperviscosity. Cytoreduction with methylprednisolone 10 mg/m2/dose q8hrs and

two doses of cyclophosphamide 30 mg/kg/dose q12hrs was attempted with reduction of the WBC count to 420 000/uL. A dialysis catheter (8 French 12 cm) was placed in the left femoral vein and the patient underwent leukapheresis using a COBE Optia circuit primed with leukocyte reduced and irradiated whole blood, reconstituted from PRBCs and FFP to a hematocrit of 45%. Leukapheresis was performed over 220 minutes with regional citrate anticoagulation. He remained hemodynamically stable and ionized calcium remained between 1.14 - 1.38 mmol/L. WBC count decreased to 228 000/uL. Chemotherapy was started under AAML 1831 protocol with the resolution of respiratory failure and other symptoms of leukostasis.

Conclusion: Leukapheresis using regional citrate anticoagulation was successfully performed in a small infant with hyperleukocytosis and leukostasis.

Poster # 464

A RARE CASE OF HISTIOCYTOID SWEET SYNDROME PRECEDING MYELODYSPLASTIC SYNDROME IN A PEDIATRIC PATIENT

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Background: Histiocytoid Sweet syndrome (H-SS) is a rare variant of Sweet syndrome where the dermal infiltrate is composed of immature histiocytoid cells of myeloid origin. Myelodysplastic syndrome (MDS) with isolated 5q deletion (5q- syndrome) is a disease of older adults with favorable prognosis. del(5q) in children is rare but can present with complex cytogenetics and appears to have a greater likelihood to progress to acute myeloid leukemia (AML). The few cases reported in the literature underwent hematopoietic stem cell transplantation (HSCT), transformed to leukemia, or passed away. H-SS is associated with hematologic malignancy in adults, including MDS, at rates of up to 55%, but to date there are no known reports in children.

Objectives: To present a pediatric patient with H-SS and MDS with isolated del(5q) and *PTPN11* mutation with rapid progression to MDS with excess blasts-2 (MDS-EB-2).

Design/Method: Case report and literature review.

Results: A previously healthy 30-month-old male presented following 2 months of painful nodules and erythematous swelling of the fingers, toes, and legs. Biopsy demonstrated features of H-SS. He had no cytopenias, but peripheral blood flow cytometry was pursued given the reported association of H-SS with myeloid neoplasia; 0.13% abnormal CD34+ progenitors of uncertain significance were detected. He was treated with systemic steroids with improvement, but the lesions reoccurred on steroid taper despite adjunctive therapies, dapsone and indomethacin. Repeat flow cytometry 2 months later detected the same abnormal population (0.25%). Bone marrow (BM) biopsy was performed and showed normocellularity without dysplasia or increased blasts. Flow cytometry detected the abnormal population (0.11%). Cytogenetic and molecular studies showed high-burden del(5q) and pathogenic *PTPN11* mutation. Repeat BM biopsy one month later showed 15% abnormal myeloid blasts (MDS-EB-2) and persistent del(5q) and *PTPN11* mutation, with peripheral macrocytosis and thrombocytopenia. Germline testing for cancer predisposition and BM

failure syndromes was negative. Due to rapid progression, AML-type therapy was initiated. The cutaneous lesions resolved. End of induction minimal residual disease was 0.05%. He received azacitidine prior to transplant with repeat negative MRD. At age 37 months, he underwent 9/10 matched unrelated donor HSCT. The patient was in remission at day +67 by chimerism.

Conclusion: We report the first known child with H-SS-associated high-grade MDS treated with an AML-like regimen and HSCT. This case broadens the epidemiology of H-SS and associated myeloid neoplasia to children and provides treatment precedent for this rare scenario.

Poster # 465

RAPID ONSET BILATERAL VISION LOSS AS A PRESENTING SYMPTOM OF BURKITT LEUKEMIA

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Background: Burkitt lymphoma/leukemia (BL) is a highly aggressive malignancy with a rapid growth rate that most often affects the abdomen or head and neck. Central nervous system (CNS) disease also occurs in approximately 9% of patients, but orbital involvement is exceedingly rare. For those with CNS involvement, cranial irradiation has not been shown to be beneficial, but has rarely been described in patients with vision loss.

Objectives: To evaluate the role of radiation to restore visual function in patients with acute vision loss secondary to BL.

Design/Method: We present a case of acute bilateral vision loss secondary to Burkitt leukemia and a review of the literature.

Results: A 2-year-old male presented with rapid onset bilateral vision loss over 24 hours duration. On exam, pupils were responsive to light, but the patient was unable to track objects or light. Imaging revealed a large sphenoid mass with mass effect on the optic nerves and multiple bony destructive lesions throughout the face, as well as bilateral nephromegaly. Steroids were initiated in the emergency department. Sphenoid mass and bone marrow biopsies revealed Burkitt leukemia and systemic chemotherapy was initiated on day 2 of hospitalization. Repeat imaging obtained two days after chemotherapy initiation showed unchanged disease burden and there was minimal improvement in vision clinically. The decision was made to give gamma knife radiation to the sphenoid mass in hopes of restoring vision; 2 Gy was given on day 6 after presentation. Repeat imaging two days after radiation showed some improvement in disease burden along with clinical improvement in vision. The patient has now been off therapy for 7 months and remains in remission. Ultimately, he regained some vision; he is able to perform his activities of daily living and can discern details at close range.

Conclusion: Acute vision loss has rarely been reported as a presenting symptom of sporadic BL. Though cranial radiation is generally not recommended in CNS positive BL given its rapid response to chemotherapy without demonstrated benefit, we suggest its effectiveness in patients

with vision loss. Our patient had significant improvement in vision following early, low-dose radiation in combination with chemotherapy. Of 7 previous pediatric cases reported, only 2 patients had some restoration of vision; one treated with chemotherapy and surgical decompression and one with chemotherapy and intermediate-dose radiation on day 11. All previously reported cases of acute vision loss in BL who received chemotherapy alone or chemotherapy plus late radiation had no improvement in vision.

Poster # 466

JUVENILE MYELO-MONOCYTIC LEUKEMIA PRESENTING AS UPPER AIRWAY OBSTRUCTION

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Background: Juvenile Myelomonocytic Leukemia (JMML) is a rare myeloproliferative/myelodysplastic form of childhood cancer that is easy to miss initially as clinical signs have significant overlap with more common illnesses, particularly viral infection

Objectives: 1- To Highlight a rare disorder (JMML) that can be confused with other common illnesses leading to delay in diagnosis.
2- Present some tips to help in making the diagnosis of JMML

Design/Method: case presentation

Results: We present a 2-year-old boy with a few-months history of recurrent fever, and recurrent lower respiratory tract infection, persistent high WBC with monocytosis and mild thrombocytopenia. He was treated with antibiotic and his pediatrician started his workup for immune deficiency evaluation. A month later, he presented to the ER with fever of 105° F, dysphagia, and vomiting. P/E showed hepatosplenomegaly, 4+ tonsils, generalized shotty lymphadenopathy, and purpura. WBC 47x109/L with predominant monocytosis (35%), hemoglobin 10.5gm/dL, platelets 41x109/L and peripheral blood smear (PBS) that showed a leukoerythroblastic reaction (LER). Patient was admitted to the hospital for IV antibiotic and further evaluation. Infectious process was the initial concern and EBV/CMV titers, and PCR were run and found to be negative. ENT, infectious disease, and hematology services were consulted. Patient was taken to the OR for emergency tonsillectomy for air way compromise. Tonsils did not show malignant involvement and bone marrow aspirate and biopsy were negative for acute leukemia or other infiltrative processes, yet it showed hypercellular marrow without increased blast count, the granulocytic series showed marked hyperplasia with dyserythropoietic and dysmegakaryocytic changes. Based on peripheral smear finding of leukoerythroblastic reaction, absolute monocytosis, young age, hepatosplenomegaly, and absence of infectious etiology, a provisional diagnosis of JMML was made and specific genetic testing was sent out. Genetic results showed two mutations that affect the RAS pathway, confirming the diagnosis of JMML. The patient successfully underwent bone marrow transplantation and his JMML remains in remission.

Conclusion: In the case of rare diseases like JMML, delayed diagnosis is common and can

increase risk of morbidity and mortality, (as airway obstruction in our case). We believe, the presence of LER on PBS, in association with absolute monocytosis and recurrent infections would be an appropriate initial alert to the physician to evaluate the patient for JMML.

Poster # 467

SUCCESSFUL TREATMENT OF DISSEMINATED MYCOBACTERIUM ABSCESSUS IN A PEDIATRIC PATIENT WITH LEUKEMIA

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Background: *Mycobacterium abscessus*, rapidly growing non-tuberculous mycobacteria (NTM) species, are ubiquitous, opportunistic pathogens that infect immunocompromised hosts or those with underlying pulmonary disease. *M. abscessus*, a highly resistant organism, requires a macrolide-containing multidrug treatment regimen making treatment in patients receiving concomitant chemotherapy challenging.

Objectives: To describe a case of successful treatment of disseminated *M. abscessus* in a pediatric leukemia patient undergoing chemotherapy.

Design/Method: A review of medical records and literature on treatment of disseminated *M. abscessus* in a pediatric patient with acute leukemia.

Results: A 16-year-old, Tongan male, with history of T/myeloid mixed phenotype acute leukemia (MPAL), presented with sepsis one month after treatment for soft tissue cellulitis of the left forearm. He was bacteremic with *Staphylococcal epidermidis*, *Microbacteria*, and NTM species, later identified as *M. abscessus* subspecies *abscessus*. Initial therapy consisted of cefoxitin, amikacin, linezolid, and clarithromycin. Upon completion of drug susceptibility testing, treatment was changed to induction therapy with intravenous imipenem, tigecycline, and amikacin, with oral linezolid and clofazimine. Diagnosis of disseminated *M. abscessus* infection was made given positive blood and bone marrow cultures, and pulmonary nodules. Despite therapy, disease progressed to septic arthritis and multifocal osteomyelitis of the right humerus, right distal femur and right proximal tibia. He underwent debridement of the right elbow which was complicated by poor wound healing and dehiscence, eventually necessitating wound vac placement and hyperbaric oxygen therapy. Intraoperative cultures grew *M. abscessus* subspecies *abscessus* (intermediately susceptible to cefoxitin, resistant to linezolid), so bedaquiline was added as salvage therapy. Work-up for underlying congenital immunodeficiency and Mendelian susceptibility to mycobacterial diseases was negative. A trial of interferon gamma therapy to upregulate host immune function was not beneficial, however, an interleukin-4 antagonist and azithromycin was started for possible immunomodulation and steroids were omitted from maintenance chemotherapy. He went home on a maintenance regimen of intravenous amikacin with oral clofazimine and bedaquiline. He had stabilization of disease, but eventually required above the knee amputation of the right leg following a non-healing pathologic tibial fracture. Histopathology revealed non-caseating

granulomas and negative cultures. The patient completed chemotherapy and remains in remission with plan to complete six months of antimicrobial treatment following amputation.

Conclusion: We report successful treatment of a pediatric patient with MPAL who developed disseminated *M. abscessus* infection using a multimodal approach including antimicrobial therapy, immunomodulation, chemotherapy modification, and surgical intervention.

Poster # 468

MANAGING CONJUGATED HYPERBILIRUBINEMIA AT PRESENTATION OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Hepatic dysfunction with conjugated hyperbilirubinemia is a rare presentation of pediatric acute lymphoblastic leukemia (ALL). Standard induction therapy for ALL includes hepatically-metabolized medications (vincristine, pegasparaginase, +/- doxorubicin for high-risk patients). In patients with conjugated hyperbilirubinemia, omitting or reducing standard induction therapy is recommended to prevent toxicity, but may be associated with increased risk of relapse.

Objectives: For patients newly diagnosed with ALL who present with conjugated hyperbilirubinemia, we present an alternate strategy of delivering non-hepatotoxic bridging systemic chemotherapy before standard full-dose induction therapy.

Design/Method: This is a single-institution case series of three patients at Children's Hospital of Los Angeles.

Results: All three patients were Hispanic males, ages 12, 16, and 18 years old, diagnosed with high-risk B-ALL, CNS1. Two of three patients were obese (Patient 2, BMI 99th percentile; Patient 3, BMI 99th percentile) with hepatic steatosis on abdominal imaging. Patient 1 was not obese (BMI 90th percentile) but abdominal imaging revealed a mass at the pancreatic head. All three patients had CTCAE v4 Grade ≥3 elevation of bilirubin with conjugated bilirubin at diagnosis 6 mg/dl, 9.6 mg/dl, and 4.4 mg/dl, respectively. All three patients started levocarnitine, ursodiol and non-hepatotoxic cytoreductive chemotherapy. In patients 1 and 2, the bilirubin responded rapidly to 3 days of steroids; Patient 1 received ~80% and 88% of planned daunorubicin and vincristine respectively, while Patient 2 received 88% of planned doses of both chemotherapies. Despite receiving 10 days of steroids, Patient 3 demonstrated refractory hyperbilirubinemia. He proceeded to a modified consolidation type regimen with cyclophosphamide (1000mg/m2) on day 1, cytarabine (75mg/m2) on day 1-4, 8-12 with complete resolution of conjugated hyperbilirubinemia (<0.01 mg/dl) by day 10. He then received standard full-dose induction therapy with 100% dosing of all hepatotoxic agents. All patients achieved minimal-residual disease (MRD) <0.01% in the bone marrow by end of induction (Patient 1) or end of consolidation (Patients 2 and 3). All three patients are currently in remission >2.5 years from diagnosis. No additional toxicity was noted from the cytoreductive chemotherapy.

Conclusion: Conjugated hyperbilirubinemia in all three patients responded to cytotoxic chemotherapy, suggesting hepatic infiltration from ALL was an underlying contributing etiology. Delivery of planned induction chemotherapy is critical for optimal ALL outcomes, but conjugated hyperbilirubinemia at disease presentation precludes initiation of routine hepatically-metabolized chemotherapy. Steroid cytoreduction, followed by cyclophosphamide and cytarabine for refractory patients, is an effective bridging strategy to enable delivery of full-dose induction chemotherapy in patients presenting with conjugated hyperbilirubinemia.

Poster # 469

A BALANCING ACT: BLINATUMOMAB USE IN A RARE OCCURRENCE OF PH+ ALL IN A PATIENT WITH DOWN SYNDROME

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Background: An 18-year-old young man with Down Syndrome (DS) was diagnosed with Philadelphia chromosome positive (Ph+) B-cell acute lymphoblastic leukemia (ALL) after reporting symptoms of fever, weight loss, fatigue, and rash. Ph+ B-cell ALL is rare in patients with DS with less than 0.7% of DS-ALL reported cases. There is a paucity of data related to treatment of these patients and no current standard of care. The prognosis of ALL in DS is significantly worse compared to non-DS patients because of chemotherapy-related toxicities and the higher rate of relapse. Providers are challenged with navigating toxicities via holding or reducing chemotherapy knowing each alteration will increase chances of relapse. New frontline therapies are needed. Blinatumomab, a bi-specific CD19 and CD3 antibody, is well tolerated and has shown promising results. A recent phase 2 clinical study in adults combined blinatumomab with a BCR-ABL tyrosine kinase inhibitor, ponatinib, and showed 100% 1-year overall survival and event free survival in the newly diagnosed cohort.

Objectives: We report a rare case of Ph+ ALL in an adolescent patient with DS who had significant toxicities from cytotoxic chemotherapy and responded well to Blinatumomab.

Design/Method: A retrospective chart analysis was conducted.

Results: He underwent a three-drug induction with vincristine, methylprednisolone (due to poor oral medication tolerance) and peg-asparaginase with daily imatinib. He was switched to the DS high risk ALL protocol on day 15 and received one dose of daunorubicin. Induction was interrupted by polymicrobial bacteremia and septic shock requiring intubation and critical care admission. His post-induction minimal residual disease (MRD) was 0.08%. He started his first cycle of continuous blinatumomab infusion, which was well tolerated. Prior to consolidation, he was found to be MRD negative. Consolidation was given with imatinib during which he had persistent pancytopenia, fungemia, and pericardial effusion. He was bridged with blinatumomab to allow him to clinically improve. He was re-challenged with chemotherapy in interim maintenance after which he developed fungal pneumonia. A third cycle of blinatumomab was given to help count recovery and given these toxicities, the decision was made to forego delayed intensification.

During maintenance therapy he has had persistent pancytopenia, so we will alternate blinatumomab with lower dose standard maintenance chemotherapy.

Conclusion: We were able to successfully achieve remission in our patient with DS and Ph+ B-ALL while avoiding further toxicities from traditional chemotherapy using three cycles of blinatumomab. Blinatumomab offers a promising addition to standard chemotherapy and imatinib for Ph+ B-ALL in DS patients.

Poster # 470

MULTI-SYSTEM INVOLVEMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA ON INITIAL PRESENTATION

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Background: Being the most common type of childhood cancer, rigorous research effort has led to an advanced understanding of Acute Lymphoblastic Leukemia (ALL) and treatment protocols with overall survival rate of up to 90%[1]. One of first things we learn as pediatric residents is common presentation of ALL that should not go unnoticed, which include fever, easy bruising, petechiae, fatigue, and bone pain. However, extra-medullary manifestations of ALL is also a well-documented phenomenon. A systematic review done by Shahriari et al. discusses eighty-seven cases of extra-medullary presentations of ALL found in major database between 1968 and 2020[2]. There was no case that had more than one system involved in this comprehensive review.

Objectives: This report aims to inform pediatric oncologists of an unusual initial presentation of ALL in order to prevent misdiagnosis or delay of proper treatment.

Design/Method: In our study, we searched for PubMed case reports on patients between 0-18 years of age using key words such as “initial presentation”, “acute lymphoblastic leukemia”, and “multiple organ involvement”.

Results: We have found few cases that reported multiple organ involvement on initial presentation of ALL, yet we weren’t able to find any cases with such an extensive involvement as seen with our patient. In this report, we describe a 15 month old, previously healthy female who presented to ED for abdominal mass with persistent fever, worsening fatigue, and decreased oral intake, later found to have systemic infiltrative process involving thymus, pericardium, aorta, IVC, pleura, kidneys, mesentery, colon, appendix, and uterus. Patient had thrombocytopenia and blasts without leukocytosis or anemia. Diagnosis of pre-B-ALL was made based on bone marrow smear, tissue biopsy, and flow cytometry. Molecular and cytogenetic analysis were negative for terminal deoxynucleotidyl transferase (TdT), CD20, CD34, and kappa/lambda. Fluorescence in situ hybridization (FISH) was negative for t(8:14) and positive for myeloid lymphoid leukemia rearrangement. Induction chemotherapy was initiated on day 4 of hospitalization.

Conclusion: We hope that this report will expand clinician’s mastery of ALL beyond its common presentation and help preventing misdiagnosis caused by focusing on some parts instead of a

whole. Furthermore, sharing this knowledge with pediatric oncologists at other institutes will potentially enable us to collect more data on such cases in the future, so that we can have better understanding of this particular type of ALL.

1. Hunger, S.P. & Mullighan, C.G., *The New England Journal of Medicine*, 2015.
2. Shahriari, M. et al., *American Journal of Blood Research*, 2020.

Poster # 471

T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA IN A CHILD WITH THROMBOCYTOPENIA ABSENT RADIUS SYNDROME

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Background: Thrombocytopenia Absent Radius (TAR) syndrome is a rare inherited bone marrow failure syndrome (BMFS) characterized by hypomegakaryocytic thrombocytopenia and bilateral absent radii. TAR syndrome is inherited in an autosomal recessive pattern and is caused by mutations in the *RBM8A* gene. Associated thrombocytopenia is nearly resolved within the first year of life (Liu, 2011). To date, TAR syndrome is one of the few BMFS not characterized as a cancer predisposition syndrome, but there are six reports in medical literature of patients with TAR syndrome developing leukemia. Four cases with Acute Myeloid Leukemia, one with B-Cell Acute Lymphoblastic Leukemia and one T-Cell Acute Lymphoblastic Leukemia. The case with T-Cell ALL involved a new diagnosis of TAR syndrome in an adult with no history of thrombocytopenia. This is the first case of a 6-year-old child with TAR syndrome, with unresolved thrombocytopenia, with early T-Cell Precursor Lymphoblastic Leukemia (ETP-ALL).

Objectives: To describe a case of a patient with TAR syndrome with unresolved thrombocytopenia and onset of ETP-ALL.

Design/Method: Clinical history was extracted retrospectively from medical records and is being monitored prospectively while undergoing treatment for ETP-ALL.

Results: The patient is a 6-year-old Caucasian male, with developmental and speech delay, diagnosed with TAR syndrome during the first year of life after having an abnormal ultrasound showing skeletal dysplasia and subsequent events of thrombocytopenia requiring blood transfusions. At five years of age, he presented with increased bruising and petechia and was found to have leukocytosis to approximately 280 000 with blast predominance, thrombocytopenia, and mild anemia. Peripheral flow cytometry identified aberrant T lymphoblasts equating 84%, and bone marrow aspiration/biopsy confirmed ETP-ALL.

After emergent leukapheresis, the patient began chemotherapy treatment per AALL1231. Induction was tolerated well with the resulting MRD = 9.7%. Treatment complications have presented including coagulopathy with hypofibrinogenemia and prolonged PTT, requiring intermittent FFP transfusions prior to procedures. Consolidation per AALL0434 with Nelarabine, was complicated by AKI requiring CRRT for renal failure for approximately two days. Exact cause of renal failure is unknown, but he was receiving potentially nephrotoxic

medications at the time. Start of consolidation part 2 was delayed due to persistent thrombocytopenia below 75 000. Start of treatment parameters were modified as platelet count has not normalized throughout treatment. However, Consolidation Day 36 bone marrow showed negative MRD.

Conclusion: Our report describes the unique presentation of a 6-year-old child with TAR syndrome, with unresolved thrombocytopenia, receiving chemotherapy treatment for T-cell leukemia.

(Liu, Current Opinion in Hematology, 2011)

Poster # 472

NUTRITIONAL COMPLICATIONS FOLLOWING PEG-ASPARAGINASE ADMINISTRATION IN PEDIATRIC PATIENTS WITH ALL

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Background: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy in the United States. Lymphoblastic lymphoma (LL) is less common than ALL in the pediatric population but is often treated with ALL protocols. PEG L-asparaginase, a mainstay chemotherapeutic to treat pediatric ALL, can cause a myriad of nutritional complications, including acute pancreatitis, hyperglycemia, hypertriglyceridemia, and exocrine pancreatic insufficiency. However, these complications and the appropriate treatments for them have not been well described in the literature.

Objectives: To expand the knowledge on potential nutritional complications that can occur secondary to PEG L-asparaginase and discuss potential interventions.

Design/Method: Three patients' electronic medical records were reviewed at Cook Children's Medical Center to extrapolate data for the case series.

Results: Two pediatric patients with ALL and one pediatric patient with LL, who received PEG L-asparaginase, faced adverse events leading to nutritional complications. The first patient, a 17-year-old-male diagnosed with ALL, experienced blood clotting issues, acute pancreatitis, hyperglycemia, and exocrine pancreatic insufficiency (EPI). The patient was managed with insulin and a low fat diet; however, due to severe weight loss and loose, oily stools, a fecal elastase was ordered and confirmed EPI. Therefore, the patient was transitioned to enteral nutrition (EN) and treated with pancreatic enzyme replacement therapy. The second patient, a 6-year-old female diagnosed with LL and on ALL chemotherapy protocol, experienced acute pancreatitis, constipation, and vomiting. Based on new recommendations developed by the team in treating pediatric oncologic patients with acute pancreatitis and the patient's poor oral intake, she was managed with a proactive EN feeding protocol. This was well tolerated by the patient. The third patient, a 7-year-old female diagnosed with ALL, experienced hypertriglyceridemia (>5200 mg/dL). Further complications of hyponatremia (presumed to be partially pseudohyponatremia

related to hypertriglyceridemia), weight loss, and excessive stooling warranted the need for EN. The patient was initially fed with a very low fat (and subsequently high in carbohydrate) formula but was later switched to a more balanced peptide-based formula with a high ratio of medium chain triglycerides and lower carbohydrate content.

Conclusion: In this case series, three patients' courses were detailed following the nutritional difficulties they faced after PEG L-asparaginase administration. Although further studies are needed, this series sheds light on potential nutritional complications and interventions.

Poster # 473

SPONTANEOUS GASTRIC PERFORATION COMPLICATING INDUCTION CHEMOTHERAPY IN A CHILD WITH B-CELL ALL

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Background: Common gastrointestinal side effects in patients undergoing treatment for B-cell leukemia include gastritis, constipation, and chemotherapy-induced nausea and vomiting. Gastric ulcers may develop as a result of immunosuppression secondary to chemotherapy and high-dose steroids, but subsequent gastric perforation has not previously been reported. Gastric perforations are exceedingly rare in the pediatric population and are associated with significant rates of morbidity and mortality, especially when involving the greater curvature of the stomach. Until now, there had been no documentation in the literature of this potentially lethal complication of chemotherapy in patients with leukemia.

Objectives: To describe a pediatric case of acute lymphoblastic leukemia (ALL) complicated by two spontaneous gastric perforations during induction chemotherapy.

Design/Method: Information was obtained through retrospective chart review from electronic medical records.

Results: A 3-year-old male with B-cell ALL was receiving standard risk induction treatment with vincristine, pegasparaginase, and dexamethasone, along with daily famotidine for gastrointestinal prophylaxis. He was admitted following 2-3 days of abdominal pain, decreased appetite, fatigue, and non-neutropenic fever on day 26 of induction. On hospital day 2, he experienced acutely worsening abdominal pain and distension with free intraperitoneal air on radiographic imaging. He underwent emergent exploratory laparotomy, which demonstrated a gastric ulcer and perforation along the greater curvature of the stomach. A gastrostomy tube was placed and he was transitioned to pantoprazole for further gastrointestinal prophylaxis. His central blood culture returned positive for meropenem-resistant *Lactobacillus*, which was treated with piperacillin/tazobactam and ampicillin line locks. On hospital day 6, he experienced a recurrence of abdominal pain and distension. A repeat exploratory laparotomy revealed a second gastric perforation along the posterior fundus. An initial gastrin level was significantly elevated, but *H. pylori* was negative. The patient made a full recovery and was discharged home on omeprazole, carafate, and famotidine after a 3-week hospitalization. He completed induction therapy during his hospitalization and end-

of-induction MRD was negative. Initiation of consolidation therapy was delayed to allow for sufficient wound healing.

Conclusion: To date, there are no documented reports of pediatric patients with leukemia who have experienced spontaneous gastric perforations as a complication of chemotherapy. This case report highlights a unique and potentially fatal complication of treatment for B-cell ALL. Additionally, it illustrates the importance of optimizing gastric prophylaxis and providing close monitoring for gastrointestinal complications in patients with ALL.

Poster # 474

PELVIC MASS IDENTIFIED AS MYELOID SARCOMA IN A PEDIATRIC PATIENT WITH ACUTE MYELOID LEUKEMIA

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Background: Myeloid sarcoma (extramedullary tumor of immature myeloblasts) is a rare condition that can present with acute myeloid leukemia (AML). In children diagnosed with AML, myeloid sarcoma is most commonly found in the skin and the orbital bones. Myeloid sarcoma can be the first manifestation of AML or can present months to years before clinical disease. The prognostic significance of myeloid sarcoma in AML has not been clarified in the literature[1].

Objectives: Describe a case of a patient presenting with pelvic mass found to be myeloid sarcoma associated with AML.

Design/Method: Case Report

Results: Five-year-old female presented with vaginal bleeding with ultrasound and MRI imaging demonstrating a large mass in the upper vagina/cervix with signal characteristics concerning for genitourinary rhabdomyosarcoma. Her complete blood count had a normal white blood cell count and hemoglobin and thrombocytopenia with platelets of 91 x 10^9/L without any abnormal cells on smear. Biopsy of the mass showed sheets of monocytic cells which expressed CD45 and CD163, consistent with a with a myeloid sarcoma. Bone marrow biopsy results were consistent with a diagnosis of acute myeloid leukemia. Cytogenetic analysis of the tumor and bone marrow revealed the same rearrangement in the KMTA2A (11q23) gene region in the form of t(9;11) which is among the numerous aberrations that have been reported in association with myeloid sarcoma.

Conclusion: This is a case of a patient presenting with a pelvic mass that was found to be a myeloid sarcoma associated with AML. Extramedullary tumors, particularly those in the genitourinary tract, are a rare finding in patients with AML. Myeloid sarcoma is difficult to diagnose due to its rarity, the many varied locations where it can be discovered, and its ability to present without bone marrow involvement. Accurately diagnosing myeloid sarcoma is important to make sure patients get appropriate and timely treatment. Currently, the treatment for patients with myeloid sarcoma with evidence of AML on bone marrow biopsy is the same as those with overt AML. If the myeloid sarcoma is causing systemic issues such as pain or organ damage or if

traditional chemotherapy has not led to resolution of the tumor surgery or radiotherapy may be indicated. Additional research needs to be done to evaluate the prognostic significance and ideal treatment protocols for myeloid sarcoma associated with AML.

1. Almond, Clin. Lymphoma Myeloma Leuk., 2017

Poster # 475

ACUTE PROMYELOCYTIC LEUKEMIA AFTER THERAPY FOR PRECURSOR T CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Acute leukemia is a hematologic malignancy affecting white blood cell precursors, classification is made according to the precursor cell affected. Acute promyelocytic leukemia (APL) causes accumulation of promyelocytes in the bone marrow, while acute lymphoblastic leukemia (ALL) affects precursor lymphocytes. The incidence of APL is 10% of all acute myeloid leukemia, and usually occurs as a primary malignancy. There have been no documented cases of pediatric APL following diagnosis and treatment of ALL. When a malignancy occurs after another, it can be considered either therapy-related or a new primary malignancy. Second primary APL has been described in the adult population, but remains uncommon.

Objectives: Document a case of APL in a patient following remission of precursor T cell ALL.

Design/Method: Case report. The authors describe an unusual presentation of an 11 yo hispanic male with APL occurring after ALL remission, as well as his treatment outcome.

Results: An 11 yo hispanic male presented with one day history of lumbar back pain one year after completion of therapy for intermediate risk pre-T ALL per COG protocol AALL1231 Arm B. Laboratory workup revealed pancytopenia including WBC 1.6, ANC 432, and platelets 35. Bone marrow aspirate demonstrated 75% neoplastic CD 45+ cells with co-expression of CD13, CD33, CD38, CD 117, CD15, CD64, CD16, and CD11b, consistent with APL. PML/RARA mRNA transcripts were detected and estimated to represent 79% of cells. Treatment was initiated with all trans retinoic acid and arsenic trioxide. Hematologic remission was achieved in 1 month, followed by molecular remission after an additional 6 weeks. He was referred to cancer genetics clinic, where evaluation for predisposing mutations and syndromes was initiated.

Conclusion: APL, either as a therapy-related secondary malignancy or as a second primary malignancy, is an unusual diagnosis. This is the first reported case of APL following treatment of pre-T ALL. It is important to differentiate between therapy-related and second primary APL, considering the implications for this patient's future. Secondary myeloid leukemia is associated with treatment using topoisomerase II inhibitors, such as etoposide. A few cases of APL have been reported after treatment of Hodgkin's, non-Hodgkin's lymphoma, retinoblastoma, and Langerhans cell histiocytosis. Because standard of care treatment for ALL does not include etoposide and only low dose of cyclophosphamide, secondary APL would not be expected in this case. An alternate

possibility of this APL being a second primary should be considered, and evaluation for genetic predisposition syndromes should be pursued.

Poster # 476

PEDIATRIC SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA: REPORT OF TWO CASES

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Background: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare primary cutaneous lymphoma composed of clonal mature cytotoxic alpha-beta T-cells. Forty percent of patients have B symptoms, 20-30% have lymphadenopathy and/or hepatosplenomegaly, and about half present with hemophagocytic lymphohistiocytosis (HLH). SPTCL often mimics benign panniculitides, making pathologic diagnosis challenging, and can be associated with autoimmune disease, further complicating clinical diagnosis. Traditionally, SPTCL was treated with multimodal chemotherapy, but in recent years, long term remission has been achieved with immunosuppressive therapy alone. SPTCL is rare in pediatrics, comprising less than 1% of Non-Hodgkin lymphomas.

Objectives: We present two pediatric patients with SPTCL diagnosed and treated at our institution.

Design/Method: The detailed clinicopathologic features were reviewed.

Results: Patient 1 presented at age 16 with a left cheek mass which spontaneously resolved. Later, he developed subcutaneous lesions on his left deltoid. A biopsy was interpreted as lupus profundus based on panniculitis-associated edema, mucinous deposits and no significant fat rimming. He was treated with hydroxychloroquine. One year later, he presented with fever and recurrent subcutaneous lesions. Biopsy revealed SPTCL based on infiltrate density and prominent fat rimming. Bone marrow biopsy was negative, and he did not meet criteria for HLH. His subcutaneous lesions were positive on PET scan. He was treated with prednisone and cyclosporine (CsA), and later developed hypothyroidism. Now 24 months off therapy, he remains in remission.

Patient 2 initially presented at age 8 with a diffuse maculopapular rash with malar involvement. He developed extremity nodular lesions associated with fevers, weakness, and a 14-pound weight loss, and was diagnosed with juvenile dermatomyositis (JDM). Subcutaneous biopsy revealed SPTCL based on fat rimming, fat necrosis, and a clonal T-cell receptor gene rearrangement. A PET scan demonstrated multiple hypermetabolic nodules, bone marrow was negative, and there was no evidence of HLH. He began prednisolone and CsA with rapid improvement. Due to intolerance, CsA was switched to subcutaneous methotrexate. His SPTCL remains in remission 14 months on therapy, although his JDM has persisted.

Conclusion: Our two pediatric patients with SPTCL share clinical features of SPTCL described in the literature: presentation with painful, migratory and progressive subcutaneous lesions; association with autoimmune disease; and pathologic diagnosis often requiring more than one biopsy. Our patients' excellent responses to steroids and CsA also mirror those reported.

Immunosuppression appears to be a safe, well-tolerated regimen for SPTCL, including those with HLH. Longer periods of surveillance may be needed to determine the natural history of SPTCL in pediatrics.

Poster # 477

A RARE CASE OF PAEDIATRIC B-CELL LYMPHOMA PRESENTING WITH SPINAL CORD COMPRESSION

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Background: Spinal cord compression (SCC) is a rare oncologic emergency in pediatrics. SCC secondary to non-Hodgkin's lymphoma (NHL), either primary or relapsed, has been described in adults, but occurs even less frequently in children, with an incidence of 1.5-2% reported in previous pediatric studies [1,2].

Objectives: To describe an uncommon case of B-cell lymphoma in a 13-year-old male, presenting with SCC secondary to an epidural tumor.

Design/Method: Case report.

Results: A 13-year-old male presented emergently describing a 1-month history of back pain and a 3-day history of progressive lower extremity weakness, paresthesia, and difficulty walking. He initially denied any bowel or bladder concerns but developed urinary retention in the subsequent 24 hours. There were no preceding fevers nor night sweats, but he reported a 3.5kg unintentional weight loss in 1 month. Examination was significant for a thoracic sensory level (T7-T8), bilateral motor weakness, brisk deep tendon reflexes, and numbness in the lower extremities. MRI of the spine revealed a posterior epidural mass at T7-T9, with significant compression of the spinal cord. Peripheral blood was unremarkable, no cytopenias, no peripheral blasts, and no features of tumor lysis syndrome. CT-guided biopsy was performed, and immunohistopathology confirmed Diffuse Large B-cell Lymphoma (DLBCL). He started on high-dose dexamethasone (4 mg QID) to reduce peri-tumoral edema, relieve SCC and preserve neurologic function. Surgical decompression was not required. Staging CT (head-to-pelvis) showed no other sites of disease. Positron emission tomography (PET) was delayed but demonstrated mild uptake only in the primary lesion. He was classified as CNS positive NHL. Chemotherapy as per COG ANHL1131 Group C3 therapy with Rituximab was initiated. Re-evaluation after 1 week of chemotherapy showed 61.7% regression of tumour mass with near complete resolution of the SCC, and progressive clinical improvement in neurological deficits.

Conclusion: SCC is an emergent clinical condition that can lead to irreversible loss of neurologic function without prompt diagnosis and management. Although rare, SCC can be an initial presentation of malignancy, including NHL, neuroblastoma, Langerhan cell histiocytosis and sarcomas. Previous studies in adults have reported that 1.8% of all diffuse large B-cell lymphomas occur in the spinal epidural location[3], and the frequency in children is has not been specifically studied. Pediatric patients presenting with back pain with or without neurologic symptoms require

prompt imaging assessment to rule out a spinal mass.

References:
1. Pui, Journal of Pediatrics, 1985
2. Mora, Med Pediatr Oncol, 1999
3. Wada, Pathol Res Pract, 2010

Poster # 478

THINKING OUTSIDE THE DEMOGRAPHIC: EPSTEIN BARR VIRUS-ASSOCIATED HODGKIN LYMPHOMA IN A YOUNG CHILD

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Background: The incidence of Hodgkin Lymphoma (HL) is highest in adolescents, ages 15 to 19, and is extremely rare in children less than 5 years of age in the United States. Histologically, mixed cellularity HL (MCHL) is the predominant subtype in children younger than 10 years old. The most common presentation is cervical lymphadenopathy with a strong association with Epstein Barr virus (EBV) infection. There are only a few cases of HL reported in children younger than five years of age in developed countries.

Objectives: We report a case of EBV-associated MCHL in a three-year-old child presenting with cervical lymphadenopathy.

Design/Method: Chart review, multi-department collaboration and literature review

Results: A three-year-old Hispanic female presented with an enlarging left neck mass, two weeks after an upper respiratory tract infection. No systemic symptoms were reported and no organomegaly was appreciated. There was no laboratory evidence of tumor lysis syndrome and no mediastinal mass identified on the chest x-ray. Initial contrast-enhanced computerized tomography (CT) scan of the neck revealed the mass-like conglomerate of lymph nodes extending from the left skull base to the lower neck, with the largest portion measuring 4 x 4 x 5 cm. Subsequent excisional biopsy showed numerous classical Reed Sternberg (RS) cells in a background of a predominantly small cluster of differentiation (CD) 4 positive T-cells and macrophages with focal eosinophilia. RS cells tested positive for CD30, CD15 and weakly positive for PAX5.The pathological diagnosis of MCHL was made. Additional immunohistochemistry demonstrated the presence of EBV latent membrane protein 1 in the majority of the RS cells. EBV DNA Polymerase Chain Reaction and immunoglobulin (Ig) G were both positive, but IgM was negative. Staging with Positron Emission Tomography CT demonstrated bilateral hypermetabolic cervical lymphadenopathy with the highest SUV of 7.79. There was no evidence of subdiaphragmatic metastases, consistent with stage IIA. A low-risk chemotherapy protocol was initiated. Thus far, the patient has tolerated one cycle of doxorubicin, vincristine, prednisone and cyclophosphamide without complications.

Conclusion: HL in a three-year-old child is exceptionally rare in developed countries. The influence of EBV infection on the pathogenesis and tumor microenvironment has been comprehensively studied in MCHL. However, an underlying genetic predisposition may contribute to oncogenesis in these rare cases and warrants further investigation.

Poster # 479

LYMPHOMA IN THE MIDST OF GUILLAIN-BARRE SYNDROME THERAPY: AN INTERESTING DILEMMA

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Background: Guillain-Barre syndrome (GBS), is characterized by distal paresthesia and progressive bilateral symmetric weakness of the extremities. It is often precipitated by underlying infection, but has also been well described in the presence of malignancies, particularly lymphomas. It's known that GBS may complicate the course of lymphoma but it's rare to precede lymphoma. Here we report a rare case of a pediatric patient who presented with GBS and was diagnosed with Hodgkin lymphoma (HL). To date there has been no pediatric case of GBS preceding the diagnosis of HL. Our case highlights the importance of considering HL in the setting of GBS.

Objectives: To raise awareness amongst clinician of the association between GBS and lymphomas and to emphasize on close follow up for patients with GBS.

Design/Method: Case report with literature review.

Results: 5-year-old Hispanic male presented with lower extremity pain and inability to walk. MRI spine revealed nerve root enhancement involving cauda equina and conus medullaris. Lumber puncture showed cytoalbuminologic dissociation confirmed the diagnosis of GBS. Patient was started on IVIg. Due to progressive weakness and worsening paresthesia he was started on IVIg and steroid infusion every 4 to 6 weeks. Five months later patient developed new onset weakness in the upper extremities with difficulty in swallowing. Work up failed to reveal the underlying etiology. Chronic inflammatory demyelinating polyneuropathy (CIDP) was most likely explanation. One month later he developed right cervical neck swelling with fever and weight loss. Work up including CT scan and biopsy confirmed diagnosis of HL, mixed cellularity. PET scan was consistent with disease above the diaphragm. He was upstaged to stage IIB due to prior treatment with steroid and elevated ESR>140. He was treated as per AHOD0831 protocol. Vincristine was avoided due to his CIDP. Patient completed 4 cycles of chemotherapy with successful remission.

Conclusion: Considering that the cells involved in both autoimmunity and lymphoid malignancies are essentially the same, the incidence of GBS and CIDP appears to be increased in association with lymphoma especially HL. Whether GBS was associated with HL as a paraneoplastic syndrome, more reflective of immune dysregulation or coincidental is not clear. Treatment of HL

in the setting of CIDP is challenging because most patients had received steroids by the time HL diagnosis was made. Although our patient is in remission it's not clear whether avoiding vincristine may increase the risk of relapse, which emphasizes the importance of close follow up.

Poster # 480

AN UNUSUAL PRESENTATION OF A RARE PEDIATRIC DISEASE.

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Background: While cutaneous T-cell lymphomas (CTCL) are uncommon in children, mycosis fungoides (MF) is the most prevalent form. Mycosis fungoides is characterized by an epidermotropic atypical T-cell infiltrate leading to skin patches, plaques or nodules, and potential extracutaneous involvement. Other forms of cutaneous lymphomas include primary cutaneous CD30-positive lymphoproliferative disease (LPD), such as cutaneous anaplastic large cell lymphoma (cALCL) and lymphomatoid papulosis (LyP). In most cases, the appearance of CTCL skin lesions is distinct, allowing the diagnosis and best course of treatment to be decided upon easily; however, at times, diagnosis can be difficult, particularly in the early phases of the disease.

Objectives: To describe a pediatric patient with MF presenting with LyP features.

Design/Method: Case Report.

Results: An 8 year-old female patient presented with annular hypopigmented plaques on thigh and neck, with borders slightly indurated and an atrophic center. A skin biopsy revealed an annular elastolytic giant cell granuloma, characterized by non-palisading granulomatous infiltrate with multinucleated giant cells, lymphocytes, and rare plasma cells and neutrophils in the upper dermis. Focal loss and fragmentation of elastic fibers were seen with elastic stain. The granulomatous inflammation was surrounded with dense, haphazard collagen fibers. Upon this finding, she was initially started on minocycline but with no improvement, followed by hydroxychloroquine, steroid and tacrolimus ointment with little improvement. A year later, patient developed a recurrent disseminated papular and papularnecrotic rash, in addition to the areas of annular plaques. A skin biopsy of the new lesions revealed pathologic features of a CD30+ lymphoproliferative disease (LyP-type A). Therapy was changed to titrating doses of systemic methotrexate over several months, with little to no improvement. Given refractoriness and severity of lesions, patient was started on brentuximab vedotin (Bv), with good tolerance and significant improvement of papular rash and some improvement of annular plaques. Based on her clinical course, the diagnosis was adjusted to MF with a LyP component. Phototherapy is now being considered given risk of recurrence of symptoms once Bv is discontinued.

Conclusion: Patients with CD30-positive LPD are under an increased long term risk of developing lymphomas, including MF. This case suggests that pediatric patients with MF can later develop LyP, and establishing the correct diagnosis may be difficult. Systemic therapy with anti-CD30 therapy such as Bv is feasible, effective and well tolerable. However, given chronic course of disease, other long term therapies should be considered specially in young patients.

Poster # 482

ACUTE RESPIRATORY FAILURE DUE TO RELAPSED INFILTRATIVE ANAPLASTIC LARGE CELL LYMPHOMA

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Background: Anaplastic large cell lymphoma (ALCL) accounts for 10-15% of all pediatric non-Hodgkin lymphomas and often presents with widespread nodal and extranodal disease. However, systemic ALCL with diffuse lung involvement and fulminant respiratory failure is rarely reported in pediatric patients.

Objectives: We describe the case of a patient presenting with respiratory failure secondary to relapsed ALCL and rapid clinical improvement following initiation of cancer-directed therapy.

Design/Method: A 9 year-old male with history of ALK+ ALCL presented with painful inguinal lymphadenopathy approximately four months after completion of therapy. Lymph node biopsy confirmed relapsed ALCL, and imaging showed widespread disease that included the cervical, supraclavicular, mediastinum, and hilar regions, but only one small pulmonary nodule in the right middle lobe. Shortly after confirming his relapse and before initiating salvage therapy, he was admitted to the hospital for cough and fever with concern for sepsis. He developed profound hypoxia with bilateral patchy opacities on chest radiograph and was started on high dose trimethoprim-sulfamethoxazole and prednisone for suspected PJP pneumonia. His respiratory status initially improved but subsequently worsened on therapy. He was intubated and placed on ECMO. PJP PCR and Beta-D-glucan were negative, so trimethoprim-sulfamethoxazole and prednisone were discontinued. Extensive infectious work-up was negative (respiratory viral panel, EBV, CMV, legionella, aspergillus galactomannan, HIV, TB, histoplasma, mycoplasma, cryptococcus, blood cultures, and KARIUS), so ALCL-directed therapy (crizotinib, vinblastine, and dexamethasone) was started due to concern for infiltrative lymphoma.

Results: He demonstrated rapid respiratory improvement after initiation of cancer-directed therapy. He was decannulated from ECMO and extubated within one week. Vinblastine was discontinued after two doses, and dexamethasone was weaned and stopped. Crizotinib was continued. Repeat CT and PET scans performed seven weeks after initiation of treatment showed a complete response. He has not had any further respiratory distress since discharge. He remains on crizotinib with the plan to proceed to allogeneic stem cell transplant as soon as possible.

Conclusion: Fulminant respiratory failure in the setting of pediatric ALCL is rarely reported, and there are no published reports on its successful treatment. Our single patient experience demonstrates the importance of considering this phenomenon in a patient with ALCL and respiratory distress, as well as the importance of swift treatment if an alternative cause is not identified. It also highlights the utility of crizotinib in the treatment of relapsed ALCL.

Poster # 483

A CASE SERIES OF CSF PLEOCYTOSIS IN PEDIATRIC LEUKEMIA AND LYMPHOMA PATIENTS

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Background: In oncology patients, cerebrospinal fluid (CSF) pleocytosis is a hallmark of central nervous system (CNS) involvement of the patient's underlying malignancy. Across treatment courses, CSF cell counts and pathology are serially followed to monitor for clearance of CNS disease or for development of CNS relapse.

Objectives: We describe three pediatric cases of CSF pleocytosis during treatment of Burkitt's leukemia and diffuse large B cell lymphoma without any evidence of CNS leukemia or infection, temporally following administration of Pegfilgrastim.

Design/Method: Case report.

Results: We present the CSF studies of three pediatric patients with either Burkitt's leukemia or diffuse large B cell lymphoma who were treated as per ANHL1131 with rituximab.

Patient 1 had Burkitt's leukemia with CNS 3 disease at diagnosis (83 nucleated cells, 122 RBC, 97% blasts). 4 months into therapy, his CSF was notable for 288 nucleated cells, 19 RBC, 91% monocytes/macrophages. Pathology showed numerous histiocytes, monocytes and lymphocytes present without evidence of malignant cells. CSF glucose was normal and CSF protein was elevated. CSF bacterial culture and blood and respiratory viral testing were negative. Complete blood count showed a normal white blood cell count (5.9 thousand/mm2) and elevated absolute monocyte count (1.82 thousand/mm3). The patient had received pegfilgrastim 37 days prior. The following month, CSF studies showed 1 nucleated cell and 0 RBC and pathology showed no malignant cells.

Patient 2 had Burkitt's leukemia with CNS 3 disease at diagnosis due intraorbital and intracranial extension of his primary lymphoma with negative CSF studies (1 nucleated cell, 0 RBC, pathology with no malignant cells). 2 months into therapy, his CSF showed 35 nucleated cells, 1 RBC, 95% monocytes/macrophages. Pathology showed a monocytic pleocytosis. The patient had received pegfilgrastim 21 days prior. Subsequent CSF studies were within normal limits.

Patient 3 had diffuse large B cell lymphoma with CNS 1 disease at diagnosis (3 nucleated cells, 1610 RBC, pathology without malignant cells). The patient had serial LPs showing CSF pleocytosis, the highest with 24 nucleated cells, 32 RBC, 64% monocytes. Pathology showed a mixed cell pleocytosis. The patient received pegfilgrastim 17 days prior.

Conclusion: We present three pediatric cases of CSF pleocytosis during treatment for Burkitt's leukemia or diffuse large B cell lymphoma treated as per ANHL1131 with rituximab. CSF pathology showed no evidence of recurrent leukemia or lymphoma; however, it showed a

monocytosis. All patients had received pegfilgrastim within the past 40 days, suggesting a potential relationship between CSF
pleocytosis and pegfilgrastim administration.

Poster # 484

A RARE CASE OF PRIMARY REFRACTORY ALK POSITIVE LARGE B-CELL LYMPHOMA RESISTANT TO NIVOLUMAB

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Background: Anaplastic lymphoma kinase (ALK) positive large B-cell lymphoma (LBCL) is a rare and aggressive type of Diffuse Large B-cell Lymphoma. It was recognized as a distinct entity 25 years ago and there are fewer than 200 cases described in the literature. ALK-positive LBCL is more common in males and typically presents in the fourth decade of life. The tumor is characterized by t(2;17) resulting in a fusion protein of clathrin heavy-chain and ALK. This is in contrast to the nucleophosmin-ALK rearrangement observed in DLBCL.

Objectives: To describe a patient with ALK positive large B-cell lymphoma refractory to immune checkpoint blockade.

Design/Method: Case report

Results: An 18-year-old female presented with a 4-month history of an enlarging right breast mass, 10 days of back pain, left axilla pain, and drenching night sweats. Examination was remarkable for firm non-tender lymphadenopathy in bilateral cervical and supraclavicular regions. Laboratory tests revealed lymphopenia, an elevated LDH of 2040, and slightly elevated ESR of 22 (Reference range 0-20). The remainder of the CBC and other laboratory tests including CRP, uric acid, and CMP were normal. Immunohistochemistry staining of the resected breast mass was positive for ALK, CD138, PAX5, BOB1, and OCT2 and negative for CD20, CD30, and CD79a, consistent with a diagnosis of ALK positive Large B-cell Lymphoma. Staging evaluation with PET/CT, bone marrow biopsy, and lumbar puncture revealed Stage IV disease. Treatment with Crizotinib and Dose adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin (DA-EPOCH) resulted in marked improvement in metabolic activity of all sites of disease except for one hepatic lesion that was found to have increased in size and activity on repeat PET/CT, consistent with a Deauville score of 5. Biopsy of the liver mass confirmed it was refractory ALK positive LBCL. Crizotinib and chemotherapy were discontinued and treatment with Nivolumab was initiated after additional immunohistochemical testing confirmed positive PD-L1 expression. This was followed by rapid progression of multifocal disease. The patient was subsequently referred for a clinical trial for anti-BCMA immunotherapy.

Conclusion: ALK+ LBCL has no established standard of care due to its rarity. Literature search for therapeutic approaches to refractory advanced stage ALK+ LBCL revealed a case report describing durable response to Nivolumab. However, here we report a case of resistance to Nivolumab despite positive PDL1 expression indicating that PDL1 expression does not guarantee

response to immune checkpoint inhibitors. This prompts the question of what other factors determine response to immune checkpoint blockade.

Poster # 485

CLINICAL MANIFESTATIONS OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ASSOCIATED WITH RARE DNASE2 VARIANT

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Background: DNase II deficiency is a rare autosomal recessive disorder which has been reported to cause a type I interferonopathy leading to a multisystem autoinflammatory syndrome. Variable clinical manifestations have been reported including recurrent fever, cytopenias, and elevated cytokines, akin to hemophagocytic lymphohistiocytosis (HLH).

Objectives: To describe a rare homozygous missense mutation of DNASE2 causing periodic fever, clinical manifestations of HLH, and autoinflammatory syndrome in a pediatric patient.

Design/Method: Review of current literature was performed, as well as medical records reviewed of a patient with recurrent periodic fever and cytopenias found to have a homozygous DNASE2 missense mutation.

Results: A 12-year-old Indian male with history of neonatal thrombocytopenia presented with a five-month history of recurrent fever, anemia and leukopenia. Weekly fever lasted 24 to 48 hours with Tmax 103ºF. Associated symptoms included failure to thrive, anorexia, nausea, and fatigue. He returned to baseline between febrile episodes. He was also found to have autoimmune hypothyroidism. Laboratory workup revealed anemia (hgb <9 g/dL), thrombocytopenia (plt <100K), hyperferritinemia (>4800 mcg/L), fasting hypertriglyceridemia, sIL-2R elevation (924 U/mL), IL-18 elevation (1,197 pg/ml), low NK cell activity, and mild bone marrow hemophagocytosis. He met majority of clinical HLH criteria without classical finding of persistent fever >5 consecutive days. Extensive infectious work-up was negative. Notably he had poor protection against 7 of 12 pneumococcal serotypes. Immunology exome sequencing revealed a rare homozygous missense variant Ch19(GRCh37):g 12986847C>T NM_00137S.2:c 1040G>A (p.Cys347Tyr) in DNASE2 gene. DNase II deficiency is an exceedingly rare autosomal recessive disorder which results in loss of DNase II endonuclease activity, leading to dysfunctional clearance of nucleic acids. This in turn triggers misidentification of self-nucleic acids as non-self, enhancing immunogenicity via inappropriate interferon overactivation. A resultant multisystem autoinflammatory syndrome ensues via Jak pathway (1). There are 4 cases describing DNASE2 mutation and a broad phenotypic spectrum, with varying degrees of cytopenias in the neonatal period, dysfunctional hematopoiesis, recurrent fevers, failure to thrive, arthropathy, cholestatic hepatitis, and intestinal inflammation (1,2). Our patient is currently undergoing biochemical validation of his variant, including analysis of transcriptional interferon signature, with the aim of guiding therapeutic management.

1. Hong, et al, *Journal of Allergy and Clinical Immunology*, 2019

2. Rodero, et al, *Nature Communications*, 2017

Conclusion: This is a case report describing a pediatric patient with periodic fever and cytopenias who was found to have a rare homozygous variant Ch19(GRCh37):g 12986847C>T NM_00137S.2:c 1040G>A (p.Cys347Tyr) in DNASE2. We report the clinical manifestations of HLH associated with this variant.

Poster # 486

CASE REPORT: CLADRIBINE THERAPY FOR REFRACTORY ROSAI-DORFMAN-DESTOMBES DISEASE WITH RENAL LESIONS

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Background: Rosai-Dorfman-Destombes disease is a rare, non-Langerhans cell histiocytosis caused by activated histiocytes accumulated in body tissues. This is a widely heterogeneous disease with no uniform approach delineated for treatment, especially in cases refractory to initial treatment. Therapeutic strategies are mostly limited to case reports in the literature.

Objectives: To describe the use of cladribine in achieving remission in a patient with Rosai-Dorfman-Destombes disease refractory to systemic steroids and 6-mercaptopurine/methotrexate in the absence of standard approach to treatment.

Design/Method: Case Report

Results: A 21-month-old female initially presented with cervical lymphadenopathy and persistent neutropenia. Lymph node biopsy obtained during workup demonstrated sinus histiocytosis with massive lymphadenopathy consistent with Rosai-Dorfman-Destombes disease. Computed tomography demonstrated bulky cervical and prevertebral lymphadenopathy causing severe narrowing of the hypopharynx and multiple hypodense lesions within the kidneys. During her initial observation period, the patient developed progressive cervical lymphadenopathy, eventually resulting in airway compromise requiring ICU admission and treatment with steroids. She was subsequently initiated on treatment with prednisone 1 mg/kg/day for 6 months. During this time, she experienced behavioral side effects with minimal response in lymph node size and inflammatory markers. Molecular sequencing of the biopsy sample revealed an *ATR* frameshift deletion but no targetable mutations. Due to minimal response and persistent side effects, the patient was transitioned to oral 6-mercaptopurine (6-MP; 50 mg/m^2/day) and methotrexate (MTX; 20 mg/m^2/week) per the most recent consensus recommendations. Prednisone was tapered over 8 weeks due to prolonged exposure. Follow-up imaging after 3 months of treatment with 6-MP and MTX demonstrated worsening disease with interval increase in size of the massive mediastinal lymphadenopathy. The patient was then transitioned to cladribine (5 mg/m^2/day x 5 days every 28 days for 6 cycles). Follow-up imaging after cycle 3 of treatment showed an interval decrease in size of the burden of lymphadenopathy as well as resolution of her kidney lesions. She tolerated all 6 cycles well without severe adverse effects and is in continued remission at 10 months off therapy

without evidence of recurrent disease.

Conclusion: Cladribine was well-tolerated and induced remission without evidence of recurrence 10 months off therapy in a patient with massive lymphadenopathy and renal lesions secondary to Rosai-Dorfman-Destombes disease refractory to treatment with prednisone and 6-MP/MTX. This case also documents a novel mutation previously not described in association with Rosai-Dorfman-Destombes disease.

Poster # 487

A CASE OF FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS PRESENTING WITH CORONARY ARTERY DILATION

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by massive, pathologic, systemic, immune inflammation that often creates a diagnostic dilemma due to the significant overlap with numerous autoimmune, autoinflammatory, and infectious conditions [1].

Objectives: We describe a patient with autosomal recessive familial HLH type 3, secondary to mutations in UNC13D, who presented with diffuse right coronary artery dilation.

Design/Method: Case report.

Results: An eight-week-old male presented with five days of fever, anemia (hemoglobin 9.8 g/dL), thrombocytopenia (platelet count 56 thousand/mm3), transaminitis (AST 258 units/L, ALT 164 units/L), hyperferritinemia (ferritin 6959 ng/mL), an elevated D-dimer (3.83 mcg/ml FEU) and hypogammaglobulinemia (IgG 375 mg/dL). Abdominal ultrasound showed splenomegaly and echocardiogram showed a diffusely dilated right coronary artery (Z-score 2.7). Initially, given his coronary abnormalities, the patient was treated for atypical Kawasaki disease with high dose IVIG.

Due to persistent fevers and negative infectious work up, additional laboratory work up was performed and notable for progressive neutropenia (absolute neutrophil count 0.4 thousand/mm3) and hypertriglyceridemia (triglycerides 387 mg/dL). NK cell function was markedly decreased, soluble IL-2 and CXCL9 were markedly elevated and C107a was low. Bone marrow biopsy showed no evidence of hemophagocytosis or hematolymphoid malignancy. Therefore, given high suspicion for HLH, the patient was started on empiric induction therapy as per the HLH-94 backbone with dexamethasone 10mg/m2/day and etoposide 5mg/kg/dose (given weight <10kg).

Ultimately, HLH Gene Sequencing Panel showed two heterozygous mutations in UNC13D (NM_1999242.2:c.766C>T) and (NM_199242.2:c.2298+1G>A). The mutations were deemed pathogenic based on parental testing confirming these two variants occurred on opposite alleles (in trans), consistent with a diagnosis of autosomal recessive familial HLH type 3 [2,3]. The patient completed induction and continuation chemotherapy and underwent curative therapy with

allogeneic hematopoietic stem cell transplant.

Conclusion: We present a case of an infant with diffuse right coronary artery dilation who was ultimately diagnosed with autosomal recessive familial HLH type 3, secondary to heterozygous mutations in UNC13D. His HLH was cured with chemotherapy and allogeneic hematopoietic stem cell transplant. This case report illustrates the potential for overlap in patients with Kawasaki-like disease and HLH and the importance of avoiding premature closure when caring for patients with systemic immune inflammation.

[1] Jordan, et. Al. Blood, 2011.
[2] Feldmann, et. Al. Cell, 2003.
[3] Gadoury-Levesque, et. Al. Blood Advances, 2020.

Poster # 488

A RARE CASE OF SECONDARY HLH DUE TO VACCINE-STRAIN MEASLES IN A YOUNG CHILD WITH HEPATOBLASTOMA

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder characterized by systemic hyperinflammation that can cause multi-organ failure and death. Viral infections during immunosuppressive therapies have on rare occasion been associated with the development of secondary HLH due to prior immunizations.

Objectives: We report a novel case of HLH secondary to vaccine-strain measles infection in a young boy undergoing treatment for hepatoblastoma.

Design/Method: Case report.

Results: A 19-month-old male was diagnosed with intermediate risk, PRETEXT III P+ hepatoblastoma at 14 months of age and treated per AHEP1531 (vincristine/cisplatin/doxorubicin/5-fluorouracil), 11 days after receiving measles-mumps-rubella and varicella vaccines. After two cycles of treatment, he developed skin lesions along his scalp, thigh, and groin with vaccine-strain varicella viremia, treated with acyclovir. The subsequent three months of chemotherapy were complicated by fevers and progressive lung infiltrates with no identified etiology. Despite broad anti-infective coverage and chemotherapy being withheld, progression of his nodules led to an extensive evaluation for bacterial, fungal and viral causes. A lung biopsy showed nodular histiocytic infiltrates with reactive multinucleate cells. Polymerase chain reaction testing and histopathology of the sample were negative for tuberculosis, varicella, adenovirus, herpes simplex and cytomegalovirus. Eventually, next-generation sequencing of a bronchoalveolar lavage sample revealed measles, later confirmed as vaccine-strain through the Center for Disease Control. He developed persistent fevers with worsening anemia, thrombocytopenia, coagulopathy, hepatosplenomegaly, and cardiogenic shock. Ferritin was elevated at 39 994 ng/mL and soluble IL-2R was 3544 U/mL. He was diagnosed with HLH per

HLH-2004 criteria. Rapid whole-genome sequencing was negative for primary HLH and other inborn errors of immunity. He began immunosuppressive therapy (dexamethasone + etoposide) for secondary HLH and Emapalumab-lzsg due to poor upfront response. Measles-directed therapy (ribavirin + IVIG + vitamin A) was initiated once measles was confirmed. Despite these interventions, he succumbed to complications from measles and secondary HLH two weeks after starting HLH-directed therapy.

Conclusion: Although there are rare individual reports of HLH secondary to primary measles infection, to our knowledge this is the first report of secondary HLH due to vaccine-strain measles [1]. Uncontrolled replication of vaccine-strain measles is highly unusual and can be difficult to diagnose when presentation is atypical. This case highlights an exceptionally rare complication of immunosuppressive therapy in a patient with recent live vaccination. We hope greater awareness can lead to earlier recognition and improved outcomes.

1. Lagousi T, Korovessi P, Panagouli E, Tsagris V, Kostaridou S. A Rare Case of Measles-Associated Hemophagocytic Lymphohistiocytosis in an Infant. Cureus. 2020;12(5):e8246.

Poster # 489

LIVER FAILURE IN A NEWBORN WITH DOWN SYNDROME

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Background: Transient abnormal myelopoiesis (TAM) occurs in 4-10% of infants with trisomy 21. TAM can be clinically silent or progress to multisystem organ failure. Hemophagocytic lymphocytic histiocytosis (HLH) is frequently observed in other patients with abnormal myelopoiesis. It is uncommon to consider these specific diagnoses simultaneously.

Objectives: To present a neonate with coagulopathy and pancytopenia who developed elevated ferritin and liver failure suspected to be secondary to HLH.

Design/Method: A chart review was completed as well as direct discussions with the care team.

Results: A full-term neonate with trisomy 21 was coagulopathic and pancytopenic at birth. After product replacement the coagulopathy normalized, however thrombocytopenia remained, and a conjugated hyperbilirubinemia developed. Notably, there were no peripheral blasts. A ferritin obtained to assess for gestational alloimmune liver disease (GALD) was 2020ng/ml on day of life (DOL) 3. On DOL 4, the patient met the following HLH criteria: splenomegaly, cytopenias, elevated ferritin, hypofibrinogenemia. sIL-2R and CXCL9 resulted mildly elevated at 2481U/ml and 994pg/ml respectively. High dose dexamethasone was initiated on DOL 6. A bone marrow aspirate completed on DOL 11 showed neither hemophagocytosis nor TAM. After developing bacteremia, ferritin peaked at >45,600ng/ml, leading to expanded HLH therapy with etoposide and emapalumab. Peripheral flow from DOL 13 returned showing 0.9% aberrant myeloid-progenitor population, concerning for TAM in a patient with low counts. Therapy shifted from HLH focus to TAM, with initiation of low dose cytarabine and discontinuation of etoposide. The patient

subsequently developed significantly elevated liver transaminases and ferritin; thus the regimen was modified to low dose cytarabine, dexamethasone, etoposide, and emapalumab. Cytarabine and etoposide were later discontinued due to urosepsis and an ANC of 0. The patient died of sepsis on DOL 30.

No additional unifying diagnosis was identified for this patient. GALD was considered, however the patient did not respond to IVIG. No GATA1 mutation was identified. A primary immunodeficiency panel and HLH gene sequencing panel resulted with no variant of significance. A clonal CD4 T cell population was identified with a monoclonal beta gene rearrangement in the bone marrow. Preliminary autopsy results showed iron deposition in the liver but were otherwise non-specific.

Conclusion: This complicated patient had GATA1 negative TAM causing secondary HLH. This case emphasizes complexities in diagnosing TAM in the setting of pancytopenia and is the first report of this entity with the comorbid hyper-inflammatory syndrome of HLH. This novel association is in keeping with the association of other myelopoiesis abnormalities and HLH.

Poster # 490

LATE ONSET NEURODEGENERATIVE LANGERHANS CELL HISTIOCYTOSIS IN A PEDIATRIC PATIENT

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Background: Langerhans Cell histiocytosis (LCH) is an inflammatory neoplasm, consisting of pathologic dendritic cells expressing CD1a and CD207. Central nervous system (CNS) involvement occurs in 4-50% of patients, presenting as either an isolated mass or rarely neurodegeneration (2%). Neurodegenerative LCH (ND-LCH) is characterized by severe progressive radiologic and clinical deficits, the etiology of which is unknown. Incidental reports show improvement with early systemic chemotherapy, although effective treatment is yet to be elucidated. Recently, cytarabine (ARA-C) has been investigated due to its ability to cross the blood brain barrier (BBB) and concentrate in the cerebrospinal fluid (CSF).

Objectives: We report an 18 year old female patient presenting with late onset ND-LCH, 8 years after diagnosis and successful treatment of multifocal LCH in infancy.

Design/Method: Case study.

Results: Patient is an 18 year old female with a past medical history of multifocal LCH, presenting at 2.5 years of age with gum and skull lesions. Punch biopsy confirmed BRAF-V600E mutated LCH, with no further organ involvement. She was diagnosed with multifocal bone involvement and treated with prednisone and vinblastine. Further treatment with prednisone, vincristine, oral methotrexate and subsequently oral 6-mercaptopurine was given for 2 relapses. At age 6, disease burden was stable with no further therapy or changes on imaging. Patient had been off therapy for several years, when she presented with progressive ataxia and nystagmus, leading to falls, dropping

objects and facial twitching. Symptoms were slowly progressive for 7 years prior, with intermittent resolution. Magnetic resonance imaging (MRI) showed mild prominence of the cerebellar folia consistent with atrophic changes in the cerebellar hemispheres, no intracranial mass was identified. Positron emission tomography (PET) showed no active disease, and she was diagnosed with ND-LCH. CSF studies were negative for BRAF mutation. Low dose monthly ARA-C 100 mg/m^2 daily x 5 days every month x 1 year was started, with stabilization of symptoms and MRI imaging. Patient has mild residual facial twitch and difficulties with balance. At 21 years old she is 2 years off therapy and attending collage with minimal cognitive deficits.

Conclusion: There is no current standard of treatment for ND-LCH. Prompt treatment is key to intervene in the degenerative course of illness. We report a case of delayed ND-LCH, responsive to ARA-C therapy. This could pose as novel intervention due to ARA-C's predilection for the CNS. Further investigation is warranted.

Poster # 491

VULVAR AND ORAL LANGERHANS CELL HISTIOCYTOSIS: A PEDIATRIC CASE REPORT

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Background: Langerhans cell histiocytosis (LCH) is an uncommon hematologic condition resulting from neoplastic proliferation of antigen-presenting cells with characteristics of Langerhans cells. These cells can accumulate in many organs including skin, bone, liver, brain and lung. Bone lesions are reported in 80% of cases of LCH. A diagnosis is made via histopathological analysis of lesions. LCH may present with single-system or multi-system lesions and lesions may be unifocal or multifocal. It is more common in children than adults. Five in one million children are diagnosed annually at a mean age of 1.8 with a male predominance. Treatment is variable based on system involvement and spans from observation for skin lesions to year long chemotherapeutic regimens for multisystem disease.

Objectives: To discuss a case of pediatric Langerhans cell histiocytosis presenting initially as a vulvar lesion.

Design/Method: A 10 year old Hispanic female presented with several months of swollen labia, scant yellow vaginal discharge and pustular lesions on her vulva. She had a remote history of straddle injury to the area with resulting unhealed left periclitoral laceration requiring operative repair. Abnormal vulvar tissue was biopsied by pediatric gynecology.

Results: Intraoperative biopsy and immunohistochemical staining revealed CD43, CD1a and S100 positive cells consistent with LCH. Eight months after initial presentation the patient reported lesions on the left hard palate confirmed to be LCH with biopsy. After initiation of steroid cream on vulvar lesions, multifocal mucosal involvement (oral and vulvar lesions) warranted treatment with a 6 month course of methotrexate (MTX) and continued follow-up. There was minimal responsiveness to MTX. Adjunct therapy for treatment of unisystem, multifocal disease was not

started at the initial institution; the patient was intermittently lost to follow-up. Oncologic management was reinstated at a tertiary care center where 6-mercaptopurine treatment was initiated without significant improvement. Intralesional steroid injections were trialed on hard palate lesions resulting in decrease in size of lesions. The patient later returned to gynecologic care for intralesional labial steroid injection as well with responsiveness to treatment.

Conclusion: LCH most commonly presents as disordered growth of dendritic cells in bone or skin, though few reported incidences of vulvar LCH in pediatric and adolescent cases are published. LCH should remain on the differential when evaluating pediatric and adolescent patients with vulvar lesions. Biopsy should be utilized when a diagnosis of LCH is considered for confirmed diagnosis so that treatment pathways can be initiated. Consider limiting chemotherapeutic treatment in patients with unisystem, focal disease.

Poster # 492

A CASE REPORT OF DISSEMINATED ERDHEIM-CHESTER DISEASE IN AN ADOLESCENT MALE

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Background: Erdheim-Chester disease (ECD) is a rare multisystemic neoplastic histiocytic disorder. Approximately 800 cases have been reported in the literature, but it's true incidence is unknow. ECD is rare in pediatric patients and has a predominance for middle-aged males. In pediatric patients ECD may present initially with a central nervous system juvenile xanthogranuloma mass lesion harboring a BRAF-V600E mutation. Pediatric patients often experience a delay in diagnosis from months to years.

Objectives: Review the presentation of rare non Langerhan Histiocytic disorder.

Design/Method: Case report.

Results: Here we present a case of a now 19 years old male with prior history of autism spectrum disorder, attention deficit and hyperactivity disorder, anxiety and major depressive disorder. He presented at 14 years to endocrinology with short stature, during initial work-up he was unfortunately lost to follow-up. He then represented at 16 years with symptoms of diabetes insipidus (DI), and work-up was consistent with DI and growth hormone deficiency, prompting a brain MRI. MRI revealed nodular enhancing suprasellar mass that extends from the third ventricular floor to the dorsum sella along the pituitary stalk. Imaging results were initially concerning for Langerhans Cells Histiocytosis (LCH) versus Germ Cell tumor (GCT) given involvement of pituitary stalk. Further work up was obtained including tumor markers in serum and cerebrospinal fluid, bone scan and complete MRI of spine were not diagnostic of these etiologies. Biopsy of the suprasellar lesion yielded the diagnosis of xanthomatous hypophysitis, confirmed with a second pathology opinion. He was once again lost to follow-up for over 10 months and returned after been evaluated at an outside hospital for recurrent pancreatitis and incidentally found to have a 7^{th} right rib expansile lytic bony lesions on abdominal computer tomography (CT)

scan. A biopsy of the lesion revealed fibroconnective tissue with xanthomatous histiocytes negative for S100, positive for BRAF-V600E mutation, given these findings the diagnosis of ECD was made. Positron Emission Tomography confirmed widespread multifocal FDG hypermetabolic activity. Given excellent results in adults with targeted therapy for the BRAF-V600E mutation, treatment with BRAF inhibitor, Vemurafenib was started.

Conclusion:
Although pediatric ECD is a rare finding, this case highlights that in addition to LCH and GCT, ECD should be on the differential for a patient presenting with sellar lesions. Sampling error in biopsy of pituitary lesions can make definitive diagnosis difficult and close follow up in this population of patients is needed for diagnosis and treatment.

Poster # 493

JUVENILE XANTHORANULOMA OF TEMPORAL BONE: A CASE REPORT

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Background: Juvenile xanthogranuloma (JXG) is a rare non-langerhan cell histiocytic infiltration. It typically presents as a solitary cutaneous nodule Systemic involvement, is rare, occurring in <5% of cases.

Comprehensive literature of multisystem JXG treated with chemotherapy suggests that symptomatic cases of multisystem JXG can successfully be treated with LCH-based regimens. Additionally, some studies investigated cladrabine showing Impressive responses with central nervous system involvement, other utilized bevacizumab with successful results.

Objectives: The objective of this report is to familiarize oncologist with an unusual presentation of JXG in order to facilitate early diagnosis.

Design/Method: Seven years old female patient, presented with protruded right eye and a fungating mass from her right nose.

Initially the CT of the brain revealed enhancing mass upon the right sphenoid bone extending to the infra temporal fossa, , while intracranially it is seen abutting and mildly displacing the internal carotid artery also eroding the posterior aspect of the orbital roof. Patient underwent endoscopic debulking. Four weeks later the patient presented with tumor recurrence and she underwent craniotomy with debulking; work –up were free of any metastases.

Marker study revealed positive reaction to CD68, S100, and CD163 while CD1a and langerin cells were negative, a diagnosis of JXG was made.

she started chemotherapy with LCH IV, but unfortunately the patient was not compliant, on treatment developed focal convulsions, her CT brain revealed post-operative sequalae. An ulcerative lesion developed locally. biopsy. revealed an inflammatory ulcer. During supportive

treatment she developed weakness in her lower limb PET scan showed multiple (FDG) avid pelvic bone , sacral lesion with intraspinal extension, hepatic and renal deposits. For the aforementioned findings, the patient was shifted to (cladrabine).

Results: We describe a unique case of extracutaneous juvenile xanthogranuloma involving the temporal bone. We went through the literature and found 4 cases of JXG of temporal bone, 3 cases of them presented with a solitary lesion and 1 case with leptomeningeal enhancement where the management was just radical excision; this is in contrast to our case with a very aggressive course and was refractory to chemotherapy.

JXG lesions are diagnosed and characterized primarily through histopathology and immunohistochemistry. Little is known about the genetics of JXG.

Diamond et al. recently identified mutations involving MAPK pathway. Another study by Chakraborty and colleagues reported 2 cases that contained the *BRAFV600E* mutation.

Conclusion: Further studies of juvenile xanthogranuloma, including mutation profiles and relationship of systemic to solitary cutaneous disease are warranted.

Poster # 494

RARE PRESENTATION OF A DEEP XANTHOGRANULOMATOUS PROCESS WITH EPIDURAL MASS AND NOVEL FUSION PROTEIN

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Background: Juvenile xanthogranuloma (JXG) is a non-Langerhans cell histiocytosis (LCH) typically presenting in the first two decades of life with cutaneous nodules. Multisystem disease is extremely rare, and there have been less than a dozen cases recorded in the literature with central nervous system (CNS) involvement. JXG with CNS involvement typically presents with neurologic changes including deficits on examination and referred pain from mass effect. There are some histiocytic disorders that may not be easily classifiable, and immunohistochemical analysis in conjunction with clinical presentation is the most reliable method to determine the need for systemic therapy.

Objectives: Describe a unique presentation of a deep xanthogranulomatous process with unusual features and a novel fusion protein.

Design/Method: Case report of an infant who presented with a deep xanthogranulomatous process with unusual features, developed an epidural mass without neurologic deficits, and was treated with vinblastine and dexamethasone as per a modified LCH-III regimen.

Results: A 2-month-old female presented with a palpable right upper quadrant abdominal mass. Computed tomography demonstrated diffuse nodules in the liver, lungs,

subcutaneous tissue, and lymph nodes. Biopsies of the subcutaneous lesions demonstrated xanthogranulomatous proliferation with foam cells and eosinophils, most consistent with a non-Langerhans cell histiocytosis, in addition to an atypical histologic pattern of a palisading granulomatous-like process around central suppurative inflammation and necrosis. A novel fusion protein, MYH9-FLT3, was identified by an investigational molecular panel, and genetics were negative for ALK and BRAF. After 4 months of close observation, screening magnetic resonance imaging showed a new enlarging epidural mass extending from T12-L2 with compression of the conus medullaris. She had no neurological deficits on examination. With several features of JXG and the concern for neurological progression, she was initiated on systemic treatment as per a modified LCH-III regimen with vinblastine and dexamethasone (due to better CNS penetration). Imaging after 6 weeks of therapy showed an interval decrease in the epidural mass, with substantial decrease in cord compression and improvement in systemic lesions.

Conclusion: JXG typically has an indolent course but in rare cases with multisystem and CNS involvement may have a more aggressive course with benefit from systemic therapy. Our patient with a deep xanthogranulomatous process with unusual features, a novel MYH9-FLT3 fusion protein, and an epidural mass showed radiological improvement and clinical stability after 6 weeks of vinblastine and dexamethasone. Further research is warranted on profiling histiocytic disorders to determine relevant genetics and optimize treatment strategies.

Poster # 495

SYNCHRONOUS THERAPY RELATED AML AND MEDULLARY THYROID CANCER IN A EWING SARCOMA SURVIVOR

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Background: Synchronous tumors are defined as tumors that arise simultaneously or within 6 months of the primary malignant tumor. The combination of primary hematologic and a solid tumor is rare in children and young adults. The development of multiple malignancies may be related to a cancer predisposition syndrome or to the exposure to carcinogens. The surveillance of synchronous tumors can be complex.

Objectives: We report a case of a childhood cancer survivor who presented as a young adult with 2 synchronous malignancies without a cancer predisposition syndrome.

Design/Method: Case Report

Results: A 20-year-old female with history of localized Ewing sarcoma at age 12, presented with 3-months of multiple emerging masses including by her clavicle, in her thyroid and on her eye. A conjunctival biopsy of the lesion demonstrated a poorly differentiated hematolymphoid neoplasm. Exam confirmed these masses as well as gingival hyperplasia. FDG-PET scan showed multiple hypermetabolic bone lesions, soft tissue nodules, and a right thyroid nodule (TN). Biopsy of the

supraclavicular mass showed myeloid sarcoma (CD45+CD33+CD117+CD15+CD11b+CD11c+HLA-DR, negative for MPO and muramidase). Molecular studies were positive for PTPN11p.E76V and MLL (11q23) rearrangement. BM and CSF were negative. Response assessment PET following induction chemotherapy showed decreased PET avidity in all regions except the TN. FNA showed medullary thyroid carcinoma (MTC); patient's calcitonin (8289pg/mL) and CEA (150ug/L) were both elevated. After a second cycle of AML therapy, a total thyroidectomy with modified radical neck lymph node dissection on the right side was performed. Histopathology confirmed metastatic angioinvasive MTC of the right lobe. MEN2A related tumors were ruled out with a normal parathyroid hormone, calcium, phosphorus and metanephrines. A dotatate-PET showed no evidence of pheochromocytoma. Offered a genetic testing to rule out cancer predisposition syndrome, but our patient decided to only test for RET, TP53 gene and chromosomal breakage analysis that were normal. Once in remission for both myeloid sarcoma and MTC, she underwent 12/12 HLA matched sibling donor transplant. Post-transplant surveillance included FDG-PET along with Somatostatin/Octreotide-PET for myeloid sarcoma and MTC, respectively. She remains in remission of both neoplasms for 1-year.

Conclusion: Our patient has a unique presentation of synchronous hematologic and solid malignancies. This case highlights the surveillance methods in a patient with synchronous tumors. FDG PET is used to monitor for myeloid sarcoma and Somatostatin/Octreotide-PET, calcitonin, and CEA for MTC.

Poster # 496

DESMOPLASTIC SMALL ROUND CELL TUMOR (DSRCT) OF THE MAJOR SALIVARY GLAND: CASE REPORT

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Background: Desmoplastic small round cell tumor (DSRCT) is an aggressive neoplasm that predominantly involves the soft tissues of the abdomen or pelvis. DSRCTs are primarily seen in children and adolescents with a male predominance ranging from 3:1 to 9:1 (male:female). The DSRCT has been reported in a wide age range of age groups with a mean of 35.5 years. DSRCT has poorly distinguishable clinical features or presentation, however, has distinct histopathological features and genetic markers. A key component for definitive diagnosis is the t(11; 22)(p13; q12) translocation. DSRCT is a very rare tumor with extra-abdominal manifestations being even more of a rare occurrence. It has been reported in uncommon locations such as the lung, pleura, paranasal sinuses, salivary glands, central nervous system, and scalp soft tissue. Upon review of the literature, there have been 8 cases of DSCRT reported in the major slavery glands.

Objectives: This case seeks to demonstrate diagnosis and clinical management of a primary parotid gland DSRCT in a 4-year-old female.

Design/Method: We present a case report of a 4-year-old female that initially presented with a right-sided neck swelling that started approximately 2 years prior to diagnosis.

Results: Progression with increase in size of right neck mass, lead to further CT imaging and resection. Initial pathology by morphology was consistent with Sialoblastoma, yet molecular testing revealed a EWSR1-WT1 translocation, which is specific and diagnostic for DSRCT. Treatment was given per AEWS-1221 Arm A interval compress chemotherapy and proton radiation.

Conclusion: DSRCT is a malignancy with poor clinical and pathological features based on traditional immunohistochemistry. This case emphasizes the need for molecular testing on all tumors to confirm or at times change diagnosis. Upon review of the literature, this patient documents the youngest reported case of DSRCT in the neck region.

Poster # 497

CALCIFYING FIBROUS TUMOR OF THE PLEURA IN A YOUNG FEMALE PATIENT

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Background: Calcifying fibrous tumor (CFT) is a rare, benign subtype of fibroblastic and myofibroblastic tumors. It is more common in children and young adults with a predilection for females. CFT arises in soft tissue and common sites include lung, pleura, abdominal cavity, and extremities. These tumors are rarely positive for anaplastic lymphoma kinase (ALK), smooth muscle actin (SMA), or desmin, which is useful in differentiating the tumor from its main differentials, inflammatory myofibroblastic tumor (IMT) and desmoid fibromatosis. Additionally, ALK rearrangements are common in IMT. Some consider CFT to be the late or “burnt out” stage of IMT, a finding supported by a methylation study from 2019.

Objectives: To describe a pediatric patient with multifocal calcifying fibrous tumor

Design/Method: Case report and literature review

Results: A 17-year-old female with superior mesenteric artery syndrome was incidentally found to have pulmonary nodules on a routine computer tomography (CT) abdomen obtained for gastrointestinal symptoms. A dedicated CT chest showed right-sided pulmonary nodules. Repeat CT obtained in six months showed multiple pleural-based nodules, ranging from 17x13mm to 32x35mm, and resolution of the right-sided nodules. She did not have a history of fever or respiratory symptoms. Laboratory tests, including CBCd, LDH, and ESR, were normal. Infectious disease workup was unremarkable. Right thoracoscopic mass biopsy showed multiple 1-3cm hard, mobile nodules that were attached to the pleura and diaphragm. Nodules were also noted on the pleura over the IVC and near the hilum of the right lung. Cultures (AFB, fungi, and bacteria) were negative. Flow cytometry was non-contributory. Histologic examination demonstrated a

hypocellular fibroblastic/myofibroblastic neoplasm with chronic inflammation and foci of calcification and no significant cytologic atypia. Immunohistochemical stains were focally, weakly positive for desmin and negative for SMA, nuclear beta-catenin, and ALK. A next generation sequencing sarcoma fusion panel was negative for gene fusions, including ALK. Taken together, the findings were consistent with a calcifying fibrous tumor. She underwent thoracoscopic right chest tumor debulking; all visible nodules were resected. She has been doing well post-operatively.

Conclusion: CFT is a rare, benign tumor in which many patients are asymptomatic and tumors are found incidentally. Pathogenesis is not well understood. Recommended treatment is resection and prognosis is excellent. Based on literature review, the presentation of multiple pleural CFT is primarily seen in adults. Thus, this case highlights a unique presentation of CFT in a pediatric patient.

Poster # 498

USE OF CRIZOTINIB IN A NEONATE WITH A LIFE-THREATENING, ALK-POSITIVE, LOW GRADE MESENCHYMAL NEOPLASM

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Background: Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that activates downstream signaling pathways mediating cell growth and survival. In pediatrics, ALK rearrangements are commonly identified in anaplastic large cell lymphoma and inflammatory myofibroblastic tumor. Ongoing trials are evaluating the effect of Crizotinib on ALK inhibition in pediatric ALK-positive tumors. These trials have included patients as young as one year of age but have not included infants under the age of 12 months.

Objectives: We describe a neonate with an ALK-positive, low grade mesenchymal neoplasm treated with Crizotinib.

Design/Method: Case report

Results: An 8-day-old full-term female presented to the emergency room for progressive neck swelling. MRI reported a large retropharyngeal mass measuring 4.4 x 4.4 x 4.5 cm. Secondary to mass effect, the patient required intubation due to a tenuous and positional airway. A biopsy was performed as the mass was deemed unresectable due to extensive involvement of critical structures. Pathology and FISH reported a low grade mesenchymal neoplasm with ALK gene rearrangement. Next generation sequencing identified ALK-CLTC fusion. As a low grade neoplasm not expected to respond to traditional chemotherapy, a request for emergency compassionate access of Crizotinib oral solution was granted. At three weeks of age the patient was started on Crizotinib oral solution 9.3 mg/kg/dose (equivalent to standard pediatric dose 280 mg/m^2/dose) twice daily via nasogastric tube. Following six, 21-day cycles of Crizotinib, MRI showed complete resolution of the neck mass. After completion of nine cycles, Crizotinib was stopped. Although not unexpected, after two weeks off therapy a repeat MRI demonstrated significant interval regrowth of the tumor. Crizotinib was restarted and again the tumor exhibited good response with complete

resolution. Crizotinib has been well tolerated. Adverse events for this patient include intermittent grade 1 diarrhea and a single episode of grade 4 neutropenia requiring brief medication hold.

Conclusion: Pediatric tumors harboring ALK gene rearrangements may benefit from ALK inhibition, either as a single agent or combined with standard chemotherapy. We report a neonate with a low grade mesenchymal neoplasm with ALK-CLTC fusion effectively and safely treated with single agent Crizotinib. As she requires ongoing treatment, we anticipate the possibility of development of drug resistance. ALK inhibition has shown to be successful in several ongoing clinical trials but further research is critical in overcoming drug resistance in a subgroup of patients.

Poster # 499

PEDIATRIC PANCREATOBLASTOMA, CTNNB1 MUTATIONS AND CHROMOSOME 16 DELETIONS: IS THERE AN ASSOCIATION?

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Background: Pancreatoblastomas (PBL) are rare tumors arising from epithelial exocrine cells of the pancreas that mainly affect children younger than 10 years old. Presenting symptoms include upper abdominal pain, vomiting, feeding difficulties and weight loss. Etiology is largely unknown but PBL has been associated with Beckwith-Wiedemann syndrome (especially congenital or infantile PBL), as well as with alterations in the APC/beta-catenin(CTNNB1) pathway and loss of chromosome 11p. New molecular associations continue to be described. Primary or delayed (after neoadjuvant chemotherapy) microscopically complete resection is the best prognostic indicator and thus the goal of treatment.

Objectives: Describe the case of a 5-year-old girl diagnosed with PBL associated with a CTNNB1 mutation and an underlying somatic deletion in chromosome 16p13.11.

Design/Method: Chart review.

Results: A 5-year-old female presented with a 3-day history of abdominal pain, diarrhea and emesis following a 2-month history of early satiety and weight loss. Abdominal US showed a 8.3x6.9x7.7 cm rounded heterogeneous mass with internal vascularity in the mid abdomen. Abdominal CT suggested this multiloculated mass was arising from the pancreas. MRCP confirmed likely origin from the pancreatic head and uncinate process, causing mass effect upon multiple adjacent abdominal organs. Initial CBC showed mild normocytic anemia. Tumor markers CA 125, bHCG and urine catecholamines were normal; CA 19-9 was 36 units/mL (normal <35 units/mL) and alpha-fetoprotein was 20.1 ng/mL (normal <12 ng/mL). She underwent open surgical biopsy, pathology showed multilineage components resembling embryologic pancreas, with immunohistochemistry showing expression of beta-catenin but negative alpha-fetoprotein, C-KIT and S-100, with a Ki-67 index >30%, consistent with PBL. Tumor molecular studies showed mutation in CTNNB1 with no loss of SMAD4. Peripheral blood karyotype 46, XX with microarray

showing 907 kb deletion on chromosome 16p13.11 involving 8 genes (MPV17L, MARF1, NDE1, MYH11, CEP20, ABCC1, ABCC6 and NOMO3). Beckwith-Widemann methylation assay was negative. Tumor staging by PET-CT N3 L0 M0, consistent with stage II A. Given tumor size and location, she started PLADO neoadjuvant chemotherapy followed by delayed surgical resection.

Conclusion: Etiology of PBL is mostly unknown but has been associated with mutations in APC/CTNNB1. We present a case of pediatric PBL with a CTNNB1 mutation together with a somatic deletion of the MYH11 gene. Translocations involving MYH11 have been described in AML, thus other mutations could potentially be associated with different cancers. More research is needed to determine if there is an association between MYH11 deletions and PBL.

Poster # 500

MALIGNANT PERIPHERAL NERVE SHEATH TUMOR FOLLOWING RADIATION IN A PATIENT WITH SMARCB1 ALTERATION

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Background: The patient was initially diagnosed with peripheral T cell lymphoma at 4 years of age, and she was treated with chemotherapy and matched unrelated donor (MUD) bone marrow transplant, including total body irradiation (TBI) for conditioning. She had localized relapse 2 years later, treated with chemotherapy and local radiation. At age 18, patient presented with left upper extremity pain and paresthesia, and several intraspinal masses concerning for neurofibromas or schwannomas were identified. A C6/C7 mass with extension into the spinal canal was progressively enlarging in size over several months. The lesion was ultimately debulked and pathology demonstrated malignant peripheral nerve sheath tumor (MPNST) with mosaic INI1 expression. PET scan subsequently showed multiple scattered areas of avidity throughout patient's trunk and extremities, and biopsies of these lesions demonstrated schwannomas without evidence of MPNST.
Of note, the patient's mother had a history of early, triple negative breast cancer, prompting prior genetic testing for cancer predisposition, which was negative for *BRCA1, BRCA2, TP53, CDH1, PTEN,* and *PALB2*.

Objectives: Demonstrate the importance of germline genetic testing prior to radiation in the setting of malignancy.

Design/Method: Comprehensive molecular profiling, including paired tumor/normal exome sequencing and RNA-sequencing of the disease-involved tissue was performed from tissue at the time of cervical lesion diagnosis.

Results: A germline heterozygous *SMARCB1* splice site variant was identified. In addition, a chromosome 22q loss was observed in the tumor resulting in biallelic loss of *SMARCB1* (in concert with the germline finding), as well as biallelic alteration to *NF2* due to 22q loss and an *NF2* splice-site alteration within the tumor. No NF germline alterations were discovered. She was also noted to have a heterozygous alteration in *TTN* which did not contribute to tumorigenesis but may

increase her risk of dilated cardiomyopathy. The germline *SMARCB1* variant was confirmed in the clinical lab by Sanger sequencing and reported in the patient medical record.
Patient remains in active surveillance for MPNST; she is undergoing whole body MRI at regular intervals for screening and is followed by the cancer predisposition team.

Conclusion: *SMARCB1* alterations can be associated with schwannomatosis, along with several malignancies, and radiation increases the risk for lifetime malignancy. This case highlights the importance of full genetic work up for pediatric patients, particularly in the setting of radiation treatment.

Poster # 501

MANAGEMENT OF REFRACTORY HYPERANDROGENISM WITH BRAF V600E INHIBITION IN A PATIENT WITH GANGLIOGLIOMA

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Background: Patients with optic pathway low-grade gliomas/glioneuronal tumors often have concomitant endocrinopathies including, rarely, central precocious puberty (CPP). Targeted therapy using MAP kinase pathway inhibitors have the potential to lead to functional improvement in such patients

Objectives: Report a case of functional improvement with *BRAF* V600E inhibition in a boy with optic pathway ganglioglioma and CPP refractory to medical suppression.

Design/Method: Case report

Results: A 10-year-old boy presented with features of precocious puberty, advanced bone age, and magnetic resonance imaging (MRI) evidence of an optic pathway tumor with solid and cystic components. Biopsy of the lesion revealed a WHO grade 1 ganglioglioma with *BRAF* V600E alteration. Pubertal suppression therapy was initiated with histrelin implant for a diagnosis of CPP. However, despite initially responding to histrelin with no further pubertal development and decreased testosterone, he subsequently experienced pubertal progression on exam, elevated testosterone levels and further advancement in bone age within 6 months, indicating inadequate response to histrelin. At this time, although MRI showed a decrease in size of cystic tumor component, there was new enhancement in right hypothalamic component and persistent enhancement in other portions of the lesion. Anti-tumor therapy was considered to assist with pubertal suppression. Treatment with dabrafenib, a *BRAF* V600E inhibitor, was added following discussion with the family in an attempt at better control of his CPP. After four months of therapy, testosterone levels gradually normalized along with a slowing of his bone age and lack of pubertal progression on exam. Follow-up MRI demonstrated resolution of all areas of tumor enhancement with stable tumor size. Pubertal suppression was discontinued at age 12 years. He continues *BRAF* V600E inhibitor therapy with no adverse effects to dabrafenib noted to date. Therapy has been continued for 18 months with plans to discontinue anti-tumor treatment

after 2 years of therapy.

Conclusion: Molecular agents targeting oncogenic pathways have resulted in improved survival for some children with brain tumors. A synergistic effect with medical pubertal suppression in CPP, though, has not been previously reported in optic pathway ganglioglioma with *BRAF* V600E inhibitor therapy. Our patient not only demonstrated resolution of tumoral enhancement but also had a positive endocrine response and was able to discontinue pubertal suppression therapy. Prospective data collection on functional improvement with molecularly targeted therapy in pediatric patients with low-grade glioma/glioneuronal tumors will help better define the role and duration of these therapies in affected children.

Poster # 502

RESPONSE OF A PEDIATRIC cKIT GASTROINTESTINAL STROMAL CELL TUMOR (GIST) TO IMATINIB

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Background: Gastrointestinal stromal cell tumors (GIST) are tumors of mesenchymal origin, and are very rare in the pediatric population. Unlike GIST in adults, in which the majority contain constitutive tyrosine-kinase (*cKIT*) or platelet-derived growth factor receptor alpha (*PDGFRA*) mutations, most childhood GIST are succinate dehydrogenase (*SDH*) deficient, leading to global tumor hypermethylation (Boikos S et al., JAMA Oncol, 2016). Adult GIST with mutations in *cKIT* or *PDGFRA* are sensitive to tyrosine kinase inhibitors, such as Imatinib (Joensuu H et al., JAMA, 2012). Due to limited cases of GIST in pediatrics, and the majority having SDH mutations, there is no consensus for optimal medical treatment for pediatric GIST.

Objectives: To evaluate the response to post-resection Imatinib monotherapy in a pediatric patient with a *cKIT* positive GIST.

Design/Method: This case report was completed by a comprehensive retrospective chart and literature review.

Results: We present a case of a previously healthy 9-year-old male who presented with fatigue and pallor, subsequently found to have microcytic anemia secondary to hematochezia. The patient was intermittently responsive to parenteral iron therapy, but continued to have hemoccult positive stools. Initial endoscopies and enterography did not reveal an obvious source of gastrointestinal bleeding. Due to persistent microcytic anemia, repeat endoscopy and enterography were performed and revealed gastrointestinal bleeding in the distal duodenum and proximal jejunum, with a pulsating mass in the proximal jejunum (4.9 x 4.0 x 4.0 cm). He underwent complete surgical resection with pathology revealing a spindle cell neoplasm with a high mitotic index (43 mitotic figures per 50 high power fields), expressing CD117(KIT). Expression of SDHB was retained, indicating likely wild-type SDH genotype. Imaging confirmed no distant sites of metastatic disease. Next generation sequencing (Oncoplex) identified a somatic mutation on exon 11 in *c-KIT* (*KIT* p.V569 L576 del) leading to constitutive activation. Based on this finding and well-

established adult literature to support sensitivity of exon 11 mutation *cKIT* GIST to Imatinib, he was started on Imatinib monotherapy to prevent recurrence. With close clinical and radiographic monitoring, he has had no recurrence of disease after two-years on Imatinib monotherapy, with minimal adverse drug effects.

Conclusion: We describe a rare case of a pediatric patient with a *cKIT* mutated GIST, who remains in remission with Imatinib monotherapy following complete surgical resection. This case highlights the importance of identifying molecular and cytogenetic aberrations in rare pediatric tumors to identify optimal treatment options.

Poster # 503

A RARE CASE OF ADENOID CYSTIC CARCINOMA IN AN ADOLESCENT FEMALE PRESENTING AS CHRONIC PHARYNGITIS

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Background: Adenoid cystic carcinoma is a malignant tumor of the secretory glands, most often affecting the salivary glands. It is known for frequently taking a prolonged course with late local recurrences, distant metastases, and poor response to systemic chemotherapy. It is a rare tumor in adults and is even less common in pediatric patients.

Objectives: This case report highlights this rare malignancy's presentation masquerading as a common pediatric complaint and our experience with the treatment and management of an adolescent patient.

Design/Method: A case review of the presentation and the multi-disciplinary management of an adolescent female patient with adenoid cystic carcinoma of the soft palate.

Results: A 17-year-old female presented to the Otolaryngology department of Children's Hospital of New Orleans for evaluation of chronic pharyngitis. She endorsed a year-long history of recurring episodes of sore throat as well as a lump on the roof of her mouth. On physical exam, a 1 cm submucosal lesion on the soft palate was noted. Surgical excision revealed adenoid cystic carcinoma with cribriform histology, perineural invasion, and positive margins. She was referred to Hematology/Oncology for concurrent management.
Tumor staging imaging revealed disease localized to the left posterior soft palate and left tonsillar bed, classifying this as Stage I disease. Due to the increased risk of recurrence with positive margins, the patient underwent a repeat excision to obtain negative margins. She experienced minimal morbidity with surgery. She was subsequently treated with 60 Gy of adjuvant radiotherapy over 6 weeks with minor complications. Surveillance PET scan at 6 months post-excision showed a positive cervical chain lymph node contralateral to the initial lesion, which excision revealed to be reactive.

Conclusion: This patient has a predicted 5-year event-free survival of 75% with a 10-20% chance she will remain disease-free at 15 years. Standard of care for the up-front treatment of adenoid

cystic carcinoma is surgery and radiotherapy, as has been the case for decades. Though she has completely resected Stage 1 disease with negative margins, the minor salivary gland tumor site and perineural invasion would suggest an increased risk of recurrence. The morbidity of recurrence as well as the near-always fatal possibility of bone marrow spread make the lack of effective systemic treatments for adenoid cystic carcinoma a dim prospect for a pediatric patient looking towards young adulthood. Further research is needed to determine optimal treatment, including genetic variants for targeted therapy, in pediatric patients to improve long-term event-free survival.

Poster # 504

A RARE CASE OF ESOPHAGEAL ADENOCARCINOMA IN A CHILD

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Background: Esophageal adenocarcinoma (EAC) is extremely rare in children, with under twenty-five cases found in literature review; in adults, the average age of onset is sixty to seventy years old. Initial clinical presentation is usually dysphagia, anemia, weight loss, and dehydration. Children who develop it often have risk factors such as reflux or underlying genetic mutations. Due to this rarity, pediatric treatment protocols are not readily available.

Objectives: We report a rare case of an eleven-year-old female with EAC who initially presented as refractory iron deficiency anemia. Upon further studies for working diagnosis of IBD (irritable bowel disease), upper endoscopy revealed a distal mass at the gastroesophageal junction, which was eventually confirmed by pathology as an EAC.

Design/Method: This eleven-year-old female initially presented to our outpatient hematology clinic after being referred for anemia by her primary care physician. She reported low appetite and weight loss in the last five months, some abdominal discomfort, and hemoglobin was 6.8. Patient was a known picky eater, and basic labs suggested iron deficiency anemia. She was placed on iron supplementation. Over the next three months, patient continued to have persistent anemia despite medication compliance. Concurrently, patient began having new onset dysphagia and worsening abdominal pain initially attributed to constipation. Fecal occult blood testing was positive, and patient was referred to gastroenterology for endoscopy as evaluation for IBD. Then, a five centimeter, highly vascular, friable mass was found at the GE junction. Imaging revealed a mass extending into the gastric fundus. Pathology confirmed EAC. Given that this tumor is very rare in children, we referred her to Memorial Sloan Kettering Cancer Center (MSKCC) for multidisciplinary evaluation which included their pediatric surgeon, oncologist, as well as their adult counterparts.

Results: Patient completed staging laparoscopy revealing localized disease only. She was started on an adjusted adult regimen of FLOT (5-fluoruracil, leucovorin, oxaliplatin, docetaxel). Her repeat imaging immediately after second cycle showed no residual thickening of tumor identified. Currently, she is awaiting reevaluation for possible surgery. Additionally, genetic testing revealed a p53 mutation which likely lead to her early presentation.

Conclusion: Esophageal carcinoma is very rare in children, however our patient presented with anemia, a common presentation of this disease in adults. She is being treated with FLOT at multidisciplinary cancer center, with experts from adult oncology. Lastly, given her young presentation, genetic testing was undertaken and p53 mutation likely caused early development of her EAC.

Poster # 505

EPSTEIN BARR VIRUS POSITIVE SMALL-CELL NEUROENDOCRINE CARCINOMA FOLLOWING MULTI-VISCERAL TRANSPLANT

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Background: Neuroendocrine tumors (NETs), including neuroendocrine carcinomas, are rare in the pediatric population, with a reported prevalence of approximately 2.8 per million cases. Despite NETs often being benign in nature, they carry a potential for malignant transformation with the gastrointestinal (GI) tract and lungs being the most commonly affected sites. Due to their frequent initial indolent course, approximately 10-20% of patients with NETs present with widespread metastases at diagnosis. In comparison to large-cell NETs, Epstein Barr Virus (EBV) positive small-cell NET cases are rare. Clinical outcomes in patients with NETs have improved since the addition of targeted immunotherapy to standardized chemotherapy. Nevertheless, this approach remains challenging in patients undergoing concomitant immunosuppression therapy.

Objectives: We describe the case of a young adult female presenting with widespread metastatic EBV-positive high-grade small cell NET who underwent multi-visceral transplantation (MVT) 20 years prior to presentation.

Design/Method: Case report.

Results: A 21-year-old female with history of megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) underwent MVT at 7 months of age. Her post-transplant course was complicated by EBV viremia, chronic kidney disease, and neurogenic bladder. Patient initially presented to an outside hospital due to acute bilateral lower extremity edema. Adequate immunosuppressive and prophylactic medication compliance was reported. An initial computed tomography (CT) scan revealed multiple ring-enhancing lesions on the liver concerning for acute infection, hepatic malignancy, versus post-transplant lymphoproliferative disorder (PTLD). Laboratory studies were only remarkable for elevated CA 19-9 and CEA levels (124.2 and 171.1 units/mL, respectively).
A positron emission tomography (PET) scan revealed innumerable liver and small bowel-avid lesions with extensive abdominal and thoracic lymphadenopathy. Ultimately, liver biopsy was consistent with EBV-positive (by PCR) high-grade neuroendocrine carcinoma, small-cell type. Upper and lower endoscopy confirmed a 0.3 x 0.3 x 0.1 cm primary mass in the duodenum. Patient started systemic chemotherapy regimen with carboplatin and
etoposide without concomitant immunotherapy due to concerns that immunotherapy could cause

rejection of her transplanted organs. Restaging PET scan, after 2 chemotherapy cycles, showed improvement on all lesions. Patient is expected to complete a total of 6 chemotherapy cycles.

Conclusion: While EBV is strongly associated with other malignancies, including large-cell NET, EBV-positive small-cell NETs are rarely described in the literature. Diagnostic approaches and treatment options for EBV-positive NETs in patients with history of MVT and ongoing immunosuppression is also scant. Although our patient did not receive targeted immunotherapy due to her post-MVT status, conventional chemotherapy showed promising results thus far, concurring with previously reported studies.

Poster # 506

SUSTAINED RESPONSE FOR STAGE 4 NEUROENDOCRINE TUMOR WITH GEMCITABINE-OXALIPLATIN-LENVATINIB

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Background: Current treatment regimens for neuroendocrine tumors include a wide variety of therapies – ranging from somatostatin analogs to platinum-based therapy – but prognosis still remains poor for certain subtypes due in part to insufficient treatment modalities.

Objectives: This case highlights a new treatment regimen that may be effective, safe, and well-tolerated in patients with high-grade neuroendocrine tumors.

Design/Method: A patient initially diagnosed with fibrolamellar hepatocellular carcinoma later found to have high-grade well-differentiated neuroendocrine tumor responded well to a novel combination of combination of gemcitabine (1000mg/m^2 intravenously every 2 weeks), oxaliplatin (100mg/m^2 intravenously every two weeks), and lenvatinib (8mg by mouth daily). The patient was initially switched from this combination to conventional treatment of capecitabine and temozolomide upon correct diagnosis, but was later switched back due to subsequent clinical decline.

Results: With this new combination, the patient gained 30 pounds within 2 months, had a volume reduction of the most prominent masses ranging from -35% to -80% and AFP reduction by 64% to 86 ng/mL at 9 weeks. After 19 cycles, the patient is now considered a surgical candidate and has had resolution of pain with return to baseline weight.

Conclusion: Other than neuropathy warranting replacement of oxaliplatin with carboplatin, this new regimen has been tolerated well and indicates a promising avenue for treatment of recalcitrant and “incurable” disease.

Poster # 507

GERM CELL TUMOR WITH MALIGNANT TRANSFORMATION

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Background: Germ cell tumors are derived from primordial germ cells of the ovary or testes. They comprise about 2 percent of all pediatric malignancies. Malignant transformation describes the rare phenomenon in which a somatic component of a germ cell teratoma undergoes malignant differentiation. The following case involves a two-year-old female who was diagnosed with a mixed malignant germ cell tumor of the ovary with malignant transformation to rhabdomyosarcoma.

Objectives: To present a rare presentation of germ cell tumor with malignant transformation.

Design/Method: Case Report

Results: Two-year-old female with a history of mixed malignant germ cell tumor of the ovary with immature teratoma, mature teratoma, and yolk-sac components, stage III with positive peritoneal implants. Initial alpha-fetoprotein (AFP) level was 917.8 ng/mL. She underwent mass resection followed by four cycles of chemotherapy per AGCT1531 standard arm consisting of cisplatin, etoposide, and bleomycin with subsequent normalization of AFP. Six months later, she presented with significant abdominal distention and discomfort. Ultrasound revealed new masses in the abdomen. She was diagnosed with embryonal rhabdomyomasarcoma grade IV stage IV. Tumor debulking was attempted but was ultimately unsuccessful due to the gelatinous, friable material of the tissue. She was started on chemotherapy per D9803 with Vincristine, Dactinomycin, and Cyclophosphamide with initial response and decreased tumor burden after 12 weeks on imaging. The regimen was continued, however imaging week 17 revealed progression of disease. Resection was attempted and she was started on whole abdomen radiation and ARST0921 involving temsirolimus, vinorelbine, and cyclophosphamide. Despite multiple modalities of treatment including chemotherapy, radiation, and multiple attempts at surgical resection she continued to have progression and passed away. Tumor tissue was sent to Foundation One and she was found to have a TP53 (466C>T) mutation, which is considered a variation of uncertain significance and likely not associated with Li-Fraumeni Syndrome.

Conclusion: This case is unique in that in that this rare phenomenon of malignant transformation associated with germ cell tumors occurred in a young two-year-old female. Teratomas with malignant transformation are mainly observed in post-pubertal males. Malignant somatic transformation in and of itself is rare occurring in 3 to 8 percent of all pediatric and adult metastatic germ cell tumors combined. Little is known regarding efficacious treatment regimens of germ cell tumors with malignant transformation. Previously documented cases of survival occurred after successful gross total resection of disease along with multimodal treatment and chemotherapy targeted to the somatic component. Unfortunately, in this case total resection was unattainable.

Poster # 508

MODIFIED CHEMOTHERAPY FOR OVARIAN GERM CELL TUMOR IN A PATIENT WITH NIJMEGEN BREAKAGE SYNDROME

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Background: Nijmegen Breakage Syndrome (NBS) is a rare autosomal recessive disorder of chromosomal instability due to defective nibrin protein formation and is characterized by progressive microcephaly, growth retardation, premature ovarian failure, immunodeficiency due to decreased numbers of both circulating T and B lymphocytes, and an increased predisposition to malignancy in particular lymphoid malignancies and certain solid tumors. Nibrin is also implicated in normal gonadal development. Due to chromosomal instability, choosing chemotherapy to treat advanced-stage ovarian cancers in NBS patients is particularly challenging.

Objectives: We report a case of ovarian germ cell tumor (dysgerminoma) in a patient with Nijmegen Breakage Syndrome treated with modified chemotherapy who continues to be in remission.

Design/Method: Case Report

Results: A 20-year-old female who was diagnosed with Nijmegen Breakage Syndrome in early childhood presented with right lower quadrant abdominal pain, vomiting, poor appetite, and significant weight loss. Magnetic Resonance Imaging (MRI) revealed a right-sided complex, 17 cm multiseptated mass with solid and cystic components along with mesenteric lymphadenopathy. Tumor markers showed mildly elevated beta-human chorionic gonadotrophin (HCG) of 17 and lactate dehydrogenase (LDH) of 312 with a normal alpha-fetoprotein (AFP) of 4. She underwent exploratory laparotomy followed by a total abdominal hysterectomy, bilateral salpingo-oophorectomy, peri-aortic, pelvic lymph node dissection, and omentectomy. Biopsy was consistent with dysgerminoma along with positive peritoneal washings and para-aortic lymph node involvement. She was classified as Stage IIIA Dysgerminoma as per the International Federation of Gynecologists and Obstetricians (FIGO) classification. Standard chemotherapy for advanced-stage dysgerminomas includes a combination of platinum (cisplatin/carboplatin), etoposide, and bleomycin. We recommended avoiding bleomycin due to its radio-mimetic action and using the other two agents (Carboplatin and reduced dosing of etoposide at 75%) for our patient. However, she opted to be treated only with IV carboplatin due to the risk of second malignancies with etoposide. She received IV Carboplatin 400 mg/m^2 every 4 weeks x 4 cycles. She continues to be in remission for 15 months. Our patient has been receiving intravenous gamma globulin (IVIG) every 3 weekly since diagnosis of NBS.

Conclusion: NBS patients with cancer need modified dosages of chemotherapy similar to other chromosomal instability disorders like Fanconi anemia and Ataxia telangiectasia. Our patient has shown sustained remission with monotherapy with carboplatin.

Poster # 509

REVERSIBLE DIGITAL CLUBBING AND ARTHRITIS ASSOCIATED WITH INFLAMMATORY MYOFIBROBLASTIC TUMOR

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Background: Inflammatory myofibroblastic tumor (IMT) is a rare intermediate grade neoplasm that primarily affects children and young adults. IMT can present in the lung, liver, bladder, orbit, and other soft tissues. Hypertrophic osteoarthopathy (HOA) is a syndrome characterized by digital clubbing, synovial effusions, and periostitis of the appendicular skeleton. HOA is well-described in adults with cancer and children with nonmalignant conditions such as cystic fibrosis and inflammatory bowel disease. It is rarely reported in pediatric neoplasms. Review of the literature between 1890–2020 reveals forty-two case reports of pediatric malignancy-associated HOA, of which four were identified in children with IMT.

Objectives: We describe a teenager with reversible digital clubbing and arthritis diagnosed with a pulmonary IMT.

Design/Method: A 14-year-old female presented with clubbing of her fingers for three weeks and lower extremity joint pain and swelling for five weeks. Her history was significant for severe food allergies, failure to thrive, and atopic dermatitis; it was negative for cough, shortness of breath, chest pain, infections, and oxygen desaturations as measured by nightly home pulse oximetry monitoring. Baseline labs were normal except for an elevated erythrocyte sedimentation rate (ESR) of 63 mm/hr (normal 0-20 mm/hr). Plain films showed periosteal thickening of the distal radii/ulna. An ovoid mass was detected in the left lung field on chest x-ray. Chest CT identified a 3.1 cm x 2.8 cm x 2.6 cm solitary solid tumor abutting the left hemidiaphragm. Patient underwent an uncomplicated total gross resection.

Results: Pathology revealed an intraparenchymal spindle cell tumor with lymphoplasmacytic infiltration incompletely surrounded by a fibrous pseudocapsule. Immunohistochemistry was positive for vimentin and smooth muscle actin; negative for anaplastic lymphoma kinase and desmin. Five months after surgery, the patient’s digital clubbing and arthritis resolved and ESR normalized. Rapid catch-up weight gain and linear growth were noted following resection. There is no evidence of disease recurrence at 24 months.

Conclusion: Digital clubbing is an unusual sign of pediatric neoplasms. However, as this report illustrates, it can be a marker for IMT and paraneoplastic HOA. The pathophysiology of this phenomenon is suspected to involve intratumoral hypoxia-induced production of vascular endothelial growth factor (VEGF). VEGF overexpression has been identified in pediatric solid tumors and the stroma of clubbed digits. Complete resolution of HOA symptoms is achievable following tumor resection.

Poster # 510

ENDOBRONCHIAL INFLAMMATORY MYOFIBROBLASTIC TUMOR: CRIZOTINIB THERAPY AND BRONCHIAL SLEEVE RESECTION

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Background: Inflammatory myofibroblastic tumors (IMTs) are rare locally invasive neoplasms, generally characterized by anaplastic lymphoma kinase (ALK) gene rearrangements. Therapy with ALK inhibition may result in an apparent complete response; however, the duration of chemotherapy is unknown, and local recurrence is common. Surgical resection can provide a definitive cure but may involve excessive morbidity.

Objectives: Describe a patient with a pulmonary IMT treated with ALK inhibition and robot-assisted surgical resection.

Design/Method: Case report.

Results: A 17-year-old female reported intermittent hemoptysis for the past three years. Chest CT-scan revealed a right upper lobe endobronchial lesion diagnosed by bronchoscopic biopsy as an IMT with ALK gene rearrangement. Positron emission tomography (PET) scan was strongly positive with a standardized uptake value (SUV) of 43. The location and size of the tumor suggested a total pneumonectomy may be necessary. Neoadjuvant therapy with the ALK inhibitor crizotinib (final dose 412mg/m^2/day) was initiated to increase the potential for a lung-sparing procedure. After two months of crizotinib, the PET scan SUV was normal, and the tumor had substantially reduced in size. The patient completed a total of 5 months of ALK inhibitor therapy, allowing for successful robot-assisted thoracoscopic right upper bronchial sleeve lobectomy. Pathology revealed a residual active tumor with clear surgical margins. The patient remains in remission now, eight months after surgery.

Conclusion: Complete surgical resection remains the standard of care for IMTs when feasible; however, adding ALK inhibitors as adjuvant or neoadjuvant chemotherapy is becoming the new standard of care in many instances for this rare tumor. This case illustrates the use of crizotinib to convert a high morbidity surgical procedure (right total pneumonectomy) to a minimally invasive lung-sparing procedure with low morbidity. The presence of an active tumor in the surgical specimen after five cycles of crizotinib, despite a normal PET scan, demonstrates that ALK inhibitor therapy alone may be insufficient. Advanced surgical technique with a minimally invasive robotic-assisted surgical approach also contributed to this case's favorable outcome.

Poster # 511

A CALL FOR GERMLINE ALK TESTING IN NEUROBLASTOMA: A CASE OF ALK+ NEUROBLASTOMA IN MOTHER & BABY

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Background: Neuroblastoma, the most common pediatric extracranial solid tumor, affects about 650 children in the United States each year. While neuroblastoma is usually sporadic, 1-2% of cases are familial, involving the *PHOX2B* or *ALK* genes, and typically present as multifocal tumors in infancy. Somatic ALK aberrations (mutations and amplifications) are found in up to 15% of neuroblastoma cases and about 8% of these patients harbor a germline ALK mutation. Targeted

ALK inhibitor agents, such as crizotinib, have been effective in the relapse setting and are currently being evaluated in combination with backbone multimodal therapy in the upfront setting for high-risk ALK+ neuroblastoma. While somatic ALK status is commonly tested in high risk and relapse patients, it is not routinely tested in low and intermediate risk patients. Furthermore, germline ALK testing is rarely performed, while results can have a large impact on family planning for survivors.

Objectives: To present a case of familial neuroblastoma in a mother and newborn harboring a heterozygous germline ALK mutation, demonstrating the importance of genetic testing in survivors.

Design/Method: Case report and review of literature.

Results: A baby was born with a 3.5cm left suprarenal mass detected on prenatal ultrasound at 33 weeks gestational age to a 22-year-old mother with a history of intermediate risk neuroblastoma treated at 2.5 years old. During pregnancy, the mother underwent genetic testing revealing a germline heterozygous ALK gene c.3575G>C (p.Arg1192Pro) mutation. At birth, the baby was noted to have respiratory distress, a hoarse cry, and right-sided tongue deviation and fasciculations. Imaging revealed a 4cm mass along the left superior cervical sympathetic ganglia with invasion of the skull base. Following biopsy, he emergently began treatment for intermediate risk neuroblastoma due to respiratory compromise. Pathology revealed stroma-poor, poorly differentiated neuroblastoma, MYCN-non-amplified, ALK immunostain positive. Germline genetic testing revealed the same ALK mutation as the mother, confirming autosomal dominant familial ALK+ neuroblastoma. He received 4 cycles of chemotherapy and remains in remission at 6 months.

Conclusion: While familial neuroblastoma is rare, early detection of germline ALK mutations in patients and survivors can have a major impact on family planning and cancer surveillance in offspring. Survivors with autosomal dominant ALK mutations, like our patient's mother, carry a 50% chance of passing the mutation on to each child who then carries a 50–60% chance of developing a neuroblastoma-spectrum tumor if inherited. Germline ALK testing should be strongly considered in survivors of ALK+ and ALK-unknown neuroblastoma.

Poster # 512

RENAL CELL CARCINOMA IN A PEDIATRIC PATIENT WITH CROHN'S DISEASE

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Background: Certain diseases, such as Crohn's Disease (CD), carry an increased, lifetime risk for extra-intestinal manifestations (EIMs). Patients with complex phenotypes such as perianal Crohn's Disease (p-CD) carry the highest risk, presumably due to chronic, transmural inflammation. Renal cell carcinoma (RCC) has specifically been associated in adults with CD, but has not been reported in pediatric CD. As a rare cancer in children, there is a lack of evidenced-based medicine to establish practice patterns, surveillance planning, or recommendations for adjunctive therapy in cases of pediatric RCC.

Objectives: This case concerns a sixteen-year-old female with p-CD who had RCC incidentally detected on screening magnetic resonance (MR) enterography (MRE) less than six months after diagnosis.

Design/Method: Case Report

Results: The patient initially presented with a one-year history of abdominal and perianal pain, hematochezia and a large perianal skin tag which was concerning for (p-CD). Endoscopy and ileocolonoscopy revealed pan-colonic granulomas to confirm CD. She was induced with infliximab and quickly established IBD clinical and laboratory remission. An IBD genetic panel demonstrated 4 separate mutations indicating a complex phenotype associated with increased risk for EIMs. A routinely scheduled surveillance MRE incidentally revealed a 6 cm left renal mass, subsequently confirmed and further characterized by Computed Tomography (CT) of the abdomen. She underwent a left radical nephrectomy with lymph node sampling and was diagnosed with stage III (T1N1M0) papillary type I RCC. Radiographic staging, including CT of the chest, MR imaging of the brain and a bone scan, were all unremarkable. Genomic sequencing revealed no pathogenic somatic or germline mutations. She is currently undergoing quarterly surveillance imaging (MR imaging of chest and abdomen) for RCC without adjuvant chemoradiation. At 3 months out she remains disease-free and her CD remains in remission on infliximab monotherapy.

Conclusion: This patient represents the youngest reported case of RCC in the setting of p-CD and highlights a salient association between RCC and IBD. Given the rarity of RCC in children, there are no specific treatment or surveillance algorithms despite the strong potential for recurrence. Ongoing CD management also requires multi-disciplinary discussions. The impact of infliximab, a TNF-alpha inhibitor, on the development or recurrence of RCC is somewhat contradictory, but recent literature suggests that patients can be safely continued on these agents with no adverse effect on outcomes. As pediatric gastroenterologists increasingly utilize abdominal imaging and IBD genetics to inform their treatment planning, pediatric oncologists should be ready to manage this historically adult-based disease.

Poster # 513

WILMS TUMOR PRESENTING WITH SPONTANEOUS NECROSIS AND CLOSTRIDIUM PERFRINGENS CO-INFECTION

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Background: Wilm's Tumor (WT) is the most common renal malignancy of childhood. The initial presentation of WT may mimic infection or other malignancies with nonspecific symptoms including fever, abdominal/flank pain, or hematuria.

Objectives: We describe a case of WT with spontaneous necrosis obscured by overlying *Clostridium perfringens* infection.

Design/Method: A previously healthy 5-year-old girl presented to the emergency department with a two-day history of flank pain and fevers. She was tachycardic (130 bpm), hypertensive (116/75), and febrile (101.7F). Her abdomen was distended with left-sided flank tenderness without a palpable mass. Initial laboratory testing revealed elevated CRP (70mg/dL) and leukocytosis (22.56 x 10^9 /L). Urinalysis showed 5-10 WBCs but was otherwise normal. A CT abdomen/pelvis with contrast demonstrated a mass-like structure in the left upper quadrant, surrounding and splaying the left adrenal gland with inferior displacement of the left kidney.

The patient was hospitalized for evaluation and received empiric ceftriaxone. Additional laboratory studies were obtained including urine cultures, plasma normetanephrine and metanephrine levels, as well as Vanillylmandelic Acid (VMA) and Homovanillic acid (HVA) levels. All were within normal limits. Her symptoms, leukocytosis and CRP improved with resolution of fevers after 5 days.

Given the ambiguous clinical picture favoring infectious versus oncologic diagnoses, open surgical biopsy of the left kidney and surrounding mass was performed. Pathology demonstrated a phlegmonous appearance of the left kidney and fibrovascular proliferation with inflammation and no evidence of malignancy. Tissue cultures were positive for *Clostridium perfringens*. At discharge, the patient transitioned to a 10-week course of cefixime for *C. perfringens* kidney infection with outpatient follow-up.

Results: Repeat CT abdomen/pelvis obtained 4 weeks after discharge demonstrated decreased size of the renal mass. In outpatient follow-up, repeat ultrasounds minimally improved, therefore a second renal biopsy was obtained 13 weeks after discharge. The biopsy identified monomorphic small cells in varying stages of cell death with positive WT1 protein, consistent with WT.

Conclusion: This case features an unusual presentation of WT with spontaneous necrosis and concomitant *C. perfringens* infection. Our patient's presentation was suspicious, however her initial negative biopsy was masked by the presence of secondary bacterial infection and necrosis, leading to delayed oncology referral and treatment. This case underscores the importance of avoiding confirmation bias in the setting of ambiguous clinical presentations. WT may mimic other pediatric renal pathologies clinically and radiologically, such as renal hemorrhage, abscess, or other malignancies. This poses a diagnostic challenge for providers, particularly when both infection and malignancy are observed.

Poster # 514

MULTIDISCIPLINARY APPROACH TO WILMS TUMOR IN A PATIENT WITH TRISOMY 18 AND HORSE-SHOE KIDNEY

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Background: Trisomy 18 is a frequent chromosomal disorder with a reported incidence of 1/6000-1/8000 live births. In the natural course of the disease, mortality is 90-95% in the first year of life. With recent advances in medical care, the overall life expectancy of Trisomy 18 has improved

significantly. With this, solid tumor reports have increased, with Wilms tumor as the second most common malignancy described.
This poses newer challenges and dilemma to healthcare teams for managing co-morbidities in these patients. A multi-disciplinary approach is the key to a successful outcome.

Objectives: We describe a patient with Trisomy 18 with multiple congenital anomalies including unrepaired congenital heart disease with Eisenmenger syndrome, a horse-shoe kidney, and unilateral Wilms tumor, who underwent a successful Wilms tumor resection through a multidisciplinary team approach.

Design/Method: Case report

Results: A 2-year-old female with Trisomy 18 was admitted with E. Coli urinary tract infection. Renal ultrasound showed a horseshoe kidney and a solid mass in the left-sided kidney. A CT scan showed a well-circumscribed solid mass in the left kidney measuring 3.1 x 3.0 cm. Renal function was normal, and catecholamine levels were negative. Given her multiple comorbidities, multidisciplinary decision was to monitor tumor growth, as parents declined intervention and eventual chemotherapy if needed. She continued ultrasound tumor surveillance with Oncology. At 4 years of age, 32-months after the initial mass was first imaged, she was admitted with progressive abdominal pain and a decrease in hemoglobin from 14.3 to 9.9g/dl in 3 months. Abdominal CT angiogram showed an increase in mass size measuring 10.2 x 9.1 x 9.2 cm (previously 6.7 x 5.9 x 5.4 cm), with no intralesional hemorrhage. Parents were now leaning towards intervention due to symptoms. After multidisciplinary discussions with Oncology, Surgery, Cardiology, Pulmonology, Intensivists and Cardiac anesthesiology, she underwent successful left nephrectomy, with no complications and resolution of abdominal pain. Pathology showed triphasic Wilms tumor, no anaplasia, extensive perilobar nephrogenic rests with diffuse WT 1 positivity on immunohistochemistry. The tumor was classified as Wilms tumor with Stage 1 favorable histology. The patient is now 5 years old, with no tumor recurrence under ultrasound surveillance.

Conclusion: Medical advances and a multidisciplinary team approach to patients with Trisomy 18 has led to prolonged survival. This allows other diseases, such as Wilms tumor, to manifest themselves. Routine abdominal ultrasound screening is recommended to detect these tumors. When detected, a multidisciplinary team approach to the surgical management allows for successful outcomes.

Poster # 515

TREATMENT OF RECURRENT WILMS TUMOR WITH IRINOTECAN/TEMOZOLOMIDE

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Background: Despite improvement in relapse free survival (RFS) in recurrent Wilms tumor, the 4-year RFS rate for patients treated with vincristine/dactinomycin/doxorubicin is approximately 40%.

Ifosfamide, carboplatin and etoposide are commonly used in relapsed solid tumors, but have significant toxicities and require hospital admission for administration. Our patient focused on quality of life, and this led to exploration of other treatment options.

Objectives: Describe a case of multiply relapsed Wilms tumor with management on oral irinotecan/temozolomide for improved quality of life and remission for almost 1 year.

Design/Method: Case Report

Results: The patient is an 11-year-old female diagnosed with Wilms tumor at 6 years of age in Honduras who received approximately 6 months of chemotherapy with Vincristine and a nephrectomy. Staging in Honduras was unknown. Due to financial difficulties, she was unable to continue treatment and family immigrated to the United States. One year after initial diagnosis, imaging revealed large chest mass and intracardiac masses. Biopsy confirmed recurrent Wilms and she received modified NWTS/AREN0534 regimen. Patient responded well to this regimen and then underwent surgical resections and whole lung radiation. At 20 months off therapy, she was found to have a lung nodule, confirmed to be recurrent Wilms tumor. As this was her second recurrence, both patient and family chose a chemotherapy regimen allowing for the best quality of life. She received Irinotecan 90mg/m2/dose PO on days 1-5 and Temozolomide 40mg/m2/dose PO on days 1-5, 8-12, 15-19. She received the 2-drug regimen for 10, 28-day cycles without toxicities or hospitalizations, allowing her to attend school. At the end of cycle 10, she had a third recurrence.

Irinotecan is a camptothecin prodrug shown to have activity against adult solid tumors. Topotecan of the same drug class also showed activity in children with favorable histology Wilms tumor with a 48% response rate in heavily pretreated patients. Temozolomide (TMZ) has activity against adult solid tumors with promising results in xenograft models of pediatric solid tumors. O6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme which inhibits the anti-tumor effect of alkylating agents, like TMZ. Negative MGMT protein expression increases the sensitivity to alkylating agents and can predict the response to temozolomide. Our patient was MGMT negative.

Conclusion: Irinotecan/Temozolomide should continue to be explored as an option for relapsed/refractory solid tumors as it can achieve remission for a substantial period while allowing for improved quality of life.

Poster # 516

MULTIMODAL TREATMENT OF SARCOMAS LINKED TO BCOR-CCNB3 FUSION IN PEDIATRICS: A 3-PATIENT CASE SERIES

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Background: Molecular genetic testing in cancer diagnosis has resulted in subclassifications of malignancies previously grouped together. In 2012, a new entity was classified according to fusion

of the B-cell lymphoma (BCL-6) corepressor (BCOR) gene and the testis-specific cyclin B3 (CCNB3) gene on the X-chromosome, known as a BCOR-CCNB3 fusion positive sarcoma. Previous studies have focused on clinical and pathologic characterization of this specific malignancy, but standard treatment modalities are not well documented.

Objectives: Given their relatively new classification, the treatment approach has remained variable. We describe three pediatric patients with BCOR-CCNB3 fusion positive sarcomas. In summarizing treatments and outcomes, we aim to add to the body of knowledge for this subtype.

Design/Method: This was a retrospective study of three deidentified patient charts. BCOR-CCNB3 fusions were confirmed in all three patients using fluorescence in-situ hybridization (FISH).

Results: Case 1 – A 2-year-old Black female presented with a firm, right calcaneal mass measuring 5.6 x 3.7 x 3.1 cm. Following diagnosis of BCOR-CCNB3 fusion sarcoma, she was promptly started on an interval compressed regimen of alternating vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide with local control accomplished through amputation of the right foot. She has been in remission for two years.

Case 2 – A 12-year-old Caucasian female presented with a two-week history of unilateral right hip pain that worsened with activity. Imaging revealed a 8.2 x 6.0 x 8.3 cm mass on the right pubic bone. She began treatment with 6-cycles of ifosfamide and doxorubicin. For local control, the patient underwent radical resection of the right pubic bone. She remains free of disease and fully active 2.5 years following completion of therapy

Case 3 – A 16-year-old Black male presented with right lateral ankle pain and swelling and was unable to bear weight. MRI revealed a soft tissue mass, measuring 6.0 x 4.0 x 6.6 cm. The mass was grossly excised with positive margins. Therapy consisted of compressed alternating cycles of interval vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide with daily proton beam therapy starting cycle 7. The patient remains in remission at his last visit 2 years from completion of therapy.

Conclusion: We notice Cases 1 and 3 were treated using 5-drug Ewing sarcoma treatment protocol while Case 2 received two drug therapy using combination of ifosfamide and doxorubicin. The variation in treatment regimens highlight existing lack of consensus and we hope that a multi-institutional trial will help solidify future course.

Poster # 517

PROLONGED SURVIVAL WITH CHECK-POINT INHIBITOR /TYROSINE KINASE INHIBITOR FOR RELAPSED OSTEOSARCOMA

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Background: Primary and relapsed metastatic Osteosarcoma(OST) has a very poor prognosis. The outcomes have not improved, nor have new effective therapies emerged, in three decades. New paradigms for OS are urgently needed. Sarcomas often express the PD-L1 ligand and have multiple complex pathogenic pathways. Inhibition of immune checkpoints (CPI), such as CTLA4 or PD-L1 with antibodies, such as nivolumab (NIVO) has emerged as an effective immunotherapy in multiple malignancies. Further, combining immunotherapy and targeted therapies is an emerging strategy in several adult malignancies. Lenvatanib (LEN) is a multi-tyrosine kinase inhibitor (TKI) of several common pathogenic sarcoma pathways. Encouraging results for relapsed pediatric-adolescent sarcoma patients with single-agent pazopanib and more recently LEN or Cabozantinib in phase 1/2 trials along with preliminary evidence of benefit with single agent CPIs, prompted our team to offer combination immune-chemotherapy with NIVO and LEN to patients who had exhausted conventional chemotherapy options.

Objectives: Describe two patients receiving NIVO-LEN immune-chemotherapy for relapsed OS with prolonged responses.

Design/Method: We conducted a literature search on PubMed and Google scholar.

Results: To our knowledge these are the first reported cases of prolonged survival in multiply relapsed OST with combination immune-chemotherapy. Patient 1 is a 16 year old girl, diagnosed with localized femur OST at 9 years,withsurgery (99% necrosis) and conventional chemotherapy of methotrexate/cisplatinum/doxorubicin (MAP) changed to doxorubicin/cisplatinum/ifosfamide/etoposide because of methotrexate toxicity, who relapsed 4 times post therapy: in bone (8 months), followed by bilateral lung relapses (5 months later),followed by massive dissemination in bones, lungs, and mediastinum (4 months later), with massive lung tumors (12 months later). After each relapse she got local control, when possible, and received different salvage regimens: denosumab, gemcitabine/docetaxel/bevacizumab/zoledronic acid, combination NIV/samarium respectively, until the last relapse when we introduced NIVO-LEN and tapered off gemcitabine and zoledronic acid.To date the patient has had 30 cycles of NIVO-LEN with her longest progression free interval (28 months),minimal toxicity and excellent QoL.Patient 2 is a 15 year old male, diagnosed with localized OST at 12 years old with surgery (60% necrosis) and conventional chemotherapy of MAP, who relapsed twice post therapy in bone (15 months), sacrum (4 months later). After each relapse he got local control and received salvage regimen of ifosfamide/etoposide, followed by NIVO-LEN with ongoing remission at 12 months and excellent QoL.

Conclusion: Our preliminary data will inform our colleagues about the possible potential for immune-chemotherapy such as CPI and TKI combinations, for these difficult to treat patients with few options.

Poster # 518

CASE OF AN EMBRYONAL RHABDOMYOSARCOMA IN A PEDIATRIC PATIENT: THERAPEUTIC TARGET IDENTIFICATION

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Background: Rhabdomyosarcoma (RMS) is the most common of the rare soft tissue sarcomas that typically affect the head, neck or genitourinary tract and have a 5-year survival rate of <30%. Within the US, the incidence of RMS is 6 cases per 100 000 per year and around 87% of cases are individuals under 15 years of age. Through many years of targeted sequencing, genomic characteristics have been defined in RMS such as loss of heterozygosity at 11p15.5, translocations of PAX3/PAX7 genes with FOXO1, and mutations in genes such as TP53, NRAS, KRAS, HRAS, PIK3CA, CTTNB1, and FGFR4.

Objectives: Here we describe a combination of molecular analyses to determine the key molecular alterations in a case of embryonal RMS.

Design/Method: A 10-year-old boy presented with a history of recurrent paratesticular RMS with metastases in the liver. Liver biopsy was available to conduct immunohistochemistry and a pathway analysis determining activity of 7 key pathways to cancer development. Additionally, a liquid biopsy that analyzes cell-free circulating tumor DNA in plasma isolated from peripheral blood was also conducted.

Results: Molecular analysis of the liver confirmed a malignant tumor consistent with embryonal RMS and PD-L1 positivity. Several potential driver mutations, including oncogenic NRAS Q61K activation and EGFR amplification, were noted via a blood test (Follow It). NRAS is mutated in a significant subset of embryonal RMS cases and can be targeted with MEK inhibition. Further, the novel oncogenic pathway analysis system (OncoSignal) revealed activation of several additional pathways including PI3K and Hedgehog, which can be targeted using a dual blockade of PI3K and MAPK inhibitors.

Conclusion: The analyses revealed important takeaways: 1) key activating mutations can be identified using a simple liquid biopsy, 2) some embryonal RMS cases have PD-L1 expression, and 3) OncoSignal analysis may be useful in identifying oncogenic driver pathways. These findings helped to identify that this child was eligible for a clinical trial that contained combined MEK and PD-L1 checkpoint inhibitors, a potential solution to treating embryonal RMS.

Poster # 519

CASE REPORT OF RECURRENT METASTATIC OSSIFYING FIBROMYXOID TUMOR WITH A BCOR-ITD ALTERATION

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Background: Ossifying fibromyxoid tumor (OFMT) is a rare, slow-growing soft tissue sarcoma (STS) that usually occurs in adults. There are three histopathologic subtypes (typical, atypical, malignant) with varying malignant potential. Tumors with a *BCOR* (BCL6 corepressor) gene rearrangement include a variety of sarcomas that involve different body organs across the age

spectrum. We present the diagnostic evaluation, pathologic findings, and initial management of a 16-year-old female with multiply-recurrent metastatic OFMT of the left neck with a BCOR-internal tandem duplication (ITD) alteration.

Objectives: To describe a novel case of a patient with an original diagnosis of localized atypical OFMT whose tumor was found to have malignant features and a BCOR-ITD alteration upon second recurrence.

Design/Method: Diagnostic and metastatic evaluation included MRI brain and spine; CT temporal bone, neck, and chest; and PET CT whole body. Fine needle aspiration and core needle biopsy of primary mass was obtained. Tumor molecular analysis was performed with targeted next generation sequencing (NGS). Response to therapy on subsequent imaging studies was measured using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines.

Results: Imaging revealed PET-avid primary tumor in the left neck/skull base and bilateral metastatic pulmonary nodules. Biopsy showed small oval-round spindle neoplastic cells that were similar to tumor specimens at original diagnosis and first recurrence, but with new malignant histologic features of higher cellularity with overlapping nuclei, focal loss of intracellular matrix, and >10 mitoses/50 high power field. NGS detected a 90-base pair duplication in exon 15 of the *BCOR* gene at a variant allele frequency of 18%, signifying an ITD. The patient underwent partial resection of the primary tumor followed by salvage chemotherapy for metastatic STS with ifosfamide 9,000 mg/m^2 and doxorubicin 75 mg/m^2 per cycle every 3 weeks. After 2 and 4 cycles, she had ongoing clinical improvement in symptoms (headache, diplopia, dysphonia, dysphagia) and interim imaging evaluations demonstrated stable disease.
Conclusion: We report a novel case of OFMT with BCOR-ITD alteration and of metastatic malignant OFMT in a child. Published data for OFMT are quite limited, with <15 pediatric cases ever reported. Almost all OFMT cases are localized at diagnosis, with overall risk of subsequent local or metastatic recurrence estimated at 10-27% and 4-11%, respectively, across all subtypes. In 15 published cases of patients who died of disease, all were adults (ages 28-77 years) and 13 (87%) had metastatic malignant OFMT. More studies are needed for OFMT and BCOR-rearranged tumors to better inform management strategies.

Poster # 520

USING OPTICAL GENOME MAPPING AND NGS TO UNDERSTAND EPITHELIOD SARCOMA IN A PEDIATRIC PATIENT

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Background: Epithelioid sarcoma (ES) is a rare and commonly misdiagnosed soft-tissue tumor. This rarity poses significant challenges for diagnosis and understanding disease pathology. A thorough understanding of the molecular events is necessary because 1) certain diagnoses are associated with specific molecular alterations and 2) identification of key actionable oncogenic drivers can help select effective therapy.

Objectives: Here we highlight a unique systematic approach to diagnose and treat epithelioid sarcoma.

Design/Method: A 10-year-old female, otherwise healthy, presented with a soft-tissue tumor of the mouth. This patient underwent surgery and traditional chemotherapy. Initially diagnosed as ES through Next Generation Sequencing (NGS) via FoundationOne Heme and TEMPUS, differential diagnosis using Bionano Optical Genome Mapping (OGM) via Saphyr confirmed ES while also indicating potential of a Rhabdoid tumor and other sarcomas.

Results: The NGS analyses returned key genomic findings including a complete SMARCB1/INI1 deletion and a MUTYH splice site at 934-2A>G. The deletion of the SMARCB1/INI1 gene leads to activation of certain pathways, which can be targeted for treatment with the drug Tazemetostat. Further OGM analysis enabled de-novo assembly of the tumor genome to efficiently reveal large scale structural alterations in a relatively unbiased approach, revealing a partial deletion of chromosome 22q and complete deletion of chromosome 4. These alterations uncovered clear deletions of SMARCB1 gene, confirming NGS analysis and ES diagnosis. OGM also revealed a partial deletion of the tumor suppressor gene, FHIT, along with structural alterations of 43 other cancer genes. Additionally, IHC analysis revealed evidence of PDL1 and PD1 expression. Presence of PDL1 positivity also opens consideration for immuno-oncology options.

Conclusion: NGS in conjunction to OGM can provide improved detection of clinically relevant variants
for genetic disease. Thus, both tests should be considered as a part of the diagnostic regimen to better characterize key mutations in rare tumors and uncover actionable targets for treatment.

Poster # 521

UNDIFFERENTIATED EMBRYONAL SARCOMA OF THE LIVER (UESL) PRESENTING AS CONGENITAL LIVER MASS

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Background: Common neonatal liver tumors include hemangioma, mesenchymal hamartoma, and hepatoblastoma. Undifferentiated embryonal sarcoma of the liver (UESL) is a rare (<1%) hepatic malignancy and typically occurs in older children (6-10 years of age) with no reported congenital cases to our knowledge.

Objectives: Describe prenatal diagnosis, clinical course and outcome of an infant with UESL.
Design/Method: Case Report.

Results: A female term infant was found incidentally to have a liver mass on prenatal ultrasound. A postnatal abdominal MRI demonstrated a 4.6 x 3.4 x 6.8 cm right heterogeneous hepatic mass, thought to represent a giant hepatic hemangioma. Alpha-fetoprotein (AFP) was 40 390 ng/mL (normal for age), which over time decreased. Routine ultrasounds every 6-8 weeks initially showed

stable size. An increase in size at six months of age prompted a biopsy (AFP 1727.4 ng/mL). The biopsy showed reactive hepatocytes with weak cytoplasmic glypican-3 immunostaining and membranous staining of beta-catenin was present. A diagnosis of well-differentiated fetal hepatoblastoma was made. The metastatic workup was negative. Chemotherapy with cisplatin monotherapy was initiated. Due to lack of response to chemotherapy and unresectability of the tumor, she underwent liver transplantation at 11 months of age, with need for second liver transplant due to hepatic artery thrombosis. The explanted liver showed a large mass involving several lobes. Histologically, the tumor was composed of undifferentiated primitive cells with focal myxoid changes. The tumor was negative for beta-catenin by immunostain. Glypican-3 immunostain was restricted to adjacent reactive hepatocytes. A final diagnosis of UESL was made. Adjuvant chemotherapy was recommended for definitive treatment; however, the family declined. Child is now six months post second transplant and continues to undergo surveillance without recurrence.

Conclusion: Diagnosis of congenital liver tumors can be problematic. Biopsy should be considered as soon as a malignant process is suspected. This case highlights the importance of recognizing that glypican-3, historically regarded as a reliable immunostain for malignancy, may show non-specific positivity in reactive hepatocytes, and absence of nuclear beta-catenin positivity should question the diagnosis of hepatoblastoma. Additionally, decreasing AFP levels in the absence of treatment is not typical in hepatoblastoma. Finally, UESL is a high-grade sarcoma with poor prognosis when not treated with multimodal therapy including neoadjuvant chemotherapy. This case, however, suggests that surgical resection (particularly with liver transplantation) may be sufficient for localized disease and allow for avoidance of long-term chemotherapy-induced toxicities, particularly in very young children.

Poster # 522

INFANTILE SPINDLE CELL SARCOMA WITH A NOVEL ALK-ERC1 FUSION SUCCESSFULLY TREATED WITH CRIZOTINIB

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Background: Anaplastic Lymphoma Kinase (ALK) is a receptor tyrosine kinase, implicated in the development of various malignancies, including inflammatory myofibroblastic tumors, lung malignancies and anaplastic large cell lymphoma. Spindle cell sarcoma is a connective tissue tumor affecting adults in the fifth to sixth decade of life and conventionally treated with a combination of surgery (when resectable) and adjuvant chemotherapy.

Objectives: Describe a case of a novel ALK-ERC1 fusion positive spindle cell sarcoma, not previously reported in soft tissue sarcomas, and discuss response to targeted ALK inhibitor therapy.

Design/Method: The case was reviewed and described by chart review.

Results: A 2-year-old male presented with a progressively enlarging right hand mass since 6 months of age. Initially believed to be vascular in origin, the mass was 3-4 cm x 2 cm, with full

function of his hand, but six months later, the mass encompassed his entire palm and impaired full flexion his fingers at the MCP joints. Repeat MRI revealed a mass spanning bone, tendons and neurovascular bundles. Biopsy revealed a "moderately cellular neoplasm composed of bland, round to slightly spindled cells in a loose collagenous background." The tumor entrapped fat and skeletal muscle with occasional giant cells. Genetic analysis revealed an ALK-ERC1 fusion. Immunohistochemical staining was focally positive for SMA, CD34, and Ki67 and negative for MYF4, S100, desmin, MUC4, and HMB45. NTRK 1, 2, and 3 were not involved. The ALK-ERC1 fusion identified had not been previously described in a spindle cell sarcoma. After an extensive literature review of ALK-positive inflammatory myofibroblastic tumors and response to ALK-inhibition, our patient started crizotinib 140 mg twice daily. After three weeks, the tumor had decreased in size and at 10 months was not identifiable on MRI.

Conclusion: We believe this case is the first reported spindle cell sarcoma with an ALK-ERC1 fusion with favorable response to ALK inhibition. Previous literature describes resistance to crizotinib within a few years of therapy, thought to be due to mutations in the tyrosine kinase that limit the binding affinity of the medication, or the formation of alternative signaling pathways, further underscoring the need for new therapies. Our case exemplifies the ever changing and intertwining landscape of molecular diagnostics and targeted therapies.

Poster # 523

TYROSINE KINASE INHIBITOR WITHDRAWAL SYNDROME IN A PATIENT WITH MULTIPLY RELAPSED EWING SARCOMA

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Background: Tyrosine Kinase Inhibitor (TKI) withdrawal syndrome is a newly described phenomenon involving diffuse musculoskeletal pain seen in adult patients primarily with chronic myeloid leukemia (CML) attempting treatment-free remission through TKI discontinuation. It has been reported with imatinib, nilotinib, and dasatinib in the literature.

Objectives: To report the first case of TKI withdrawal syndrome from pazopanib in a patient with relapsed Ewing Sarcoma.

Design/Method: A 16-year-old previously healthy male presenting with back pain, leg paresthesia, and foot drop was found to have localized Ewing sarcoma of the L5 vertebra. He was initially treated with chemotherapy and surgical resection per COG AEWS0031 and achieved remission, however had isolated pulmonary relapse one year following treatment. The nodule was removed, and the patient opted to proceed with observation. Within nine months, subsequent pulmonary metastases were detected. At this time, the patient underwent four cycles of chemotherapy initially, with whole lung radiation several months later. Following radiation, at the age of 20 years, he elected to begin pazopanib (a TKI and VEGF inhibitor) daily, which halted disease progression for 18 months. At signs of progression, plans were made to stop pazopanib for one week before starting cabozantinib. At five days off therapy, the patient developed diffuse arthralgias and

headaches, prompting presentation to the emergency department (ED).

Results: At 21 years of age, the patient presented to the ED with a temperature of 38.1C, headaches, and arthralgias. Work-up including a basic metabolic panel, complete blood count, blood cultures, and urinalysis was unremarkable. An MRI of the brain showed no evidence of metastatic disease or other acute intracranial process. He was started on IV cefepime, IV acetaminophen, oral cyclobenzaprine, and was given two normal saline boluses, then admitted for further management. It was felt his presentation was attributable to TKI withdrawal after review of the literature, and he was treated with naproxen and cyclobenzaprine with adequate pain control.

Conclusion: Our patient experienced withdrawal musculoskeletal pain after discontinuation of pazopanib that improved with non-steroidal anti-inflammatory drugs and muscle relaxants. This is the first report of a patient with Ewing sarcoma on TKI therapy for less than three years experiencing TKI withdrawal syndrome with the particular medication, pazopanib.

Poster # 524

SUCCESSFUL TREATMENT OF EWING SARCOMA IN SETTING OF INHERITED CHOLESTATIC LIVER DISEASE

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Background: An 11 year old female with progressive familial intrahepatic cholestasis type I (PFIC1) (Byler disease) was diagnosed with localized Ewing sarcoma of the chest wall. PFIC1 typically leads to progressive liver dysfunction. PFIC1 results from variants in ATPase Class I Type 8b Member 1 (*ATP8b1*). The co-occurrence of this gene variant and PFIC1 with Ewing sarcoma has not previously been reported. Many active agents in the treatment of Ewing sarcoma undergo hepatic metabolism presenting treatment challenge for this patient. This patient's underlying liver disease necessitated dose adjustment of chemotherapy to account for chronic elevated bilirubin.

Objectives: To describe the approach to successful treatment of a patient with Ewing sarcoma and cholestatic liver disease as well as the potential for increased toxicity and infectious complications.

Design/Method: Literature regarding dose reduction and safety of chemotherapy agents active in Ewing sarcoma in the setting of liver dysfunction was performed. Consent was obtained from patient/family to submit this case report.

Results: This patient was treated as per AEWS1031 regimen B (addition of cyclophosphamide and topotecan). Her treatment plan included elimination of vincristine and doxorubicin and 50% dose reduction in etoposide supported by previous reports of hepatic metabolism of these agents. Given positive margins at surgical local control, she additionally received radiation. The patient is currently 6 months post-completion of therapy without evidence of disease. Notably the patient has developed significant infectious complications post-therapy including cryptococcal meningitis and

bacterial meningitis.

Conclusion: AEWS1031 regimen B, with the addition cyclophosphamide and topotecan (CT) to the established backbone of vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE) for Ewing sarcoma showed similar survival outcomes to that of VDC/IE alone. Regimen B of AEWS1031 was successfully used to treat a patient with underlying cholestatic liver disease and Ewing sarcoma with adjustments to account for chemotherapeutic agents that rely on biliary excretion and adequate hepatic function. This approach offers a therapeutic option for patients with liver dysfunction of any etiology who cannot tolerate full dose VDC/IE. However, we also report significant and rare infectious complications in this patient that may indicate more profound toxicity in the setting of liver dysfunction and immunosuppression from chemotherapy. This finding may warrant closer monitoring of these patients given the potential for increased toxicity. Possible considerations would include antimicrobial prophylaxis and enhanced evaluation during episodes of new fever or other infectious symptoms.

Poster # 525

CUTANEOUS EWING SARCOMA PRESENTING AS A SECOND PRIMARY MALIGNANCY: A CASE REPORT

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Background: Ewing sarcoma is a fusion oncoprotein-driven pediatric malignancy most commonly arising from bone. Cutaneous Ewing sarcoma is a rare variant of this malignancy that harbors the characteristic EWS::FLI1 fusion oncoprotein but demonstrates an immunohistochemical (IHC) staining pattern distinct from classic Ewing tumors. Cutaneous presentations of Ewing sarcoma are exceedingly rare with only ~100 cases ever reported in the literature which can be diagnostically challenging.

Objectives: Here we report a patient with a history of low-risk neuroblastoma treated with resection only who developed a cutaneous Ewing sarcoma a decade later. We additionally discuss the IHC findings and sequencing necessary (FISH) and panel sequencing) to make this rare diagnosis. Additionally, we review treatment options and relevance of germline genetic testing in a pediatric patient diagnosed with two independent cancers.

Design/Method: This patient presented with a nodule on his right foot. The nodule was resected and sent for pathologic evaluation. The specimen was additionally sent for FISH and next-generation-sequencing-based gene fusion analysis (NGS). A Blueprint Genetics Comprehensive Hereditary Cancer Panel was performed. Consent was obtained from the parent and assent was obtained from the patient to report this case.

Results: Pathologic examination of the nodule demonstrated a small round blue cell tumor that immunophenotypically demonstrated widespread expression of CD99, SOX10. S100, and vimentin, and patchy expression of synaptophysin and CK AE1/AE3. The tumor did not express

CK-20, CD45, TdT, HMB-45, MART-1, myogenin, desmin, EMA, or WT-1. *EWSR1* gene rearrangement by fluorescence in situ hybridization (FISH) was positive and the specimen was initially diagnosed as dermal clear cell carcinoma. NGS identified *FLI1* as the *EWSR1* fusion partner, thus leading to a final diagnosis of cutaneous Ewing sarcoma. A Blueprint Genetics Comprehensive Hereditary Cancer Panel (testing 154 genes) was negative for any germline pathogenic variants.

Conclusion: To date, occurrences of bone or soft tissue Ewing sarcoma as a second malignancy have been noted following prior chemotherapy administration. The patient we report here had a rare cutaneous Ewing sarcoma as a second primary cancer a decade after having neuroblastoma treated with surgery only, raising concern for germline-based cancer predisposition. Whole exome sequencing was recommended given the negative sequencing panel result. The presence of pathogenic germline variants in patients with Ewing sarcoma is an evolving area and warrant reporting/ongoing reassessment of the literature.

Poster # 526

A CASE OF SMALL CELL OSTEOSARCOMA WITH RARE REARRANGEMENT OF EWSR1 (22Q12.2) LOCI BY FISH

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Background: Small cell osteosarcoma (SCO) is a rare variant of high-grade osteosarcoma with cytomorphologic features resembling Ewing Sarcoma (ES). Both are characterized as small round cell tumors and while SCO can be distinguished by focal osteoid production, this may be missed in small biopsy samples due to focality. Fluorescence in situ hybridization (FISH) is a useful tool for rapidly identifying *Ewing sarcoma breakpoint region 1* (*EWSR1*) gene rearrangements, distinguishing tumor types. However, a positive finding is not diagnostic of ES as rare cases of *EWSR1* rearrangements in SCO have been reported. Furthermore, due to complex genomic rearrangements associated with osteosarcoma, FISH findings may reflect genomic gains and losses involving the *EWSR1* loci rather than a true chimeric fusion.

Objectives: To report a case of metastatic bone tumor with a rare *EWSR1* (22q12.2) loci rearrangement by FISH confirmed to be SCO by histology and negative for EWSR1 chimeric fusion by targeted sequencing.

Design/Method: Case report and review of literature

Results: 18-year-old male presented with a pathologic fracture of the right femur. Imaging revealed a 20cm infiltrative lesion in the femoral diaphysis with extraosseous soft tissue component and diffuse pulmonary metastases. Biopsy was performed. Interphase FISH using the *EWSR1* dual color-labeled break-apart probe showed two normal copies of *EWSR1* signals with two additional *3'EWSR1* (telomeric portion) gene signals suggesting the presence of an *EWSR1* gene rearrangement with loss of 5'EWSR1 (centromeric portion), consistent with a preliminary diagnosis

of ES. However, final histologic diagnosis was high-grade osteosarcoma with small cell and osteoblastic features. EWSR1 chimeric fusion was not detected on targeted fusion panel. Cancer whole exome sequencing (cWES) with transcriptome showed an unstable genome with copy number gains and losses on several chromosomes and multiple somatic variants including in *RB1*, *ATRX*, and *MED12*.

Conclusion: FISH for *EWSR1* rearrangements is a useful tool for distinguishing ES from SCO early in the pathological workup of a bone tumor. However, a positive finding should be "taken with a grain of salt" as rare EWSR1 gene fusions have been reported in SCO and positive FISH findings may reflect complex chromosomal rearrangements in SCO. We hypothesize in our case that a breakpoint occurred distal to EWSR1 in the 3'EWSR1 region resulting in copy number gain of only the 3'EWSR1 portion involving <1Mb region. Careful histological evaluation for focal osteoid production and targeted fusion panel and/or cWES with transcriptome for chimeric EWSR1 fusion are critical as the treatment for these tumor types differs significantly.

Poster # 527

LATE RELAPSE OF OSTEOSARCOMA IN THE STOMACH: CASE REPORT AND REVIEW OF LITERATURE

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Background: Late osteosarcoma relapse, occurring 5 years or more after diagnosis, is rare. The most common sites of recurrence include the primary site and lung metastasis. Relapsed osteosarcoma in the gastrointestinal (GI) tract is extremely rare. Of these cases, only a few involve the stomach. Standard treatment for recurrent osteosarcoma is surgical resection if feasible. Adjuvant chemotherapy in relapsed disease is less standardized, and treatment decisions are often left to individual providers. There is paucity of prospective data on chemotherapy use for multiply relapsed osteosarcoma due to low patient numbers.

Objectives: We present a 23-year-old female who experienced a third metastatic osteosarcoma relapse. Eight years after initial diagnosis, recurrence occurred in the stomach. She remains disease-free one year following completion of therapy including gross total resection and adjuvant chemotherapy.

Design/Method: Our patient presented with left humerus primary osteosarcoma without evidence of metastasis and was treated per AOST0331 with neoadjuvant and adjuvant MAP chemotherapy. Surgical resection post neoadjuvant therapy noted 95% necrosis and negative margins. First and second pulmonary relapses occurred six years after diagnosis and were managed with pulmonary nodule resection. Integrative tumor/normal DNA/RNA sequencing demonstrated copy number variants and amplification of KIT, KDR, and PDGFRA and TP53 loss of heterozygosity for which she was treated with adjuvant Dasatinib for 18 months. Two months after discontinuation she presented with symptomatic anemia and a gastric fundus mass. Pathology confirmed relapsed osteosarcoma and noted extensive angiolymphatic invasion. Surgical resection with negative

microscopic margins was achieved. Due to the concerns for distant relapse and microvascular pervasiveness, the decision was made to treat with adjuvant chemotherapy, 6 cycles Ifosfamide and Etoposide. Gastric tumor sequencing showed similar gene aberrations to prior report with new homozygous PTEN deletion. She remains disease-free for one year.

Results: A unified consensus on the treatment of multiply relapsed osteosarcoma does not exist outside of surgical resection. Literature review includes modalities of surgery alone, palliative care, and adjuvant chemotherapy. There is a trend to administer chemotherapy to patients who do not achieve surgical remission, however efficacy data on chemotherapy use for >2 relapse remains unclear.

Conclusion: This case highlights a unique GI site of relapse for osteosarcoma, the need for guidance recommendations for multiply relapsed osteosarcoma, and the ability for osteosarcoma to recur late after primary diagnosis.

Poster # 528

B-HCG AS A TUMOR MARKER IN OSTEOSACROMA: A CASE REPORT

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Background: Osteosarcoma is the most common malignant cancer of the bone. Overall survival rates are ~70% and survival rates have not been improving in recent years. There are no standardized tumor markers used to diagnose or guide treatment. When patients fail initial standardized chemotherapy it is a challenge to choose a subsequent regimen. Human chorionic growth hormone (HCG) is a marker of pregnancy, as well as several tumors. There have been documented case reports and series with B-HCG found elevated in osteosarcoma.

Objectives: Single case presentation highlighting a possible biomarker that may help improve the care and outcomes of patients with osteosarcoma.

Design/Method: Case Report of Single Patient

Results: A previously healthy 16 year old girl was diagnosed with localized osteosarcoma of the left distal femur WHO grade 3, initial workup revealed beta human choriogonadotropin (β-HCG) in urine and confirmed on blood test with quantitative value of 866 mIU/mL (normal 0-5). Abdominal ultrasound showed no intrauterine sac and repeat β-HCG levels were stable-findings inconsistent with viable pregnancy. Levels were deemed likely related to osteosarcoma and were followed throughout the treatment course. β-HCG levels resolved during AOST0331 protocol. She underwent limb salvage surgery with negative margins and 65-70% necrosis. 7 months after completing treatment protocol, she began to have recurrence of pain, MRI showed new lesion in left distal femur and repeat β-HCG level was 3582 mIU/mL. High dose ifosfamide was begun, however tumor spread with CT chest showing new pulmonary metastases and β-HCG continuing to rise at 9934 mIU/mL. Left distal femur mass was resected and β-HCG decreased to 5361 mIU/mL. Treatment with denosumab, mifamurtide, methotrexate and doxorubicin commenced,

coupled with amputation of limb, and β-HCG levels peaked during therapy at 14,932 mIU/mL and fell to 749 mIU/mL. Sirolimus was added to regimen and β-HCG continued to fall to 161 mIU/mL with marked improvement on CT chest. She developed severe mucositis and sirolimus was held**.** She was begun on thalidomide and gemcitabine and β-HCG levels continued to rise. Sirolimus was restarted, pazopanib was added and palliative radiation to pulmonary lesions was begun and β-HCG levels continued to rise. She subsequently received cyclophosphamide, etoposide, and carfilzomab without improvement and β-HCG levels continued to rise. She soon passed secondary to respiratory failure.

Conclusion: B-HCG may be a sensitive marker to guide treatment choices in some cases of osteosarcoma.

Poster # 529

A CASE SERIES OF POSITIVE OUTCOMES IN NEONATAL MALIGNANT BRAIN TUMORS

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Background: Outcomes of malignant brain tumors presenting in neonates and early infancy are reported to be very poor. We present a series of 3 infants with brain tumors who were initially recommended palliative care due to their tumors' "aggressive" nature but survived with appropriate management.

Objectives: Highlight the potential curability of malignant brain tumors presenting in the neonatal period.

Design/Method: Case series

Results: Case # 1: A 1-month old girl was diagnosed with a biopsy proven massive glioblastoma of left cerebral cortex after she presented with a rapid increase in head circumference to her pediatrician. Due to her young age and histological diagnosis, she was recommended hospice care. Parents sought a second opinion with us, and she underwent 6 cycles of conventional chemotherapy and complete resection of her tumor at our institution. She remains disease-free, 18 months post completion of her therapy and gaining milestones steadily. Case #2: This newborn girl was found to have hypotonia, feeding difficulty, and seizure activity soon after her normal delivery. MR imaging of the brain showed a diffuse pontine lesion, most compatible with diffuse intrinsic pontine glioma (DIPG). Due to the presumed fatal outcome, she was discharged home on palliative care. She was then referred to us by her pediatrician for evaluation and management. We elected to follow her with surveillance imaging and no therapeutic intervention since these tumors can regress spontaneously over time. Serial imaging has demonstrated improvement of the lesion. She is thriving well, gaining age-appropriate milestones, and is 5 years from diagnosis. Case # 3: A 7-week-old girl was found to have a large right cerebral mass after presenting to the emergency room with irritability, bulging fontanelle, and emesis of a few days' duration. Surgical resection

was complicated by intratumor hemorrhage and seizure activity. A palliative care approach was recommended to the family by the primary team due to a histopathological diagnosis of high-grade glioma. However, following discussion with the neuro-oncology team, the family opted to pursue systemic chemotherapy. She remains disease-free approximately 3 years since the completion of her 6 cycles of systemic chemotherapy.

Conclusion: Our case series highlighting the successful treatment of brain tumors in newborn and young infants, despite their "aggressive" imaging and histological features, underscores the importance of timely consultation and referral to a tertiary care center with the appropriate multidisciplinary expertise for management decisions.

Poster # 530

A RARE CASE OF MODIFYING MEDULLOBLASTOMA THERAPY DUE TO MOLECULAR MARKERS

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Background: Advances in molecular profiling have revolutionized the diagnosis and treatment of Medulloblastoma (MB); a disease once thought of as a single entity which now has many subtypes, four commonly recognized (WNT, SHH, Group 3 and Group 4) and up to 12 possible further classifications. WNT MBs have the most favorable prognosis with greater than 95% overall survival (OS) at 5 years. The majority harbor mutations of CTNNB1, which encodes beta-catenin and are often, but not always associated with monosomy 6. In contrast, Group 3 MBs with Myc-amplification are the most aggressive and portend the worst prognosis, 42-66% OS at 5 years (Doussouki, Future Neurology, 2019). Despite, the differences in survival, heterogeneity exists within these subtypes and reports of patients harboring combined molecular alterations are rising.

Objectives: A case of WNT-activated, Myc-amplified Medulloblastoma

Design/Method: Case report

Results: An 8-year-old previously healthy male presented to Nemours Children's Hospital in Delaware with four weeks of emesis and dizziness. Subsequent Brain MRI revealed a heterogenous, lobulated, avidly enhancing mass centered in the midline of the fourth ventricle measuring up to 4cm. Following gross total resection, pathology was consistent with WNT-activated, classic variant MB, M0, WHO grade 4. WNT-activation was confirmed by positive beta-catenin nuclear staining and CTNNB1 mutation. Chromosomal microarray found no evidence of monosomy 6, but surprisingly was positive for Myc-amplification. No evidence of isochromosomes 17q nor MYCN amplification. Methylation profiling resulted in a non-classifiable score (calibrated score <0.9) but is most consistent with WNT-activated MB (top class score = 0.78). The co-occurrence of WNT-activation and Myc-amplification were verified by three separate labs. All FISH analyses were performed with control probes on adequate cellularity tissue blocks.

Due to the presence of Myc-amplification and the dismal outcome associated, the child was stratified as high-risk and initiated high-dose craniospinal irradiation to 36 Gy with a boost totaling 54 Gy.

Conclusion: The findings of a child with MB that is both WNT-activated and Myc-amplified adds further complexity to the existing molecular classification of MB into four exclusive subtypes. Not only are the genomics of this tumor unusual but they are clinically significant in that they represent distinct and disparate prognoses. In this rare case, we utilized molecular data to modify therapy; a technique routinely implemented for other pediatric malignancies but not standard of care for MB. It is imperative that we harness prognostic information for patient stratification as the heterogeneity of this disease has the propensity to effect overall survival.

Poster # 531

INTRAPARENCHYMAL BRAINSTEM SCHWANNOMAS IN PEDIATRIC PATIENTS: TWO UNUSUAL CASE REPORTS

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Background: A schwannoma is a tumor that originates from the myelin sheath of peripheral nerves. Intracranial schwannomas constitute 8-10% of primary brain tumors with many of these tumors associated with the vestibular nerve. Less than 1% of schwannomas are intraparenchymal with development unrelated to cranial nerves. Four pediatric cases have been previously documented in the English literature. Many developmental and non-developmental theories have been proposed to explain the histogenesis of these tumors; however, their origin is still largely unknown.

Objectives: To present two cases of intraparenchymal brainstem schwannoma both without neurofibromatosis and to discuss the radiographic and pathologic characteristics of the lesions.

Design/Method: We reviewed electronic medical records for two patients with schwannoma (WHO Grade I) at Cook Children's Medical Center for this case series.

Results: An 8-year-old female presented with a history of ataxia, visual impairment, right hemiparesis, and school decline for three months. Magnetic resonance imaging (MRI) revealed a midbrain mass and the patient underwent a posterior fossa craniotomy. The tumor was completely resected. The patient developed secondary hydrocephalus, and later, a right occipital ventriculoperitoneal shunt was internalized. Four years after the resection, the patient had no evidence of residual tumor and remained with spastic hemiparesis, seizure disorder, and the presence of a cerebrospinal fluid drainage problem. The second patient, a previously healthy 15-year-old female, experienced diplopia, and headache for 24 hours. MRI revealed a lesion involving the midbrain and pons. The patient underwent a left subtemporal craniotomy with gross resection of the tumor and a small cyst remained deep in the fourth ventricle. Six months postoperative, MRI showed no evidence of disease recurrence with a stable decompressed cyst; however, she continued to experience ongoing right hemiparesis and neuropathic pain. Her muscle strength and diplopia

gradually improved.

Conclusion: Further investigation is necessary to determine the exact origin of these tumors and to explain their unusual location. Also, considering the rarity of these tumors, they should always be considered during workup. Furthermore, it is important to obtain an intraoperative frozen section to obtain good patient outcomes as gliomas appear similar to schwannomas on MRI and are more likely to be found in the brainstem. Lastly, complete resection is more difficult in the brainstem; therefore, a partial resection and intracapsular decompression also may obtain favorable outcomes.

Poster # 532

SINUSOIDAL OBSTRUCTION SYNDROME (SOS) IN A PATIENT WITH ATYPICAL TERATOID RHABDOID TUMOR (AT/RT)

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Background: SOS is a serious complication of hematopoietic stem cell transplant (HSCT) but can develop outside the setting of HSCT while receiving chemotherapy. Given the degree of morbidity and mortality associated, one must have a low threshold to suspect the diagnosis in order to institute early management.

Objectives: To describe the case of a patient with AT/RT who developed SOS during her second cycle of induction chemotherapy.

Design/Method: Case Report

Results: A 4-month-old female with AT/RT localized to the pineal region tolerated her first cycle of induction according to the Children's Oncology Group (COG) protocol ACNS0333. Nine days into her second cycle, she had symptomatic thrombocytopenia refractory to repeated platelet transfusions. Additional investigations revealed hyperbilirubinemia with a transaminitis. Examination showed weight gain, respiratory distress, edema, and tender hepatomegaly. An urgent ultrasound of the abdomen showed an enlarged liver with phasic portal venous flow.

SOS was diagnosed and ursodeoxycholic acid and a twenty-one-day course of defibrotide were started. She was managed supportively with strict regulation of her fluid balance, correction of coagulopathy, and pain management. Her day 15 vincristine was withheld, and her symptoms resolved with normalization of her labs. Due to severe toxicities associated with induction and absence of residual/recurrent disease on imaging, she proceeded to consolidation with high-dose chemotherapy and stem cell rescue.

SOS in children with malignant brain tumors is rare. Three cases have been described in patients with medulloblastoma. Risk factors considered were craniospinal irradiation, and the use of cyclophosphamide and vincristine, which have been reported in patients with rhabdomyosarcoma. In patients with AT/RT, the incidence of SOS varies with the regimen. The Head Start IV protocol

reported 4 cases in children > 3 years old who received body surface area dosed induction chemotherapy. This led to an amendment to use weight-based chemotherapy in all children < 6 years. COG trials report increased transaminases in the patients receiving high-dose methotrexate but no episodes of SOS. The European rhabdoid registry reported 7.5% of patients developing SOS (did not distinguish central nervous system tumors from other tumors). All but one case occurred following dactinomycin which is known to be associated with HSOS in patients with rhabdomyosarcoma and Wilms tumor.

Conclusion: SOS can occur in patients receiving induction chemotherapy for AT/RT but is dose and regimen-dependent. It is life-threatening and one should have a high index of suspicion in the absence of classic risk factors when unexplained refractory thrombocytopenia presents after chemotherapy.

Poster # 533

ADAPTED TREATMENT PROTOCOL: SYNCHRONOUS ATYPICAL TERATOID/RHABDOID CNS TUMOR AND EXTRA CNS DISEASE

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Background: Atypical teratoid/rhabdoid tumors (AT/RTs) of the central nervous system (CNS) are rare, aggressive, early childhood tumors with unfavorable prognosis. In addition to its aggressive tendencies, malignant rhabdoid tumors (MRTs) of the kidney have also shown similar morphology and a common genetic abnormality-inactivating mutation of SMARC B1/INI-gene.

Objectives: Present the case of a patient with a rare synchronous malignant atypical teratoid/rhabdoid tumor of the CNS and rhabdoid tumor of the kidney responding favorably to an adapted treatment protocol consisting of an intensive chemotherapy and radiation approach.

Design/Method: We report a 22-month-old male who presented at 15 months of age with metastatic AT/RT of the posterior fossa and synchronous malignant rhabdoid tumor of the left kidney. The patient presented with 5-month history of developmental regression and spasticity of the lower extremities.

Results: MRI of the brain demonstrated a large midline posterior fossa mass with heterogeneous signal intensity with associated restricted diffusion and obstructive hydrocephalus. Imaging of the spine showed no evidence of metastatic disease; however a left renal mass was noted incidentally. Ultrasound and Doppler of the kidneys showed an enlarged left kidney with a 4.1 x 3.5 x 3.7 cm heterogeneous solid mass with cystic versus necrotic spaces. Pathology revealed lack of nuclear expression of INI-1. There was strong diffuse expression of vimentin and focal strong expression of cyclin D-1 consistent with MRT of the kidney. No pathogenic or likely pathogenic alterations were identified in the peripheral blood sample, however pathogenic variant was found in the tissue from tumor sample, specifically SMARCB1 homozygous/biallelic deletion.

An external ventriculostomy drain was performed and the patient underwent a subtotal resection of

the posterior fossa tumor and subsequent radical resection of the mass on left kidney stage 1 rhabdoid tumor. He was treated as per ACNS033 protocol with 2 cycles of induction with high-dose methotrexate followed by vincristine, cyclophosphamide, cis-platinum, and etoposide with complete response followed by three tandem stem cell transplants with Thiotepa and Carboplatin for which patient has been tolerating and responding favorably. Focal radiation therapy to the brain and flank area is planned at end of therapy.

Conclusion: We demonstrated a case with a favorable response to current treatment with our intensive combined chemotherapy and radiation therapy modalities. Treatment continues to be challenging given the tumor's rarity and mortality as there are no standardized protocols or randomized controlled trials.

Poster # 534

PRIMARY SPINAL ATYPICAL TERATOID RHABDOID TUMOR: A SINGLE INSTITUTIONAL CASE SERIES

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Background: Atypical Teratoid Rhabdoid Tumors (ATRT) are clinically aggressive central nervous system (CNS) malignancies accounting for 1-2% of all pediatric CNS tumors, but 50% of those in children <1-year-old. Biallelic *SMARCB1* or *SMARCA4* inactivation are the defining ATRT genetic alterations; germline (GL) mutations define *Rhabdoid Tumor Predisposition Syndrome* (RTPS). ATRT primarily occur within the brain. Primary spinal (PS) ATRT is rare. Aggressive multi-modal therapy improves survival in brain ATRT; data regarding PS-ATRT are sparse.

Objectives: To describe the University of Utah/Intermountain Primary Children's Hospital PS-ATRT experience.

Design/Method: In this IRB-approved study, retrospective chart review, tumor histopathology including INI-1 immunohistochemistry, and germline *SMARCB1* genomic analyses were conducted.

Results: From 1989-2021, 5 children were diagnosed with PS-ATRT following presentation with sensorimotor impairment. Mean age at diagnosis was 12.1 years. One of the 4 patients who had germline analysis demonstrated SMARCB1 germline mutation, diagnostic of RTPS.
Case 1: A 9-year-old girl was diagnosed with localized C5-6 PS-ATRT by biopsy. She underwent gross total resection (GTR) then multiagent chemotherapy per AEWS02P1 and focal radiation. She remains alive with no evidence of disease (ANED) 13 years following therapy completion.
Case 2: A 7.5-year-old girl was diagnosed with localized C6-7 PS-ATRT. She underwent GTR, then treatment per ACNS0332A with craniospinal radiation (CSI) and tumor site boost, then 6 courses of cyclophosphamide/cisplatin/vincristine. She remains ANED 4 years following therapy

completion.
Case 3: A 4-year-old girl was diagnosed with localized T2-3 PS-ATRT. She underwent GTR then treatment per ACNS0333 with focal radiation. She remains ANED 6 years following therapy completion.
Case 4: A 20-year-old man with known RTPS was diagnosed with C7-T2 PS-ATRT and regional brachial plexus disease 15 years following successful treatment for a molecularly distinct cerebellar ATRT. He underwent near total resection (NTR), CSI re-radiation with boost to primary and brachial plexus sites, and then 8 courses of cisplatin/ifosphamide/etoposide. He remains in remission 3 months later.
Case 5: A 20-year-old man diagnosed with a C7-T2 PS-ATRT associated with regional brachial plexus disease underwent NTR, then CSI with boost to the primary site. He just completed 6 courses of cyclophosphamide/cisplatin/vincristine per ACNS0332A.

Conclusion: Though limited by small numbers, this series suggests PS-ATRT presents at older age and is associated with a better prognosis compared to published outcomes for children with brain ATRT. CSI with primary site radiation boost likely contributes to this improved outcome. Germline testing for RTPS, with subsequent long-term surveillance when detected, is essential.

Poster # 535

CRANIOPHARYNGIOMA PRESENTING WITH PSYCHIATRIC MANIFESTATIONS IN A PEDIATRIC PATIENT: CASE REPORT

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Background: Craniopharyngiomas are benign, slow growing hypothalamo pituitary tumors that can present with visual, neurological, endocrine and even psychiatric symptoms. In a subset of patients, psychiatric symptoms may be the only manifestation of the tumor upon presentation. Reports of psychiatric presentation of a craniopharyngioma can be found in adults but reports of that in the pediatric population are rare.

Objectives: We report on a pediatric patient with craniopharyngioma identified incidentally after presenting with depression, caloric restriction, and suicidal behavior guided by auditory hallucinations. The patient's acute condition was initially misinterpreted as a primary psychiatric pathology.

Design/Method: Presenting history, psychiatric examinations, imaging, and other data was acquired from the patient's chart at the presenting hospital. Recent literature was examined for similar presenting symptoms of a craniopharyngioma. The search was conducted via PubMed, using the following medical subject headings (MeSH): brain neoplasms, psychotic disorders, psychiatric, suicidal ideation, craniopharyngioma, and anorexia. Article types were limited to case reports in English, and age was restricted to birth to 18 years old.

Results: The patient's psychiatric symptoms abated after the resection of the craniopharyngioma showing a temporal relationship between the tumor and psychiatric manifestations that the patient

presented with. Our literature search demonstrated that pediatric brain tumors, particularly craniopharyngiomas, presenting with psychiatric symptoms are exceedingly rare. Our search identified 5 unique case studies that revealed a similar presentation to that of our patient, however different tumor types were identified once imaging and biopsies were performed.

Conclusion: This case presentation illustrates the importance of taking a detailed history, along with considering structural lesions, especially when a patient in this age group presents with acute behavioral and psychiatric symptoms. Clinical judgment should be used when determining the threshold for ordering a brain scan in pediatric patients.

Poster # 536

MULTIFOCAL AND MULTIPHASIC DEMYELINATING LESIONS AFTER RADIATION FOR EPENDYMOMA

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Background: Both healthy and diseased tissues are exposed to radiation during treatment of brain tumors. This may cause changes in fluid status, myelination and integrity of the blood brain barrier (BBB), therefore altering how peripheral and central immune systems interact. This is hypothesized to perpetuate chronic neuroinflammation as in multiple sclerosis (MS). Rare case reports have described multifocal, multiphasic demyelinating lesions after radiation, the etiology of which is unknown. We report two cases of MS signs and symptoms in children with supratentorial ependymoma.

Objectives: We discuss two pediatric cases of relapsing demyelination in conjunction with radiation for ependymoma, similar to a MS phenotype.

Design/Method: Case series.

Results: Patient 1 is a 6 y/o female diagnosed with a left frontoparietal anaplastic grade III ependymoma. She was treated with near-total resection, experiencing weakness of the RUE and gradual recovery. Patient received adjuvant double scatter proton therapy, with no new neurologic signs. MRI brain/spine was negative for residual neoplasm. Nine months post-radiation, she developed episodes of RUE weakness, numbness, expressive aphasia, ataxia and right sided blurry vision. Clinical events were distinct and relapsing over 7 years, correlating with T2 hyperintensities on MRI. LP showed oligoclonal bands, consistent with MS. She was treated with a course of steroids, leading to resolution of symptoms. The lesions continued to progress, then resolve with subsequent resolution of neurologic symptoms. Patient 2 is a 17 y/o male presenting with episodes of left eye twitching, facial weakness, diplopia and blurry vision. Brain MRI demonstrated a round T2 hyperintense mass in the fourth ventricle as well as multiple patchy T2 hyperintensities in the brain and spinal cord. He was diagnosed with a WHO grade II ependymoma, undergoing gross total resection and double scatter proton therapy. LP showed oligoclonal bands, consistent with MS. Six weeks after radiation, he developed gait imbalance, diminished fine motor skills, dysarthria, flat affect, and inappropriate laugh. MRI showed new T2 hyperintensities outside the

radiation field. He was treated with rituximab and steroids with symptomatic improvement.

Conclusion: Demyelination after radiation for intracranial tumors is a rare phenomenon. Patient 1 presented with demyelination after radiation treatment, where patient 2 presented concurrently. We hypothesise damage to the BBB, whether from characteristics of ependymoma or radiation, creates a dysregulated inflammatory response and subsequent relapsing demyelination. It is yet to be elucidated whether this is due to antigenic mimicry, as indicated in MS or other biochemical process. Further in vivo and in vitro studies are needed.

Poster # 537

EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES: CASE SERIES OF CHILDREN TREATED WITH MULTIMODAL THERAPY

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Background: Embryonal Tumor with Multilayered Rosettes (ETMR) is a rare embryonal central nervous system tumor molecularly characterized by 19 microRNA cluster (C19MC) amplification in most cases. ETMR is most commonly diagnosed in infants and toddlers, thus limiting neuraxis radiation despite the known propensity for leptomeningeal dissemination (LMD). Standard therapy has yet to be defined. Multimodal therapy, including resection, aggressive chemotherapy, and radiotherapy (RT) is occasionally curative, but most children with ETMR will succumb to progressive disease (PD).

Objectives: To describe University of Utah/Intermountain Primary Children’s Hospital ETMR experience.

Design/Method: Retrospective review of patients’ medical records, radiographic imaging, and pathology.

Results: Between 2019-2021, we treated 5 children with localized ETMR at diagnosis.

A 3-year-old boy was diagnosed with non-resectable pontine WHO grade IV ETMR, C19MC+ by biopsy. He was treated on HEADSTART4 but experienced local PD after induction. He underwent focal photon RT. Post-radiation MRI showed stable pontine disease but new LMD. He died 9 months following diagnosis.

A 1.5-year-old girl was diagnosed with non-resectable cervicomedullary WHO grade IV ETMR, C19MC+ by biopsy. She was treated on HEADSTART4, experiencing stable disease (SD) after induction. Following tumor debulking then single high-dose-chemotherapy/stem-cell-rescue (HDC-SCR), MRI showed primary tumor partial response (PR) but new LMD. After craniospinal proton RT, MRI showed primary tumor SD and LMD PR. She continues metronomic chemotherapy and intra-Ommaya topotecan.

A 2.5-year-old boy with cerebellar WHO grade IV ETMR, underwent gross total resection (GTR), then focal proton RT, then temozolomide and intra-Ommaya topotecan/etoposide. He experienced cerebellar recurrence. Despite repeat GTR then modified IRS-III protocol chemotherapy, he experienced local PD then LMD. He died 17 months following diagnosis.

A 2-year-old girl with supratentorial WHO grade IV ETMR, LIN28A+, underwent GTR, then treatment on HEADSTART4, including 3 HDC-SCR, then focal proton RT. She remains disease-free 20 months later.

A 2-year-old girl with supratentorial WHO grade IV ETMR C19MC+ underwent GTR, then chemotherapy per ACNS0334A. She experienced local PD pre-induction course 3, underwent GTR, then HDC-SCR x2 but again experienced local PD. Following GTR then focal proton RT, she remains disease-free 40 months later.

Conclusion: Despite aggressive multimodal therapy, most patients with ETMR experience local relapse, LMD progression, and then death. The only 2 patients in this series amenable to GTR remain disease-free following HDC-SCR and focal RT. Development of molecularly targeted agents will be critical to improving outcomes for children with this challenging malignancy.

Poster # 538

THE ISSUE OF TISSUE: PITUITARY STALK LESION IN 14-YEAR-OLD HIGHLIGHTS NEED FOR HISTOLOGIC DIAGNOSIS

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Background: A 14-year-old female presented with nearly two years of headaches, polyuria, and polydipsia. Extensive laboratory evaluation was only significant for an elevated prolactin and water deprivation test confirming diabetes insipidus. α-Fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) were not elevated in serum nor cerebral spinal fluid (CSF). Magnetic resonance imaging (MRI) of the brain showed thickened infundibulum. Biopsy was declined. A second opinion recommended chemotherapy for treatment of suspected central nervous system (CNS) Langerhans' cell histiocytosis (LCH), which was rejected in favor of close monitoring. Follow-up imaging showed leptomeningeal dissemination, prompting transsphenoidal biopsy which revealed a diagnosis of non-secreting germinoma.

Objectives: To highlight the importance of histological diagnosis prior to establishing a treatment regimen.

Design/Method: Case report developed from patient chart review.

Results: At time of diagnosis, high quality neuroimaging was obtained and was accurate. Unfortunately, neuroimaging is unable to distinguish the exact diagnosis from among a range of pituitary lesions, reinforcing the need for histologic examination of the lesion in confirming diagnosis. While biopsy risks panhypopituitarism, postponing biopsy may lead to delayed

diagnosis and consequences of that, as in this case. This patient had a delay in treatment start time, as well as increased radiation therapy dose and field given her metastases. The delay of tissue diagnosis in this case allowed time for disseminated disease, which required broader radiation to our patient's CNS, associated with long-term neurocognitive complications. In efforts to prevent these complications, early diagnosis through biopsy is crucial.

Conclusion: Pituitary germinomas are both rare and difficult to diagnose, with histologic diagnosis being essential to determine appropriate therapy.

Poster # 539

NOVEL FUSION IN CONGENITAL BRAINSTEM DIFFUSE HIGH-GRADE GLIOMA

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Background: Infant-type hemispheric glioma, previously termed infantile glioblastoma multiforme, is a rare infantile neoplasm with improved survival and distinct molecular features when compared to other pediatric and adult-type high-grade glioma. Infant-type high-grade gliomas are typically located in the cerebral hemispheres and are characterized by *ALK*, *ROS1*, *MET*, and *NTRK* fusions. Typical brainstem gliomas (diffuse midline glioma, H3 K27-altered or diffuse intrinsic pontine glioma) are comparatively rare in this age group. As a result, the biology of brainstem congenital high-grade gliomas is poorly described.

Objectives: To describe a novel fusion and clinical course in a rare infantile brain tumor

Design/Method: RNA sequencing analysis of congenital high-grade glioma, review of patient medical records, and review of literature

Results: A 3 month old female who initially presented with failure to thrive had an apneic event and was found to have an infiltrative mass in the medulla with expansion into the pons and cervical spine on magnetic resonance imaging. She underwent surgical biopsy with pathology revealing diffuse high-grade glioma, WHO grade 4. Next generation sequencing showed no alterations to *H3F3A, IDH,* or fusions involving *BRAF*, *ALK*, *ROS1*, *MET*, or *NTRK*. Whole-transcriptome sequencing revealed a novel fusion of PDGFRB:APOBEC3C. She received chemotherapy with 2 cycles of carboplatin/etoposide and 2 cycles of carboplatin/etoposide/imatinib before having disease progression. She then underwent palliative radiation (35 Gy in 10 fractions) with near complete regression of her disease. Surprisingly, our patient has not had any progression of disease or new lesions now two years from her last therapy.

Conclusion: Congenital high-grade glioma is a rare, unique entity that greatly differs from its adult and childhood counterparts. Recently, pediatric high-grade glioma has been separated into numerous subgroups that differ based upon anatomic and molecular features. There is no World Health Organization category for brainstem infant diffuse high-grade glioma, and its biology is largely unknown. Here, we discuss a previously-unreported fusion of PDGFB:APOBEC3C in a

patient with congenital brainstem diffuse high-grade glioma with a favorable clinical course. This highlights the importance of routine molecular characterization, both to better understand the complex biology of this rare disease and to guide prognosis and clinical decision making for individual patients and families.

Poster # 540

HAPLOIDENTICAL SCT WITH POST TRANSPLANT CYCLOPHOSPHAMIDE FROM A CARRIER DONOR FOR XLP-1 DISEASE

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Background: X-linked lymphoproliferative disease type 1 (XLP1) is a rare primary immunodeficiency disorder caused by pathogenic variants in *SH2D1A*, resulting in SAP protein deficiency that can manifest as hemophagocytic lymphohistiocytosis (HLH). Allogeneic hematopoietic stem cell transplant (HCT) is the only curative therapy, with best results using fully matched donors prior to infection or development of HLH. While it is more frequently used for hematologic malignancies, there is less data on haploidentical transplant in patients with immunodeficiencies. We describe the clinical course of a patient with XLP1 who successfully underwent haploidentical HCT with post-transplant cyclophosphamide, tacrolimus, and mycophenylate mofetil as graft versus host disease (GVHD) prophylaxis.

Objectives: N/A

Design/Method: N/A

Results: The patient was a mixed-ancestry male infant whose older brother was diagnosed with XLP1 after developing EBV-associated HLH. Despite matched sibling donor transplant, the brother died due to a rhinovirus infection. Genetic testing was performed shortly after the patient's birth, which confirmed the familial pathologic *SH2D1A* variant [c.295C>T (p.Q99*)]. At seven months of age, he underwent bone marrow transplant using his 31-year-old haploidentical, ABO matched mother, who was a carrier for XLP1 but clinically healthy. Both mother and patient were CMV IgG positive/PCR negative at the time of transplant. Reduced intensity conditioning regimen with melphalan, thiotepa, and fludarabine were used. He had count recovery on day +14, with molecular chimerism on day +34 showing full donor engraftment. Subsequent results and most recent testing four years post-transplant continued to show full engraftment in both lymphoid and myeloid lines. His transplant was complicated by Grade II acute GVHD responsive to steroids. He was discharged home on day +40. At day +231 he had a flare of skin GVHD that was successfully treated with increase in steroid and pulse cyclophosphamide. He later had onset of intermittent non-erythematous, dry, scaly rash and skin hypopigmentation that required long term immunosuppression. His steroid was discontinued on day +918, his tacrolimus on day +973, and his mycophenylate on day +1400. He has been off all systemic immunosuppression since then, with CD4 and CD19 recovery, post-transplant vaccination, and is now five years old with normal

growth and development.

Conclusion: This report adds to the literature using this transplant approach in pediatric immunodeficiencies. Haploidentical transplant can be especially useful for minority and mixed ancestry patients, where access to fully matched donors is limited, as well as where graft engineering presents technical or economic challenges.

Poster # 541

TISAGENLECLEUCEL FOR RELAPSED B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA IN A PATIENT WITH A CHEK2 MUTATION

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Background: Checkpoint kinase 2 (*CHEK2*) is a tumor suppressor gene. Pathologic germline heterozygous mutations in *CHEK2* (c.1100delC) have been associated with hereditary breast, prostate, kidney, thyroid, and colon cancers. Congenital *CHEK2* inactivation is associated with risk of myelodysplastic syndrome (MDS). However, B-cell acute lymphoblastic leukemia (B-ALL) has never been described as a presenting manifestation. Also, there is no published report of tisagenlecleucel use in patients with *CHEK2* mutation.

Objectives: We present a case of pediatric patient with *CHEK2* mutation who developed B-ALL followed by papillary thyroid carcinoma and was successfully treated with tisagenlecleucel for relapsed B-ALL.

Design/Method: Case report

Results: A 12-year-old boy with a history of hypothyroidism presented with petechiae and hematuria. Labs revealed elevated WBCs and thrombocytopenia. Bone marrow aspirate showed CD19+ blasts suggestive of B-ALL with normal karyotype, but fluorescent in situ hybridization showed 93% positivity for *CRLF2/P2RY8* rearrangement. The patient was treated per COG AALL1131 chemotherapeutic regimen. Seven months following diagnosis of B-ALL, he underwent a total thyroidectomy for a thyroid nodule that was consistent with papillary thyroid carcinoma on fine needle aspiration cytology. Germline genetic testing revealed a pathogenic *CHEK2* mutation (c.1100delC; p.Thr367Merts*15) and additional variants of unclear significance: *CDKN2A* (c.370C>T; p. Arg124Cys), *FLCN* (c.62G>A; p. Cys21Tyr) and *SDHAF2* (c.139A>G; p. Met47Val). His family history was suggestive of hypothyroidism in the fraternal twin who remains cancer free to date, and anaplastic thyroid cancer in the maternal uncle who died due to metastatic disease at 44 years of age. Mother is from El Salvador and father is from Guatemala with no history of consanguinity. Given the risk for solid tumors, whole body magnetic resonance imaging was done which did not reveal any neoplasia. Familial targeted genetic testing revealed the same heterozygous *CHEK2* mutations in biological mother and fraternal twin. Biological father was not available for genetic testing. Fifteen months after initial diagnosis, patient had both bone marrow and central nervous system relapse. He was treated with

tisagenlecleucel alone to avoid hematopoietic cell transplant (HCT). He remains in remission 28 months after treatment, with intermittent appearance of abnormal karyotype with loss of 7q and t(1;19) clones but no abnormal immunophenotypic cells or any evidence of MDS on surveillance bone marrow aspirates.

Conclusion: Tisagenlecleucel should be considered in patients with cancer predisposition syndromes like *CHEK2* mutations described above to avoid HCT in relapsed B-ALL or for post-HCT relapse to avoid second transplant that has significant risk of transplant related mortality in these patients.

Poster # 542

VENETOCLAX AND AZACITIDINE FOR DONOR CELL-DERIVED LEUKEMIA IN A PATIENT WITH FANCONI ANEMIA

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Background: Fanconi anemia (FA) is the most common inherited bone marrow (BM) failure syndrome and involves chromosomal instability and predisposition to malignancy. Hematopoietic stem cell transplantation (HSCT) is considered first-line treatment for BM failure in patients with FA. Due to sensitivity of FA cells to alkylating agents and radiation, pre-conditioning is typically restricted to reduced intensity conditioning (RIC) regimens. Donor-cell derived leukemia (DCL) is a malignant complication of allogeneic HSCT arising from post-engraftment donor cells and has a poor prognosis.

Objectives: The aim is to describe a patient who developed donor derived *NPM1*-mutated myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) after umbilical cord blood transplant (UCBT) for FA and achieved minimal residual disease (MRD) negative remission with venetoclax/azacitidine prior to her second UCBT.

Design/Method: Case report.

Results: The patient was first transplanted at the age of 6 years, presenting with thrombocytopenia resulting in a diagnosis of FA. She underwent 4/6 unrelated UCBT conditioned with cyclophosphamide, fludarabine, total body irradiation, and equine antithymocyte globulin (ATG). Forty-five months post-transplant she developed recurrent thrombocytopenia; BM evaluation showed MDS with 10% myeloblasts and 100% of BM cells demonstrating donor chimerism consistent with DCL. Molecular testing demonstrated *NPM1*, *GATA1*, & *WT1* mutations, suggestive of MDS/AML. A second RIC HSCT without pretransplant therapy was deemed unlikely to be curative. A debulking regimen with low hematopoietic toxicity was preferred given sensitivity of non-hematopoietic FA cells to chemotherapy. She achieved MRD negative remission after one course of venetoclax/azacytidine. The duration of venetoclax was shortened to limit myelosuppressive severity, and the dose was reduced due to concomitant posaconazole prophylaxis. She received a second cycle due to RSV and subdural hematoma resulting in delay of HSCT. She underwent RIC (cyclophosphamide, fludarabine, busulfan, rabbit ATG) and 8/10

unrelated UCBT and remains in remission over 1 year post-transplant.

Conclusion: Recent studies have demonstrated efficacy with venetoclax and azacitidine followed by HSCT in older adults with AML unable to receive intensive chemotherapy and in children with relapsed/refractory AML and high-risk MDS. *NPM1* mutations are predictive of a good response to venetoclax-based regimens in adults with AML. We report a complicated scenario of DCL in a patient with FA who achieved pre-transplant MRD negative remission with limited toxicity with venetoclax and azacitidine. This case suggests that venetoclax/azacitidine is a feasible option for inducing remission prior to HSCT in children with DCL who cannot tolerate intense regimens.

Poster # 543

A MULTI-MODAL APPROACH TO OPTIMIZE COMPLETE RECOVERY IN ZYGOMYCETES OSTEOMYELITIS OF THE HAND

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Background: Primary mucormycosis presents as sinusitis, rhino-cerebral invasive disease, or pulmonary infection. Extra-sinopulmonary sites of infection are typically due to direct inoculation. Neutrophil dysfunction is the most common underlying pathogenic mechanisms. Osteoarticular abnormalities include osteolytic lesions, bone destruction, focal regional lucencies, and increases in radionuclide uptake in 99-technecium bone scans without distinctive radiological characteristics.

Objectives: This case describes an adolescent who, after undergoing mismatched Hematopoietic Stem Cell Transplant (HSCT), developed Mucor osteomyelitis of the right hand requiring an intense treatment regimen with multidisciplinary care.

Design/Method: Case Report.

Results: A 16-year-old female with pre-B cell acute lymphoblastic leukemia (B-cell ALL) underwent consolidative haploidentical HSCT due to relapsed disease and subsequent remission with CAR T-cell therapy. She was started on prophylaxis for Graft versus Host Disease (GVHD) and opportunistic infections. 5 months post HSCT, she complained of deep-seated pain in her right hand and wrist with associated swelling. The plain radiographs were unremarkable and she was treated for cellulitis. MRI was (performed due to lack of improvement) showed marrow edema consistent with osteomyelitis. Operative debridement and excision of necrotic infected bone was performed, and overlying soft tissue abscess was drained. Biopsies of the hamate bone and fourth metacarpal bases showed fungal osteomyelitis with necrosis, and the cultures confirmed mucormycosis. She initially improved, but later worsened with purulence from the surgical wound. Repeat MRI was performed confirming disease progression. Surgical exploration with debridement of necrotic soft tissue was performed. In addition to systemic amphotericin B and Posaconazole, the operative team manufactured and placed amphotericin, vancomycin, and tobramycin cement beads. Bi-weekly debridements with bead exchange were performed for approximately six weeks. At the final surgery, a single amphotericin cement spacer bridging between the hamate and the base

of the fourth metacarpal was placed and the surgical wound was closed primarily. Motor and sensory function was preserved throughout with no further signs of osteomyelitis on follow-up. Follow up CT and MRI scans showed no evidence of infection in other sites.

Conclusion: Osteo-articular mucormycosis is relentlessly progressive, with bone destruction that often necessitates extremity amputation. Mortality remains high especially in immunocompromised patients but recovery is enhanced following resolution of neutropenia and return of T-cell function. However, this case demonstrates that early diagnosis and aggressive anti-fungal therapy with surgical debridement and amphotericin cement bead drug delivery can allow for limb sparing and complete treatment response.

Poster # 544

TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY SUCCESSFULLY TREATED WITH RAVULIZUMAB

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Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is an increasingly recognized complication of hematopoietic stem cell therapy (HSCT) with incidence rates ranging from 10-35%. The predominant mechanism leading to TA-TMA is endothelial cell damage leading to complement dysregulation and microvascular hemolysis. Complement dysregulation is particularly important in the pathophysiology of TA-TMA as initial trials have shown response to complement blockade using eculizumab, a humanized monoclonal antibody targeting the terminal complement pathway. Ravulizumab is a longer acting monoclonal antibody with the same target as eculizumab that is increasingly used for treatment of atypical hemolytic uremic syndrome. Herein, we describe the case of an African American female with relapsed/refractory infantile B-cell acute lymphoblastic leukemia (B-ALL) who underwent 10/10 HLA-matched sibling donor allogeneic transplant (conditioning: busulfan/fludarabine/thiotepa; GVHD prophylaxis: tacrolimus/methotrexate) who developed TA-TMA marked by pericardial effusion, elevated LDH, proteinuria, hypertension, thrombocytopenia, anemia, and evidence of microangiopathy. Upon diagnosis, as ravulizumab was on formulary and readily available unlike eculizumab, she was treated with ravulizumab instead of eculizumab.

Objectives: To describe the therapeutic response to ravulizumab in one patient diagnosed with TA-TMA.

Design/Method: A retrospective chart review was performed regarding this patient's ravulizumab treatment course, and direct discussions were had with the patient's care team.

Results: Ravulizumab (loading dose of 600 mg followed 2 weeks later by maintenance dosing of 600 mg every 4 weeks) was administered. Pre-treatment CH50 was >75 U/mL (range: 30-75 U/mL) with sC5b9 and C3 complement levels at the upper limit of normal at 220 ng/mL (range: ≤244 ng/mL) and 143 mg/dL (range: 72-164 mg/dL), respectively. Clinical normalization of the patient's TA-TMA was achieved two weeks after loading dose administration with normalization

of LDH and blood pressure values, improved proteinuria, decreased transfusion requirements, absence of schistocytes on peripheral smear, and complete resolution of pericardial effusion. A total of 5 maintenance doses of ravulizumab were administered approximately every 4 weeks with CH50 ranging <3-33 U/mL during this time period. Five maintenance doses were administered as the optimal duration was unknown and the patient's TA-TMA treatment course was complicated by COVID-19 infection, for which there was concern could lead to TA-TMA reactivation (which did not occur). The ravulizumab was well tolerated throughout with amoxicillin used for meningococcal prophylaxis.

Conclusion: While studies evaluating ravulizumab for treatment of TA-TMA are ongoing, ravulizumab successfully led to complement blockade and clinical improvement in this patient with TA-TMA.

Poster # 545

SCURVY AFTER ALLOGENEIC STEM CELL TRANSPLANT MIMICKING SKIN GVHD

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Background: The clinical deficiency syndrome of Vitamin C is called scurvy and until recently was thought to be a disease of the past in developed countries. Scurvy commonly presents with follicular hyperkeratosis and perifollicular hemorrhage with petechiae [1]. Rashes are one of the most common complications after hematopoietic stem cell transplant (HSCT) and can be from a variety of causes. In this report, we describe a HSCT patient who presented with a scurvy rash mimicking skin GVHD.

Objectives: Describe an adolescent female who developed scurvy after allogeneic bone marrow transplant.

Design/Method: Case report and literature review.

Results: The patient is a 19-year-old female with relapsed B-cell acute lymphoblastic leukemia who underwent a 10/10 matched unrelated allogeneic bone marrow transplant. Her course was complicated by steroid refractory gastrointestinal acute GVHD (GI-aGVHD) (peak stage 2, grade 3) requiring ruxolitinib and etanercept. Around 175 days post-HSCT, she developed dark pink, folliculo-centric papules on her bilateral upper and lower extremities, bilateral flanks, and abdomen. Punch biopsy showed curved follicles with perifollicular mucinous fibrosis. Her serum ascorbic acid was undetectable confirming the diagnosis of scurvy. She received 1 g of ascorbic acid for 3 days, followed by 500 mg for 1 week and 100 mg daily. After 2 weeks, her ascorbic acid level increased to 0.8 mg/dL (normal range 0.4-2.0 mg/dL) and she had gradual resolution of her rash.

Conclusion: HSCT patients have multiple risk factors for scurvy. Transplant patients tend have prolonged periods of limited PO intake and mucositis. When mucositis is present, these patients

tend to avoid citrus containing foods as these items can exacerbate the pain. A case series identified multiple pediatric and adolescent chronic GVHD patients who developed scurvy due to mucositis pain and poor intake [2]. Iron overload has also been associated with scurvy [3] as ferric deposits can increase the breakdown of ascorbic acid [4]. HSCT patients require frequent blood transfusions and iron overload after transplant is common [5]. Ascorbic acid absorption occurs primarily in the distal small intestine and the impact of GI GVHD, which can cause various nutritional deficiencies, is unknown. Scurvy may represent an underappreciated post-HSCT complication and should be considered in a post-HSCT patient with a rash.

Poster # 546

PURE RED CELL APLASIA AFTER ABO MISMATCHED HSCT SECONDARY TO ANTI-A AND ANTI-B ISOAGGLUTINS

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Background: Pure red cell aplasia (PRCA) after ABO incompatible hematopoietic stem cell transplantation (HSCT) can occur from recipient anti-ABO isoagglutinins targeting donor erythroid precursors, and it is defined as anemia and reticulocytes <1% requiring transfusions of red blood cells past 30-90 days post-HSCT. The diagnosis requires a bone marrow (BM) examination showing normal cellularity except for paucity of erythroid precursors in the absence of viral infections, hemolysis, relapse, or drug adverse effects. The incidence of PRCA in major ABO-incompatible grafts range from 1-50%. Other risk factors include reduced intensity conditioning (RIC), use of Busulfan/Fludarabine, sibling donor, RBC-incompatibility involving donor A antigens and the absence of graft versus host disease (GVHD)

Objectives: Describe a case of PRCA after matched sibling donor (MSD) transplant.

Design/Method: Case report.

Results: A 16-year-old Caucasian female with severe aplastic anemia (SAA) with presenting CBC showing leukocyte count of 1,300/μL, Hb 2.5g/dL, platelets of 7,000/uL and ANC of 320. BM aspirate/biopsy (BMA/BX) showed trilineage hypocellularity (10%) without blasts or abnormal cytogenetics. Evaluation for infectious and genetic causes of SAA were negative. Patient underwent a 12/12 HLA MSD BM HSCT using a RIC of cyclophosphamide (200 mg/kg) and rATG (90mg/kg) with Tacrolimus/Methotrexate for GVHD prophylaxis. Blood type was AB+ for the donor and O- for the recipient, with anti-A and anti-B antibody titers of 64 and 14, respectively. Rh antibody was not detected. Neutrophil engraftment occurred on T+23 with ≥98% donor chimerism. Two months after HSCT, patient remained transfusion dependent with reticulocytopenia (0.1%). BMA/BX performed on T+65 showed 40-50% cellularity with marked erythroid hypoplasia. However, repeat Anti-A and Anti-B titers (T+79), were 16 and 4, suggesting decreased targeting of donor erythroid precursor. Per hospital SOP, she received IVIG on T+86 and immunosuppression was tapered starting on T+93. After 3 weeks, Anti-A and Anti-B titers, 8 and 2, respectively, continued to decrease with increase in reticulocytes to 1.6%. At 3 months, complete

resolution of anemia was seen with a sustained hemoglobin >12g/dL.

Conclusion: We report a pediatric case of PRCA after major ABO-incompatible RIC HSCT secondary to loss of donor erythroid precursors in BM due to recipient anti-ABO isoagglutinins. PRCA may spontaneously resolve, and patients should be supported with PRBC while waiting for recovery. In patients with PRCA>9 months, alloimmunization or iron overload, treatment should be considered. In the case of our patient, immunosuppression tapering allowed resolution of anemia and alloimmunization.

Poster # 547

REFRACTORY B-LYMPHOBLASTIC LYMPHOMA TREATED WITH TISAGENLECLEUCEL FOLLOWED BY STEM CELL TRANSPLANT

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Background: B-lymphoblastic lymphoma (LBL) is a rare, aggressive Non-Hodgkin Lymphoma without established standard of care in relapsed or refractory disease. Patients with B-LBL were not included in the initial anti-CD19 chimeric antigen receptor T (CAR-T) cell therapy trials. Although they have been included in subsequent trials, the outcome measures for this patient population specifically have not been evaluated.

Objectives: To report two cases of relapsed or refractory B-LBL treated with tisagenlecleucel therapy.

Design/Method: Case series

Results: Patient 1, a 21 year old male, initially presented with several days of headache and double vision. His cerebrospinal fluid (CSF) showed 810 WBCs/microliter and 90% CD19+ lymphoblasts, and he had no bone marrow involvement. Brain MRI showed supratentorial dural thickening suggesting a diagnosis of central nervous system (CNS) B-LBL. He was initially treated per Children's Oncology Group (COG) protocol AALL1131. He suffered his first CNS relapse 23 months into therapy and was treated with reinduction per protocol POG9412. A second relapse at 32 months was treated with Capizzi methotrexate and triple intrathecal therapy. His third relapse occurred 6 months later, and disease remained refractory to weekly intrathecal therapy. Brain MRI showed multiple areas of increased T2 signal in bilateral cingulate gyri as well as the corpus callosum leading to referral for CAR T therapy. He received tisagenlecleucel, with course complicated by grade 2 cytokine release syndrome (CRS) and grade 3 neurotoxicity. Brain MRI on Day +30 showed resolution of the above lesions. Bone marrow and CSF revealed no evidence of leukemia. He underwent consolidative hematopoietic cell transplantation (HCT) with ongoing remission 26 months post-HCT.

Patient 2, a 23 year old male, presented with disseminated B-LBL of the skin, CNS, pleura, testes, and bones without bone marrow involvement. The diagnosis was confirmed by presence of CD19+ blasts on skin biopsy. Serial PET scans showed partial response to chemotherapy (per COG protocol AALL1732), with persistence of the cutaneous lesions by positron emission tomography (PET). Due to refractory disease, he was referred for CAR-T therapy. He tolerated treatment with tisagenlecleucel without any toxicity. He had a complete remission based on PET, CSF, and bone marrow evaluations on Day +30. He underwent consolidative HCT and remains in remission based on PET on Day +42 post HCT.

Conclusion: These cases demonstrate excellent response of B-LBL to tisagenlecleucel and contribute to growing evidence that CAR-T is an effective therapy for this rare and aggressive disease, including bulky
and CNS disease.

Poster # 548

BCMA CAR-T AFTER ALLOGENEIC HCT INDUCES REMISSION IN REFRACTORY PLASMABLASTIC LYMPHOMA

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Background: Refractory plasmablastic lymphoma (PBL) confers a dismal prognosis despite aggressive therapies and may express B-cell maturation antigen (BCMA). Ciltacabtagene Autoleucel (cilta-cel), a second-generation chimeric antigen receptor T cell (CAR-T) therapy targeting two BCMA binding domains is efficacious for the treatment of multiple myeloma (NCT03548207*).*

Objectives: Report an adolescent with refractory PBL following B-cell acute lymphoblastic leukemia (B-ALL), treated with cilta-cel.

Design/Method: Case report

Results: A 17-year-old male diagnosed with B-ALL was refractory to induction therapy but achieved complete remission (CR) following CD22 antibody-drug conjugate treatment. He subsequently received humanized CD19 CAR-T therapy but relapsed 60 days later. Reinduction achieved CR of B-ALL, however, a longstanding chest mass worsened, and a new tibial lesion were biopsied and demonstrated PBL. Extensive testing for underlying immunodeficiency was negative. PBL-directed therapy included etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and bortezomib. After resolution of the chest mass, but persistent tibial uptake on

imaging and with B-ALL in CR, he underwent myeloablative total body irradiation-based matched sibling HCT with tibial, brain, lung boosts. He relapsed with PBL 60 days after HCT at the prior tibial disease site and with abundant liver and bony lesions. Immunohistochemistry demonstrated CD138+ and targeted testing showed CD38+ and BCMA variably positive. Despite calcineurin withdrawal, and treatment with etoposide, ibrutinib, and daratumumab, the disease progressed. After regulatory approval, the patient was enrolled on a single patient protocol using cilta-cel. Following apheresis, rapid disease progression led to the addition of lenalidomide to daratumumab and ibrutinib 150 days post HCT resulting in a dramatic reduction in disease burden but also grade III acute graft versus host disease (GVHD). Once GVHD was quiescent with steroids and tacrolimus, the patient began fludarabine and cyclophosphamide conditioning with persistent disease. He then received 0.75 x 10^6 cita-cel CAR+ T cells/kg, 217 days post HCT while on tacrolimus. CAR+ T cells expanded post-infusion peaking on day 15 and were detectable peripherally until day 29. At the time of peak expansion CAR+ T cells CD4/CD8 ratio was 1.2 with CAR+ CD8 T cells mainly effector memory phenotype. The course was uncomplicated, without GVHD, CRS, nor ICANS, though with expected brief neutropenia. The patient remains in CR by imaging and without detection of B cell receptor clones of PBL and B-ALL by next generation sequencing 9 months following cilta-cel.

Conclusion: Our data support consideration of BCMA CAR-T for refractory PBL, which has high mortality, which was well-tolerated and induced a remission in this multiply refractory patient.

Poster # 549

SUCCESSFUL ADMINISTRATION OF CD19 CART IN A CHILD WITH B-ALL AND SEVERE CYANOTIC HEART DISEASE

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Background: One major side effect of CD-19-CART infusion is cytokine release syndrome (CRS), which may be associated with cardiotoxicities. It is not known how patients with cyanotic congenital heart disease (CHD) would tolerate CART therapy.

Objectives: Describe clinical course of a child with trisomy 21, severe cyanotic CHD and B-ALL , treated with CD-19-CART.

Design/Method: Chart review.

Results: A 4.8-years-old girl with trisomy 21 and severe cyanotic CHD was diagnosed with standard risk B-Acute Lymphoblastic Leukemia (B-ALL). She had double outlet right ventricle, hypoplastic left ventricle, large inlet VSD, and large ostium primum ASD. In infancy, she underwent pulmonary artery banding and ligation of the PDA and later right BT shunt. Baseline oxygen saturations were 75-85%; ventricular function was normal.

Initial B-ALL chemotherapy was complicated by multiple intensive care admissions; Bacillus

cereus septicemia and brain abscess; and two episodes of respiratory failure complicating viral illnesses. Complete remission (CR) was reconfirmed at end of chemotherapy.
She relapsed 7.4 years after completion of chemotherapy (14.3-years-old). T-lymphocytes were collected, followed by moderate intensity cytoreductive chemotherapy. She received vincristine 1.5 mg/m2 and non-escalating IV methotrexate 100 mg/m2, with subsequent one-week hospitalization, severe mucositis and severe pancytopenia. Therefore, a second dose of vincristine and reduced dose methotrexate (75 mg/m2) were administered 14 days later. Bone marrow aspiration showed 22 % blasts prompting administration of 14 days of prednisone at a dose of 40 mg/m2/day. This resulted in reduction of lymphoblasts in bone marrow to 4%. She received lymphodepleting chemotherapy with cyclophosphamide 500mg/m2/day IV x2 doses, fludarabine 30mg/m2/day x4, followed by CD19-CART infusion 6 days later. She developed fever, increasing O2 requirement, 10 hours after CD19-CART infusion, one dose of tocilizumab (8mg/kg) was administered preemptively. She subsequently developed grade-3 CRS with hypotension with MAP<60 requiring low dose norepinephrine , therefore received a second dose of tocilizumab 36 hours after CART infusion. Norepinephrine was successfully discontinued 24 hour later. There were no neurologic symptoms. One month later CR was confirmed. She remains in remission 6 months after the infusion of CD19-CART with continued B-cell aplasia.

Conclusion: Successful and safe administration of CD19-CART cells for relapsed B-ALL was possible in a child with trisomy-21 despite cyanotic CHD. This was facilitated by reduction of leukemia burden prior to CD19-CART administration using moderate intensity cytoreductive chemotherapy, followed by standard lymphodepleting chemotherapy. Cytokine release syndrome was successfully managed by prompt and early administration of tocilizumab without added morbidity attributable to her underlying cardiac issues.

Poster # 550

A NEW ERA: TARGETED THERAPY FOR RECURRENT GLOMUS TUMOR

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Background: Glomus tumors (GT) are rare, vascular, benign soft tissue neoplasms that are composed of cells resembling modified smooth muscle originating from glomus bodies. Glomus bodies are specialized forms of arteriovenous anastomosis found in the reticular dermis that serve as thermoregulators. These glomus bodies are highly concentrated in the hands and feet, and thus, GT typically present as solitary lesions in the subungual region but may also occur elsewhere in the skin and soft tissues. Classically, GT are diagnosed with the following triad of symptoms: focal tenderness, spontaneous pain, and temperature sensitivity. Total surgical excision remains the mainstay of treatment. Here, we describe an atypical case of multifocal GT resistant to surgical excision and discuss alternative treatment modalities for recurrent cases in a pediatric patient.

Objectives: The treatment of recurrent GT remains a challenge due to lack of literature supporting alternative options. Management is especially difficult following a series of failed surgical excisions. Our objective is to explore the efficacy of non-surgical targeted-therapy treatment for recurrent GT based upon molecular genetic findings.

Design/Method: Medical records of the patient were reviewed at Cook Children's Medical Center (CCMC) and the case was discussed extensively at CCMC's Molecular Tumor Board to study the molecular profile of GT and identify different treatment options.

Results: Molecular genetic testing of GT in this patient revealed genomic changes in the platelet-derived growth factor receptor gene (PDGFRβ- R561_E563>Q). This gene transcribes platelet-derived growth factor receptor beta (PDGFRβ), which is part of a family of proteins called receptor tyrosine kinases. Accordingly, the patient started Sunitinib, a multi-receptor tyrosine kinase inhibitor which decreases phosphorylation of PDGFRβ and subsequently inhibits proliferation and survivability. Initially, treatment was intermittently held due to side effects of syncope, rash and plantar erythrodysesthesia. Nevertheless, as a result of improvements in pain and size of the tumors, she resumed treatment at a lower dose. Following trials of two dose reductions, she tolerated the medication well with resolution of side effects. The patient continued to note a decrease in the size of her GT, confirmed by imaging and her ability to return to work successfully.

Conclusion: This case highlights the insufficiency in current mainstay treatment options of GT with surgical excision. Our findings emphasize the significance of incorporating molecular genetic testing into the treatment and management of recurrent GT to prevent disease relapse. Further research into alternative gene therapies is warranted.

Poster # 551

RARE CASE OF PEDIATRIC ALL WITH CONCOMITANT SPINAL HEMANGIOMA CAUSING PARAPLEGIA AND PRES

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Background: Patients with leukemia are predisposed to coagulopathy and have an increased risk of bleeding. Depending on the location of bleeding, several comorbidities can develop. Neurological complications such as posterior reversible encephalopathy syndrome (PRES) can be seen during acute leukemia treatment in children, especially during induction. Factors affecting PRES development include cytotoxic chemotherapy, infections, and hypertension. We present a rare case of a 6-year-old male with newly diagnosed B-ALL who developed paraplegia during induction therapy due to a bleeding complication surrounding a previously undiagnosed spinal hemangioma that led to spinal cord compression. His induction was also complicated with PRES.

Objectives: To present a complex case using a retrospective chart analysis illustrating treatment challenges in a patient with coagulopathy, PRES, and spinal cord compression during induction phase of ALL therapy.

Design/Method: Case report. Literature review have been completed.

Results: A previously healthy 6-year-old male, was diagnosed with high- risk B cell ALL. Induction therapy was started with Vincristine, Daunorubicin, and intrathecal Cytarabine. On day 2, the patient started to have prolonged epistaxis and was found to be severely coagulopathic requiring intensive care and multiple transfusions. Two days later, he developed complaints of lower extremity weakness and incontinence. MRI spine showed dorsally located lesions spanning T3-T8 with more prominence at the T5-T6 levels leading to cord compression. Patient started on high dose steroids and underwent emergent laminectomy and spinal cord decompression. Pathology report showed a benign vascular lesion suggestive of hemangioma. He subsequently developed hypertension needing a nicardipine drip. He then developed aphasia and drowsiness. MRI brain findings were suggestive of hypertensive encephalopathy and PRES. EEG was normal, and the patient was started on Keppra prophylaxis. PEG asparaginase was given (10 days late) once the risk of spinal re-bleed was lower, aphasia had improved and blood pressures stabilized. Vincristine was not held despite the risk of neuropathies. His end of induction MRD test was negative. He is currently receiving interim maintenance in addition to physical and occupational therapy. His aphasia and paraplegia continue to improve to this day.

Conclusion: While hematological complications are commonly seen and managed, neurological complications during induction therapy can be challenging to address as they can impact optimal timing for therapies. This can affect achieving remission and thus impacting long term survival. Previous studies have shown the importance of PEG-Asparaginase and Vincristine to achieve complete remission during induction. This is a unique case of neurological and bleeding complications occurring early during induction therapy.

Poster # 552

KAPOSIFORM HEMANGIOENDOTHELIOMA: A CASE SERIES AND LITERATURE REVIEW

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Background: Kaposiform hemangioendothelioma (KHE) is a rare, locally aggressive, vascular tumor that occurs primarily in infancy or early childhood and usually involves superficial and deep soft tissues of the extremities but can also involve the trunk and facial regions or, more rarely, invade the retroperitoneum, mediastinum, and other viscera. Approximately 70% of these tumors present with Kasabach-Merritt phenomenon (KMP), a consumptive coagulopathy characterized by severe, refractory, thrombocytopenia and hypofibrinogenemia, as well as anemia secondary to sequestration of red blood cells in the mass and sometimes microangiopathic hemolytic processes. The diagnosis of KHE is often not straightforward, and requires integration of clinical, radiographic, hematologic, and histologic findings. The variability in presentation leads to an extensive differential diagnosis that includes infantile hemangioma, venous malformation, congenital hemangioma, and Kaposiform lymphangiomatosis, among others. Morbidity and mortality of KHE with KMP is quite high, ranging from 24% to 50% in recent literature. However, despite the high mortality burden, incidence is very low making it difficult to complete clinical

trials. Due to the poorly understood pathophysiology of these masses, the rarity with which they occur, and the heterogeneity in their presentation, management of KHE remains challenging. Complete resection is preferred but often impossible due to the mass's size, degree of infiltration into multiple, surrounding tissues, and extremely high risk of bleeding. As such, medical therapy is the mainstay of treatment, though there are no medications currently FDA-approved for use in KHE and no treatment is wholly effective or without relapse or risk of complications. While steroids, vincristine, and sirolimus have been used both separately and in combination therapy, optimal treatment regimen remains unclear. A guideline for the long-term observation and surveillance of patients with KHE is also lacking. Given the diagnostic challenge and management of this disease process, we present three cases of KHE with KMP, all varied in diagnosis and disease course, with associated literature review.

Objectives: To highlight variability and complexity of presentation of KHE

Design/Method: Retrospective chart review for a case series

Results: These three patients presented with a mean age of 4.5 months and mean platelet level at presentation of 8,000. Case 1 presented with a rib fracture, thyroid hemorrhage, and hemothorax, Case 2 presented with severe, necrotizing pancreatitis, and Case 3 presented shortly after birth with an axillary mass.

Conclusion: This case series highlights the variability and complexity of presentation of KHE that can often lead to prolonged work-up and subsequent delay in diagnosis and treatment.

Poster # 553

NOVEL ZAP70 MUTATION CAUSING IMMUNODEFICIENCY TREATED WITH HEMATOPOIETIC STEM CELL TRANSPLANT

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Background: Zeta-Chain Associated Protein Kinase 70 kDa (ZAP70) combined immunodeficiency (CID) is an autosomal recessive severe immunodeficiency characterized by abnormal T-cell receptor signaling. ZAP70 deficiency is characterized by low/absent CD8+ T cells with normal/elevated numbers of non-functional CD4+ T cells. Children with the disorder typically present during the first year of life with diarrhea, failure to thrive, recurrent bacterial, viral or opportunistic infections. The only potential cure is hematopoietic stem cell transplant (HSCT).

Objectives: Describes an infant with ZAP70 deficiency resulting from previously undescribed mutations treated successfully with hematopoietic stem cell transplant.

Design/Method: The case was reviewed and described by chart review.

Results: worsening respiratory distress. She developed acute respiratory failure requiring mechanical ventilation. BAL was performed and cultures grew *Pneumocystis jiroveci (PJP)* on silver stain.

Evaluation for an underlying immunodeficiency was notable for normal number of TRECs, negative HIV test, down-trending ALC, elevated CD4+, decreased CD8+, and normal NK/CD19+ absolute cell counts. She had minimal T mitogen response to PHA and PWM on 2 evaluations and a skewed CD45 RA/RO ratio. Genetic testing revealed heterozygous variants of unknown significance in the ZAP70 gene (c.109C>G p.Arg37Gly and c.1519G>A pAla507Thr), neither of which had been previously reported. ZAP70 flow cytometry revealed no ZAP70 expression in either T- or NK- cell populations.

There were no potential unrelated HSCT donors, though her father was confirmed to be a haploidentical match. A RIC regimen with alpha/beta T cell depletion was used, and included anti-thymoglobulin, thiotepa, methylprednisolone, busulfan (targeted cumulative busulfan exposure cAUC 60 mg*hr/L) and fludarabine (targeted cumulative fludarabine exposure cAUC 18 mg*hr/L) as conditioning agents.

She tolerated conditioning without event with neutrophil engraftment on day+13. On day+16 she developed laboratory findings and clinical changes consistent with sinusoidal obstructive syndrome (CTCAE Grade 3). She received defibrotide for a 21-day course with improvement. The remainder of her course was unremarkable and she was discharged on day+44. Repeat ZAP70 flow cytometry on day+85 showed recovered expression in both T- and NK- cell populations.

Conclusion: To our knowledge, this is the first case to describe a novel compound heterozygote mutation involving the SH2 and kinase domains in the ZAP70 protein causing disease treated successfully with stem cell transplantation. Our case exemplifies the need for ongoing description of mutagenic events that lead to immunodeficiencies, but also the use of emerging treatment techniques due to the limited HSCT donor options for some of our most vulnerable and demographically underrepresented patients.

Poster # 554

TAFRO SYNDROME: A RARE VARIANT OF MULTICENTRIC CASTLEMAN DISEASE IN A 15-YEAR-OLD FEMALE

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Background: Castleman Disease (CD) is the umbrella diagnosis to four disorders that are characterized by lymph node involvement with unique histopathological features, resulting in a spectrum of clinical manifestations. This case report will present a case of iMCD-TAFRO, known as Idiopathic Multicentric Castleman Disease - Thrombocytopenia, Ascites, reticulin Fibrosis, Renal dysfunction, Organomegaly.

Objectives: The goal of this report is to highlight the unusual presentation of this disease, effectiveness of IL-6 inhibitors, and management of organ dysfunction specifically in the TAFRO subtype of iMCD.

Design/Method: A 15-year-old female presented with a month-long course of recurrent episodes of abdominal pain, emesis, fatigue, and headaches. Initial workup significant for ESR >120, elevated CRP, thrombocytopenia, and iron studies suggestive of anemia of chronic inflammation. CT Abdomen Pelvis revealed generalized lymphadenopathy. Lymph node biopsy revealed morphological and immunophenotypic findings most consistent with iMCD. Bone marrow aspiration and biopsy revealed no evidence of malignancy or HHV-8 staining and presence of bone marrow fibrosis. At the same time, this patient's presentation was complicated by hypoalbuminemia, diffuse anasarca, and acute kidney injury. CT, biopsy, and labs fulfilled sufficient criteria to make the diagnosis of the TAFRO clinical subtype.

Results: After recognition of the patient's iMCD-TAFRO flare, high dose IV corticosteroids and an IL-6 inhibitor, siltuximab, were started. The steroids and IL-6 inhibition, paired with close fluid and lymphedema management, improved the patient's AKI, anasarca, and systemic inflammatory symptoms. The renal involvement was particularly interesting in that it was a pre-renal AKI due to impairment of lymphatic drainage. Giving fluids would have only been a detriment. Instead, a strict salt and fluid restriction was put in place, along with albumin and subsequent lasix infusions, and physical therapy to manage the lymphedema. Due to the aggressive nature of the disease, she continues to receive steroid and IL-6 inhibitor therapy.

Conclusion: Idiopathic MCD - TAFRO is a difficult but important diagnosis to make due to its multi-organ involvement and aggressive clinical course. The index of suspicion for MCD should remain high for patients for whom rheumatologic processes are suspected. While this disease has significant lymph node involvement, it should be noted that this patient's lymphadenopathy only became apparent with imaging; her unusual presentation made it so her physical exam did not immediately reflect lymph node abnormalities. Additionally, given her success with our treatment methods, IL-inhibition remains a mainstay in treatment of MCD, but the TAFRO variant requires further attention to organ dysfunction management.

Poster # 555

CEREBRAL VENOUS SINUS THROMBOSIS AS A RARE COMPLICATION OF ACUTE PEDIATRIC COVID-19

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Background: A previously healthy 13-year-old male was admitted to the hospital for a bacterial superinfection in the setting of recent COVID-19, including orbital cellulitis and pansinusitis with subgaleal, epidural, and subdural empyema. Further workup identified an occult, non-occlusive cerebral venous sinus thrombosis (CVST) along the length of the superior sagittal sinus.

Objectives: To evaluate the reported cases of CVST as a potential complication of COVID-19 in the pediatric population and identify meaningful trends in demographics, presentation, and diagnostic course.

Design/Method: A literature search was run with various combinations of the following terms, always including "COVID": "pediatric," "adolescent," "CVST," "cerebral venous sinus thrombosis," and "sinus thrombosis." Articles were individually reviewed to identify specific cases.

Results: Six cases were identified, five from the literature in addition to the case from the presenting institution. Notably, four cases were published individually, one as the only pediatric patient in a small case series on CVST in COVID, and one as part of a retrospective cohort study of thrombosis in children with COVID-19 or MIS-C.

Four patients were previously healthy, one had cancer, and the other had tuberculosis meningitis. Patients ranged in age from 2-17; five of the patients were at least 12 years old, and the two-year-old was the patient with tuberculosis. Four of the six were males. Five patients had identified timelines of COVID symptoms; one patient had asymptomatic COVID, while the other four presented for medical care between 3-16 days after initial COVID symptoms.

Five of the patients had identified presenting symptoms, which most commonly included altered mental status, headache, papilledema, and emesis. Notably, the patient at our institution was not suspected of having symptoms of CVST, with episodes of emesis initially attributed to pain from his cellulitis. These same five patients had identified imaging modalities and timelines; four of the five were identified using MRA/MRV, and four were identified on initial presentation, with our patient having a three-day lag from presentation to diagnosis.

All patients were treated with anticoagulants. One patient had an identified major bleeding event from this treatment.

Conclusion: These cases highlight the importance of consideration of CVST as a potential late sequalae of COVID-19 infection in the pediatric population. They remind clinicians to consider the heightened risk of serious thrombotic complications in the immediate post-COVID period and to have a low threshold for vascular imaging in these children.

Poster # 556

PULMONARY EMBOLISM IN A 4-YEAR-OLD SICKLE CELL PATIENT WITH ACUTE CHEST SYNDROME AND COVID-19.

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Background: Sickle Cell Disease (SCD) and Covid 19 infection both are associated with prothrombotic states that increase the risk of venous thromboembolism (VTE) and may be

associated with high levels of D-dimer and other inflammatory markers. Pulmonary embolism (PE) signs and symptoms overlap with acute chest syndrome (ACS) in SCD.

Objectives: Describes the presentation of a pediatric sickle patient with PE and ACS in the setting of COVID 19 related illnesses including multisystem inflammatory syndrome in children (MIS-C).

Design/Method: Case Report

Results: We describe a case of a 4-year-old female with SCD and ACS due to Covid 19 developing PE. She initially presented to the emergency department (ED) with dyspnea, chest pain, fever, and hypoxia. She was diagnosed with ACS due to Covid 19. Her inflammatory markers including D-dimer were elevated. She was started on oxygen, and antibiotics were given for ACS. Prophylactic anticoagulation and oral steroids were started per hospital guidelines for MIS-C. She improved clinically, but her inflammatory markers remained persistently high on discharge. She was sent home on antibiotics, an oral steroid wean, and her anticoagulation was stopped. Ten days later she re-presented with increasing respiratory distress and fever to the ED. Chest X-ray showed worsening pulmonary infiltrates and her inflammatory markers including D dimers continued to be elevated. Due to these reasons and in the setting of a COVID-related illness, PE was suspected. A CTA was done which confirmed the diagnosis of PE. She was admitted to the pediatric intensive care unit and started on an Unfractionated heparin (UFH) drip. She was successfully transitioned to Lovenox after 2 days of UFH and completed 3 months of treatment for her PE. She was able to be discharged home on the Lovenox as her symptoms resolved and her inflammatory markers were also significantly improved. Two weeks after discharge, repeat labs including her D dimer were back to normal.

Conclusion: This case highlights the need for a low index of suspicion to screen for a PE in a sickle cell patient presenting with Covid pneumonia/MIS-C versus ACS and worsening hypoxia. It also highlights the importance of early initiation of anticoagulation in sickle cell patients with covid related illnesses especially those with persistently elevated inflammatory markers. Lastly to this author's knowledge, our case is the first case of a pediatric sickle cell patient less than 12 years of age presenting with a PE in the setting of a COVID-related illness.

Poster # 557

APLASTIC ANEMIA FOLLOWING COVID-19 INDUCED HEPATITIS: A CASE REPORT

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Background: Pediatric patients who become infected with coronavirus disease-2019 (COVID-19) may develop a range of symptoms, from asymptomatic to severe respiratory disease to postinfectious multisystem inflammatory disease (MIS-C). Additionally, there has been a case report published regarding two cases where SARS-CoV-2 infection has been coincident with newly diagnosed severe aplastic anemia and required immunotherapy for treatment.[1] We present a case in which a patient with initial COVID-19 infection and hepatitis, who developed aplastic anemia and

recovered with supportive care alone.

Objectives: We report a case of a patient who experienced aplastic anemia following an COVID-19 infection.

Design/Method: This study is a case report highlighting a unique presentation of aplastic anemia following COVID-19 infection.

Results: We report a 4-year-old previously healthy male who initially presented with jaundice and found to have severe hepatitis with unremarkable complete blood count. Workup for infectious, metabolic (alpha-1 antitrypsin, Wilson's disease) and autoimmune hepatitis was largely negative, with exception of COVID-19 PCR positivity. His liver biopsy showed severe inflammation with apoptotic cells and minimal cholestasis and no biliary pathology. His transaminitis improved with two-month course of prednisone, however, two weeks after completing steroid course he developed pancytopenia. His absolute neutrophil count was 600/ul, absolute lymphocyte count was 600/ul, his hemoglobin was 8.3 g/dl and platelets were 29,000/ul. He underwent a bone marrow biopsy which confirmed moderate aplastic anemia with 30% cellularity, without evidence of malignancy or dysplastic changes and normal cytogenetics. Telomere studies at time of diagnosis showed concern for short telomere syndrome as he had low B-cell and NK cell telomere length and very low telomere length in granulocyte and t-cell lineages. Supportive care was given for six months without transfusions and he showed gradual count recovery in all three cell lines. Repeat marrow at this time is stable with 30% cellularity and no abnormalities, however, telomere studies improved and do not reflect diagnosis of a short telomere syndrome.

Conclusion: Aplastic anemia has been associated with viral infections, hepatitis, toxins, and short telomere syndrome. COVID-19 is a viral infection that has been associated with short telomeres, though no causation or clear pathogenesis of this finding has been shown at this time. Further studies will be needed to determine whether aplastic anemia could be a direct result of infection with COVID-19 or secondary to hepatitis that develops due to COVID. Further research should also evaluate if COVID-19 infection causes transient telomere length shortening.
[1](Chakravarthy, Pediatric Blood Cancer, 2021)

Poster # 558

SEVERE APLASTIC ANEMIA IN AN ADOLESCENT PATIENT WITH COVID-19-ASSOCIATED MIS-C

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Background: COVID-19 complicated by multisystem inflammatory syndrome in children (MIS-C) is known to be associated with multisystem organ involvement along with hematological complications. This syndrome has similarities to Kawasaki disease, hemophagocytic lymphohistiocytosis and toxic shock syndrome, with notable hematological findings of thrombocytopenia, lymphopenia with neutrophilic leukocytosis, and coagulopathy.

Objectives: Previous literature has shown pancytopenia as a known complication of MIS-C. However, there is only one case report of severe pancytopenia in an infant. The aim of this case report is to describe the course and management of aplastic anemia in an adolescent patient with MIS-C.

Design/Method: Case Report

Results: A previously healthy 15 year-old male with past medical history of anxiety and asthma presented with 4 days of fever (38.9-39.4°C), cough, sore throat, tremors, and fatigue in the setting of known sick contacts. He tested positive for SARS-CoV-2 by NAAT/PCR (nasopharynx). Physical exam revealed petechiae on left neck. Labs were significant for absolute neutrophil count 0.884 x 10*3/mcL, platelets 12 10*3/mcL, and absolute reticulocyte count 0.016*6/mcL, meeting criteria for aplastic anemia. Inflammatory markers were elevated, including CRP (0.6 mg/dL), D-Dimer (1.94 mcg/mL), fibrinogen (569 mg/dL), ferritin (519.6). Lactate dehydrogenase was normal (190 U/L). Peripheral smear showed macrocytic anemia with leukopenia and marked thrombocytopenia. B troponins and echocardiogram were normal. IVIG and methylprednisolone were initiated. The patient continued to have epistaxis; aminocaproic acid and oxymetazoline were added to treatment regimen. Cell counts remained low, necessitating 1 unit platelet transfusion and bone marrow aspirate biopsy for further assessment. Biopsy revealed hypocellular bone marrow with 10% cellularity, but no dysplastic features in the bone marrow precursors. Flow cytometry showed normal T and B cell populations. Chromosome analysis by FISH showed normal 46, XY karyotype with no translocations. Next generation sequencing revealed PIGA c.524T>C, p.leu175Pro, a variant of unknown significance with 5.3% variant frequency. There is no evidence of Ph-like or PML-RARa translocation.

The patient's symptoms improved but he persisted to have fatigue and minimal epistaxis. Platelets improved (33 10*3/mcL) post-transfusion, but other cell counts remained unchanged. He was discharged from the hospital but returned 9 days later due to continual fatigue and bruising. He was thrombocytopenic (8 10*3/mcL) and received one more unit of platelets, improving platelet count to 46 10*3/mcL. He was discharged with close follow up.

Conclusion: In conclusion, this case describes severe, persistent aplastic anemia as a novel complication of COVID-19 associated MIS-C. The pathogenesis of this presentation is not yet fully elucidated.

Poster # 559

DON'T "MIS-C" THE CANCER: A CASE REPORT OF INCIDENTALLY DIAGNOSED WILMS TUMOR DURING ACUTE MIS-C

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Background: Incidental diagnosis of malignancy during unrelated illness is challenging, both for diagnostic clarity and therapeutic decision-making. There are reported cases of incidental discovery of Wilms tumor (WT) in the setting of trauma, but there are none reported in the setting of acute

inflammatory illness, such as Multisystem Inflammatory Syndrome in Children (MIS-C), and thus no guidance regarding timing of definitive therapy.

Objectives: We describe a patient with MIS-C and incidentally diagnosed WT in order to inform the management of future patients with simultaneously diagnosed malignancy and acute inflammatory illness.

Design/Method: Information was obtained by retrospective review of the electronic health record.

Results: A healthy 5-year-old female presented with six days of fever, cervical lymphadenopathy, urinary symptoms, and rash. Labs showed acute kidney injury, prompting imaging that revealed a left-sided renal mass, most likely a WT.

The constellation of signs and symptoms was initially suggestive of obstructive uropathy resulting in urinary tract infection. However, subsequent development of conjunctivitis and oral mucosal changes, positive SARS-CoV-2 nucleocapsid antibodies, rising inflammatory markers, and mild-moderate coronary artery dilation on echocardiogram, made MIS-C the most fitting diagnosis.

The patient rapidly improved after initiation of aspirin, methylprednisolone, and intravenous immunoglobulin. Cross-sectional imaging showed no metastatic disease or local tumor invasion. A multidisciplinary team of pediatric subspecialists discussed appropriate timing for upfront resection and decided to defer surgery for at least two weeks while inflammation resolved.

Unfortunately, the patient continued to have ongoing inflammation requiring a prolonged steroid course, and surgery was ultimately deferred until one month following diagnosis. Surgery was uncomplicated and pathology demonstrated stage II favorable histology WT. Chemotherapy began on post-operative day 9.

Conclusion: The lack of published cases of malignancy incidentally discovered during acute illness, coupled with the rapidly rising rate of pediatric cases of COVID-19 and MIS-C, present a challenge for clinicians who must treat the concurrent conditions. This report highlights the complexities of managing a WT for which upfront resection is standard in the United States. Surgery is typically performed quickly due to the fast-growing nature and risk of rupture. Reports of paraneoplastic inflammatory syndromes (non-WT) suggest that tumor resection in the setting of acute inflammation is safe, but pediatric data remains scarce. This patient's multidisciplinary team chose to delay tumor resection given the potential morbidity of major surgery in the setting of a raging inflammatory state. The patient had a favorable clinical outcome both in terms of her MIS-C and WT.

Poster # 560

COVID-19 INFECTION INCREASES THE RISK OF HYPERCOAGULABILITY IN INDIVIDUALS WITH MTHFR GENE MUTATION

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Background: COVID-19's clinical spectrum ranges from asymptomatic to severe illnesses. In addition, several complications such as venous thromboembolism have been reported. Methylenetetrahydrofolate Reductase (MTHFR) enzyme plays an essential role in converting homocysteine to methionine. However, genetic variation in the MTHFR gene impairs enzyme function, possibly increasing hypercoagulability.

Objectives: To report the associated risk of hypercoagulability in individuals with MTHFR gene mutation due to COVID-19 infection.

Design/Method: A case series of 3 patients admitted to our institution between 03/03/2021 and 08/20/2021 to manage venous thromboembolism. The patient's charts were reviewed. History, basic work-up (complete blood count, comprehensive metabolic panel, D-dimer, PT/INR/PTT, and COVID serology), and extended work-up for various congenital/ acquired causes of hypercoagulable states (MTHFR gene mutation, factor V Leiden mutation, Prothrombin II mutation, antiphospholipid panel, protein C level, protein S level, and antithrombin 3 levels) were reviewed.

Results: Three previously healthy females, 15-17 years old, were referred to manage different spontaneous Thromboembolic diseases like pulmonary emboli/ superior mesenteric vein clots. Risk factors include: two patients were on oral contraceptive pills (OCPs) for about six months prior to presentation; two had an extensive family history of clots; whereas all three patients had COVID-19 infection as evident by positive COVID-19 IgG. Thrombophilia work-up showed a mutation in the MTHFR gene in all patients (one showed a C677T heterozygous mutation, the second patient a C677T heterozygous & A1289C heterozygous mutation, and the third a C677T homozygous mutation); however, interestingly, homocysteine levels were normal in all patients. Only one patient also showed G-20210-A heterozygous prothrombin II mutation. All patients were treated with subcutaneous Enoxaparin @1mg/kg/dose BID with a target dose level of 0.6-1, significant improvements were noted in all three cases, and were discharged with six weeks of Enoxaparin.

Conclusion: Previously healthy young females presented with unprovoked clots had underlying MTHFR gene mutation and COVID-19 infection. Despite having MTHFR gene mutations, no hyperhomocysteinemia was noted, thus raising concern for a possible association between COVID-19 infection and increased risk of hypercoagulability in individuals with MTHFR gene mutation. Therefore, more research is needed to study further the impact of COVID-19 and/or post COVID-19 infections in an individual with MTHFR gene mutations with normal homocysteine levels on getting Venous Thromboembolic phenomena.

Poster # 561

A CASE OF EVALI PRESENTING WITH COAGULOPATHY IN THE SETTING OF A RECENT COVID-19 INFECTION

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Background: Electronic-cigarette or vaping product use–associated lung injury (EVALI) and COVID-19 are both relatively new diagnoses. The symptoms and lab abnormalities associated with EVALI and COVID-19 overlap. Both can present with shortness of breath (SOB), cough, nausea, vomiting, abdominal pain and fever; both can lead to a coagulopathy, with different causes and approaches for each.

Objectives: We present the unique case of a patient with respiratory symptoms and coagulopathy, diagnosed with EVALI in the setting of a recent COVID-19 exposure.

Design/Method: Case report.

Results: A twenty y.o. presented to the emergency room (ER) with 5 days of fever, worsening cough, SOB, and chest pain worsened with inspiration. The patient's father died from COVID-19-related complications 1 month prior. Patient vaped with THC and nicotine-related products with recent increased frequency.
In the ER, he was tachycardic, hypoxic (oxygen saturation 90%, improved to 96% on 2L oxygen via nasal cannula), and hypertensive. Chest x-ray showed a left lower lung field opacity consistent with pneumonia; he was treated with ceftriaxone. He reported a recent positive COVID-19 PCR, but COVID-19 PCR was negative in the ER. He was found to have COVID-19 IgG antibodies (65.80 AU/mL, [positive > 15 AU/mL]).

Chest CT angiogram showed bilateral lower lobe predominant, consolidative, and ground glass opacities with areas of subpleural sparing, consistent with vaping-associated injury. He was started on Methylprednisolone 1mg/kg IV q12h and completed 2 days of IV treatment inpatient. SOB improved within hours of starting steroids and he defervesced.

Prothrombin time (PT) was elevated at 20.90 sec (normal range 9.95-12.87), INR 1.82 (0.65 - 1.30), activated partial thromboplastin time was normal. Patient was initially started on enoxaparin prophylaxis due to concerns of COVID-19 or MIS-C related thrombotic complications. Repeat PT and INR trended up to 26.9 sec and 2.34 respectively, which prompted a hematology consultation. Factor II and VII activity levels were decreased per reference range at 67% and 27%, respectively. Vitamin K level was low (<0.13ng/mL [normal 0.13- 1.88 ng/dL]).

On follow-up 2 weeks after discharge, he was asymptomatic without respiratory distress or fevers, he reported no further vaping, and PT/INR normalized.

Conclusion: Understanding of COVID-9-associated coagulopathy and thrombosis has evolved. Coagulopathy associated with vaping has also been described; vitamin E acetate, as an additive to THC-containing e-cigarette, can lead to antagonism of Vitamin K. It is important to keep EVALI on the differential diagnosis given appropriate history, even when COVID-19 related disease is a primary
concern.

Poster # 562

FRACTURE OF A PORT-A-CATH LEADING TO EMBOLIZATION INTO THE RIGHT PULMONARY ARTERY: A CASE REPORT

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Background: Dislodgement and embolization of a fractured Port-A-Cath is a rare but potentially life-threatening consequence of pediatric oncology patients. A Port-A-Cath is a commonly used central venous catheter used for long-term chemotherapy treatment but also for the sampling of blood and total parenteral nutrition. Infrequently, these catheters can fracture and become displaced which necessitates surgical removal and replacement. In children, rates of dislodgement and fracture happen in between 1.4% to 3.6% of patients according to previous reviews.

Objectives: We describe a case of a 6-year-old male with precursor B-cell acute lymphoblastic leukemia with an asymptomatic fracture of a Port-A-Cath leading to embolization into the right pulmonary artery.

Design/Method: Case Report

Results: A 6-year-old male with precursor B-cell acute lymphoblastic leukemia presented to the hematology/oncology service for scheduled chemotherapy. However, after two attempts to flush the port, extravasation into the subcutaneous tissue was noted and there was a concern for misalignment of the Port-A-Cath. The patient has had no recent history of trauma and has been asymptomatic leading up to this chemotherapy session. Failure of chemotherapeutic injection warranted further investigation. Chest x-ray with contrast showed a mispositioned fractured left chest Mediport with the long segment of the tubing migrated to the location of the inferior right pulmonary artery. Follow-up CT of the chest without contrast confirmed the location of the fractured segment, the shunt tube overlying the right pulmonary artery as well as edematous changes within the soft tissues adjacent to the port chamber along the left anterior chest wall.

Interventional radiology successfully removed the migrated fractured catheter from the right pulmonary artery and left anterior chest wall. The Port-A-Cath was also removed during the procedure without complications. There were no subacute postoperative issues. He subsequently returned for insertion of a new Port-A-Cath on the following week which was achieved. Follow-up CXR showed the line in excellent positioning with the tip at the junction of the superior vena cava and the right atrium with a normal smooth course and no pneumothorax.

He was successfully able to resume treatment and was discharged on an adjusted chemotherapeutic schedule.

Conclusion: This case report highlights a rare albeit important complication in a pediatric patient with long-term port-a-catheter usage. Although catheters may have been placed correctly with proper postoperative care, it is important a careful radiographic examination given that patients with dislodged catheters may present with no symptoms or history of trauma.

PTCTC Abstracts

1) Hospital Readmissions Following Pediatric Allogeneic Stem Cell Transplantation
Theme: Allogeneic HSCT

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Background:
Advances in therapeutic and supportive care strategies for hematopoietic stem cell transplant (SCT) have increased survival rates for pediatric patients with advanced, recurrent, or refractory malignancies, and some non-malignant diseases. Safer, more effective preparative regimens with expanded donor source options help balance toxicity with efficacy and minimize transplant-related morbidity and mortality. However, there remains a paucity of data on hospital readmissions for transplant and disease-related complications beyond the first 100 to 180 days post-transplant.

Objective:
Ascertain the rate of hospital readmissions and evaluate associated risk factors in the first year following pediatric allogeneic SCT.

Design/Methods:
All patients who received a first allogeneic SCT between 2008 and 2020 and survived to initial hospital discharge were identified using the Pediatric Health Information System (PHIS) administrative database using encounter-level ICD-9/10 and APR-DRG codes. Information was collected on all hospital readmissions within one year of the initial SCT discharge. The Kaplan-Meier method was used to assess freedom from readmission, and a multivariable Cox proportional hazard model identified independent risk factors for hospital readmission.

Results:
A total of 7025 patients were identified for inclusion. During the first year following transplant, 71% of patients (N =5005) required at least one readmission. The median time to first readmission was 50 days. There was an average of 3 readmissions per patient, for a total of 15,057 readmission encounters. The median readmission length of stay was 4 days (interquartile range 2-10 days). Common diagnoses associated with readmssion included infection (N=8978; 60%) and graft-versus-host disease (GVHD) (N=5670; 33.3%). Intensive care unit (ICU) care was required for 15% of re-admissions (N=2253). In a multivariate model, factors (assessed at the time of the initial SCT encounter) independently associated with readmission included GVHD (Hazard Ratio [HR] 1.27; 95% Confidence Interval [CI] [1.17, 1.38]; p-value <0.001), infection (HR 1.15; CI [1.08, 1.22]; p-value <0.001), and age <1 year (HR 1.12; CI [1.01, 1.24]; p-value 0.039).

Conclusion:
While SCT has become safer and more effective, patients continue to require hospitalization for treatment related complications. In this cohort, most patients required at least one admission during the first year following transplant. Notably, infection, GVHD, and age were significantly associated with risk of early readmissions. Further analysis is ongoing to determine how risk factors for readmission change with ongoing time from transplant as well as understanding the impact of acute versus chronic GVHD and type of infection.

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2) Reduction in neutrophil extracellular traps may contribute to the effect of abatacept on clinical outcomes in pediatric patients undergoing allogeneic hematopoietic stem cell transplant.

Theme: Allogeneic HSCT

Authors: Azada Ibrahimova MD, Nathan Luebbering MS, Lauren Strecker BS, Sheyar Abdullah BS, Jane Koo MD, Nicholas Gloude MD, Alexandra Duell BS, Kelly E Lake BS, Adam Lane PhD, Kasiani Myers MD, Pooja Khandelwal MD, Christopher Dandoy MD MSc, Sonata Jodele MD, Stella M. Davies MBBS PhD

Background:
Abatacept decreases risk of acute GVHD in adult and pediatric patient populations, but its effect on other clinical outcomes of HSCT has not been well studied. Abatacept's effect in reducing GVHD has been linked to T-cell dependent mechanisms, but it's effect on neutrophils and complement activation is largely unknown.

Objective:
To analyze the effect of abatacept prophylaxis in clinical outcomes of HSCT and explore potential mechanisms.

Methods:
We reviewed medical records of 262 consecutive patients who underwent allogeneic HSCT from 2013 to 2020. We then analyzed day +14 plasma samples for circulating double stranded DNA (ds-DNA) as a surrogate of NETs formation (Quant-iT PicoGreen, P7589; Molecular Probes), and reviewed day 7 sC5b9 levels to investigate the level of terminal complement activation.

Results:
Patients who received abatacept based GVHD prophylaxis together with a CNI and MMF (Group B, n=48) had significantly higher absolute neutrophil count (ANC) (725 vs 1590 vs 3285, $p<0.001$) and shorter duration for neutrophil recovery (13 days vs 12.5 days vs day 10.5 days, $p<0.001$) compared to patients who received CNI based therapy without abatacept (Group A, n=140). Patients in the abatacept group (Group B) had lower NETs (164,8 ng/dL vs 125.7 ng/dL vs 169.5 ng/dL, $p<0.001$) and day 7 sC5b9 levels (144 ng/mL vs 123 ng/mL vs 151 ng/mL, $p=0.0048$) compared to CNI based and T-cell depleted (Group C, n=74) groups. Those who received abatacept were less likely to develop an oxygen requirement (39% vs 15% vs 34%, $p=0.005$), engraftment syndrome (21% vs 8% vs 27%, $p=0.035$), respiratory failure (8% vs, 4%, vs 7%, $p=0.57$), GVHD (24% vs 2% vs 0, $p<0.001$), thrombotic microangiopathy (36% vs 19% vs 26%, $p=0.047$), and 1 year mortality (13% vs 4 % vs 14%, $p=0.21$).

Conclusion:
These data demonstrate a broader clinical benefit of abatacept than previously described, with reduction in pulmonary injury, engraftment syndrome, TMA, and survival in addition to reduction in GVHD. Searching for possible mechanisms, we show reduction in complement activation and NET production in children receiving abatacept. Moreover, NET production and complement activation were controlled more effectively by abatacept than T-cell depletion. These findings support a possible direct effect of abatacept on both neutrophils and endothelium in addition to the better recognized effect on T-cells. These are not prospective data and larger studies are needed to confirm these findings. In vitro analyses are currently underway to investigate potential direct effects of abatacept on neutrophils and endothelium.

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3) **Outcomes following CD34 Stem Cell Boost in Pediatric Allogeneic Stem Cell Transplant Recipients: A Single Center Study**

Theme: Allogeneic HSCT

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Background:
Allogeneic hematopoietic cell transplant (HCT), can be associated with poor graft function (PGF) or mixed donor chimerism (MC). While PGF manifests as severe cytopenia in at least 2 cell lines with full donor chimerism (DC) in the absence of graft versus host disease (GvHD) or relapse, MC (DC between 5-95%) if steadily declining can portend relapse of primary disease. A CD34-selected stem cells boost (SCB) from the initial donor can improve both MC and PGF.

Objective:
We retrospectively analyzed a cohort of pediatric patients who received a SCB for either PGF or MC at our center. The primary endpoint was resolution of PGF or improvement in MC (≥15% increase in DC) with secondary endpoints of overall survival (OS) and rates of GvHD post-SCB.

Methods:
Clinical data was analyzed using descriptive statistics and nonparametric methods.
Results: Fourteen patients with a median age of 12.8 (range: 0.08-20.6) years at HCT underwent SCB for either PGF (n=12; 5 malignant and 7 non-malignant; all transfusion-dependent) or MC (n=2, both non-malignant, transfusion-independent) at a median interval of 155 (range: 39-6924) days post-HCT. Donors were matched related (n=5), unrelated (n=6), and haploidentical (n=3). Four patients (1 MC, 3 PGF) received lymphodepleting chemotherapy pre-SCB. Median CD34 and CD3 doses infused were 7.47 x 10^6/kg (range: 3.51 x 10^6/kg-3.39 x10^7/kg) and 1.74 x10^3/kg (range: 7.84 x 10^2/kg-1.77 x 10 ^{4}/kg), respectively. In patients with PGF, we observed a significant decrease in the number of red blood cell transfusions pre-SCB vs post-SCB [median=8 (range: 0-46) vs median=2.5 (range: 0-18); p=0.008], platelet transfusions [median=21 (range: 0-92) vs 1.5

(range: 0-69); p=0.014], and GCSF doses needed [median=10.5 (range: 0-63) vs median=1 (range: 0-12); p= 0.041]. Overall response rate (ORR) was 50% (n=7); with 29% (n=4) complete response (CR), 21% (n=3) partial response (PR), and 50% (n=7) no response (NR). ORR in patients who received lymphodepletion (n=4) and those who did not (n=10), was 75% (2 CR, 1 PR, 1 NR) vs 40% (2 CR, 2 PR and 6 NR), respectively (p=0.56). In patients with MC, there was 1 CR and 1 NR. Rates of acute and chronic GVHD post-SCB were 7% and 14%, respectively. At a median follow up of 283 (range: 1-3305) days post-SCB, the 1-year OS was 57% (95% CI: 24-76%).

Conclusion:
SCB was an effective treatment for PGF or MC in half of our cohort with possible benefit of lymphodepletion pre-SCB.

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4) Venetoclax-based combination therapy as a bridge to allogeneic hematopoietic cell transplant in children with relapsed/refractory AML.

Theme: Allogeneic HSCT

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Background.
The use of the selective Bcl-2 inhibitor venetoclax in combination with cytarabine has been shown to be effective in heavily pretreated pediatric patients with relapsed/refractory (r/r) AML. Its lack of significant organ toxicity, aside from myelosuppression, makes venetoclax an attractive candidate for salvage therapy prior to hematopoietic cell transplant (HCT). The literature on the use of venetoclax in this context is limited, particularly in the pediatric population.

Objective.
To evaluate the impact of venetoclax-based salvage therapy on key HCT outcomes including engraftment, GVHD incidence, relapse free (RFS) and overall survival (OS).

Methods.
We performed a retrospective review of pediatric patients with r/r AML who received venetoclax prior to HCT between October 2017 and April 2021 at St. Jude Children’s Research Hospital.

Results.
Twenty-eight children with r/r AML received venetoclax-based salvage therapy prior to HCT. The median age at HCT was 13.4 years. Patients received a median of two cycles of venetoclax in combination with: cytarabine (n=17), cytarabine/idarubicin (n=5), cytarabine/azacitidine (n=3), decitabine (n=2), or azacitidine (n=1). The last dose of venetoclax was administered at a median of 16.5 days prior to the start of conditioning. At the time of HCT, 14 patients were in MRD-negative CR, 11 patients were MRD+ (≥ 0.01%) and three patients had active disease (bone marrow blasts >

5%). Donor sources included haploidentical (n=19), matched unrelated (n=6) and matched sibling donors (n=3). Twenty-one patients received reduced-intensity conditioning and seven underwent myeloablative conditioning. Neutrophil and platelet engraftment occurred in all patients and were observed at a median of 11 days (range 9-26) and 17 days (range 9-67), respectively. At a median follow up of 343.5 days (range 111-1056) from HCT, the 1-year OS was 80% (CI 64-100%) and 1-year RFS was 74.5% (CI 56.4-98.5%). Survival outcomes were similar between patients who underwent first (n=18) or second/third (n=10) HCT. Five patients (17.9%) developed Grade ≥ 2 aGVHD (grade 2, n=1; grade 3, n=4). Eight patients (28.6%) relapsed at a median of 144 days. Five of six deaths were from relapsed disease and one from bronchiolitis obliterans.

Conclusions.
Our study demonstrates that venetoclax based therapy prior to allogeneic HCT did not adversely impact transplant outcomes in a cohort of heavily pretreated children with r/r AML. The low rate of non-relapse mortality is encouraging and supports the use of venetoclax salvage therapy prior to first or subsequent HCT.

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5) The Effect of Donor Type on Survival in Children Receiving Hematopoietic Stem Cell Transplant (HCT) for Hematologic Malignancies (HM) in Florida (2015-2020):
Comparison of Matched Sibling Donor (MSD), 8/8 HLA-Matched Unrelated Donor (MUD), and Haploidentical Donor (HD) Transplants
Theme: Allogeneic HSCT

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Background:
Improved HCT outcomes with HD transplants with post-transplant cyclophosphamide (PTCy) has challenged the established donor selection criteria based on HLA-typing and donor relation. A recent CIBMTR retrospective study showed no difference in outcomes of adult patients with HM receiving myeloablative (MA) conditioning regimens and 8/8 MUD vs HD with PTCy[1]. A study comparing HD with PTCy and MSD HCT for adults with acute myelogenous leukemia (AML) in CR1 indicated similar outcomes[2], and an abstract describing survival after HD and MSD transplants for adults with acute lymphoblastic leukemia (ALL) indicated better outcomes in the MSD group[3].

Objective:
Compare outcomes of MSD, HD and 8/8 MUD transplant recipients in a recent cohort of pediatric patients with HM who received HCT in Florida Consortium centers.

Methods:

Retrospective data from 5 Florida pediatric BMT programs were gathered through the Florida Pediatric Consortium (FPBCC). Descriptive statistics and Kaplan-Meier survival analyses are presented.

Results:
A total of 130 children received 1st transplant for HM in one of the 5 Florida pediatric HCT centers (2015 to 2020). Donor types included MSD, HD, and 8/8 MUD in 34 (26.2%), 53 (40.8%) and 43 (33.1%) recipients, respectively. The majority (91%) of HD recipients received PTCy. Diagnoses included AML, ALL, mixed phenotype leukemia, and myelodysplastic syndrome (MDS) in 47%, 45%, 3% and 5% of recipients. Bone marrow was used in 75.5% of recipients and peripheral blood in the remainder. Favorable disease status (1st or 2nd complete remission) was present in 85.5% of patients with leukemia. Survival at 24-months post-transplant was 63.6% [95%CI 46.2-81%], 67.3% [95%CI 53.8-80.8%], and 82.2% [95%CI 70.1-94.3%] for MSD, HD, and MUD recipients, respectively; however, there was not significant difference (log rank p=0.1). The proportion of deaths attributed to relapse was 66.7%, 35.3%, and 28.6%, and the proportion attributed to organ failure or infection or GVHD was 33.3%, 64.7% and 42.9% in MSD, HD, and MUD HCT recipients, respectively. The proportion of patients without any acute GVHD was 61.8%, 58.5% and 41.9% and those without any chronic GVHD was 70.6%, 80.8% and 67.4% among MSD, HD, and MUD recipients, respectively.

Conclusion:
Based on 2-year overall survival, haploidentical donors can be considered first-line choice, together with MUD and MSD. Additional analyses of graft-versus-host disease-free survival, rates of infections and relapse rates are necessary to better describe risks and benefits of different donor types in pediatric HCT recipients.

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6) Role of Cytokine Secretion Signatures of Donor-derived T Cells and Recipient Serum Cytokine Profiles as Predictive Biomarkers of Acute Graft-Versus-Host Disease in αβT-cell/CD19 B-cell Depleted Hematopoietic Stem Cell Transplant Pediatric Recipients

Theme: Allogeneic HSCT

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Keywords: T cells, aGvHD, αβhaplo-HSCT, polyfunctionality, single-cell, proteomics, cytokines

Background:
Despite extensive ex-vivo αβT-cell depletion (αβTCD), grade II-IV acute graft-versus-host disease (aGvHD) still occurs in 25-30% of αβT-cell/CD19 B-cell depleted hematopoietic stem cell transplant (αβhaplo-HSCT) recipients.[1,2] Studies aimed at predicting aGvHD ocurrence in αβhaplo-HSCT specific to children are lacking.

Objective:
To test the hypothesis that highly polyfunctional αβT-cells adoptively transferred with the graft ($<1x10^5$/Kg) and recipient serum regenerating islet-derived 3α (REG3α) and suppressor of tumorigenesis-2 (ST2) predict aGvHD early after αβ haplo-HSCT (Day 7).

Methods:
Patients with hematologic malignancies receiving fully myeloablative αβhaplo-HSCT at Lucile Packard Children's Hospital, Stanford, between 08/2018 and 05/2020 were enrolled upon signing IRB approved informed consent. Aliquots from seven αβTCD donor grafts and twenty-three αβhaplo-HSCT recipients' serum at Days 0, 7, 14, 28, and 100 were collected. Graft-derived single-sorted $CD4^+$ and $CD8^+$ T-cells were stimulated and profiled by single-cell barcode chip assay (IsoPlexis, Brandford, CT) for assessment of polyfunctionality (secretion of ≥2 immunomodulatory cytokines from individual T-cells across five functional groups: effector, stimulatory, chemoattractive, regularotry, and inflammatory) and polyfunctional strength index (PSI= %polyfunctional T-cells x secreted proteins' MFI). Furthermore, REG3α and ST2 were analyzed by ELISA to calculate the risk of severe aGvHD using the Mount Sinai Acute GvHD International Consortium (MAGIC) algorithm probability (MAP score)[3] (Viracor, Lee's Summit, MO).

Results:
Elevated $CD4^+$ and $CD8^+$ T-cell polyfunctionality (4+ cytokines) and PSI with effector and stimulatory dominant functions were observed only in the grafts of patients that eventually developed aGvHD (n=4). Average PSI was driven by Granzyme-B, TNF-α, IFN-γ, MIP-1β, IL-2, and IL-8. Combinatorial cytokine secretion analysis showed that T-cells from grafts of patients that did not develop aGvHD (n=3) had unique co-secreting signatures for $CD4^+$ and $CD8^+$ T-cells with three predominant cytokine secretion signatures: IL2, IL8, TNF-α; MIP-1β, IL8; and MIP-1β, IFN-γ. MAP-score and ST2 expression differences between patients with (n=10) or without (n=13) aGvHD were only statistically significant at Day 28 (p=0.007 and p=0.009, respectively) but not at Day 7, as it's been proposed to occur in the T-cell replete HSCT setting[3]. REG3α expression did not reveal any significant differences throughout different timepoints.

Conclusions:
Increased donor T-cell polyfunctionality with a Th1 dominant functional phenotype may predict increased risk of aGvHD whereas MAP scores may be more suitable for predicting non-relapse mortality in αβhaplo-HSCT pediatric recipients.

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7) OUTCOMES OF PEDIATRIC PATIENTS WHO UNDERWENT DONOR SPECIFIC ANTIBODY DESENSITIZATION PRIOR TO RECEIVING A HAPLOIDENTICAL HEMATOPOIETIC CELL TRANSPLANT: A SINGLE CENTER EXPERIENCE

Theme: Allogeneic HSCT

Authors:
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Background:
Presence of donor specific anti-HLA antibodies (DSA) is associated with a higher incidence of poor graft function, engraftment failure, and poor survival after haploidentical stem cell transplantation (haploHCT). Desensitization of the recipients prior to graft infusion is recommended and has been shown to decrease DSA titer and improve engraftment and graft function in patients. Several strategies to decrease antibody levels have been adopted and are based on inhibition of antibody production, neutralization of antibodies with intravenous immunoglobulin or donor HLA antigens, and removal of the antibodies with either plasmapheresis or immunoadsorption. There is limited experience with adoption of these strategies in a pediatric setting in patients undergoing haploHCT.

Objective:
To describe the procedure of desensitization and outcomes of patients that underwent desensitization prior to receiving a haploHCT at our institution.

Method:
Medical records of patients under 21 years of age who underwent a haploHCT at St. Jude Children's Research Hospital from 2012 to 2021 were retrospectively reviewed and patients who required desensitization were identified.

Results:
Four patients required desensitization prior to haploHCT during the study period. These ranged from 9 to 11 years old. Three patients had non-malignant disease (2 sickle cell disease [SCD], 1 severe aplastic anemia) and one had AML. The two patients with SCD were treated with Rituximab (375 mg/m2/dose for 3 to 4 doses) and Bortezomib (1.3mg/m2/dose for 4 to 8 doses), while the remaining patients were treated with Rituximab alone (375 mg/m2/dose for 2 doses). All patients underwent plasmapheresis (3 to 6 sessions) immediately prior to the start of conditioning for haploHCT. Three patients received IVIG (0.3 to 1 gram/kg/dose) following plasmapheresis and prior to conditioning. HLA class I antibodies were found in all 4 patients and 2 patients had additional class II antibodies prior to desensitization. DSA prior to treatment ranged from 1627-4671 mean fluorescence intensity (MFI) and one patient had positive antibody levels prior to

conditioning. Median neutrophil engraftment time was 18±4 days. All patients are alive and are between 1 to 7 years from haploHCT. The patient with AML remains in remission and all 4 patients have had robust blood cell counts and graft function.

Conclusions:
Rituximab with or without Bortezomib followed by plasmapheresis is a successful treatment strategy for antibody desensitization prior to haploHCT. Desensitization is a safe option for pediatric HCT patients with limited donor options.

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8) Racial disparity in pediatric hematopoietic stem cell transplantation - a single center experience

Theme: Allogeneic HSCT

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Background:
There is significant evidence to suggest that there are inferior hematopoietic stem cell transplant outcomes in ethnic minorities. However, research to date is limited by the scope of patients included (focusing primarily on African American individuals whose outcomes are greatly affected by poorly matched donors) and adult patients whose experiences do not reflect pediatric care. There is a lack of studies looking at the impact of race, particularly among Hispanic & Native American patients, on outcomes following pediatric allogeneic hematopoietic stem cell transplant (HSCT).

Objectives:
To evaluate the impact of race and socioeconomic status on rate of relapse and overall survival after allogeneic HSCT.

Method:
Clinical and socioeconomic data of 109 pediatric patients who underwent their first allogenic HSCT for hematologic malignancy at Phoenix Children's Hospital from November 2007 to October 2017 were analyzed. Relapse and survival rates were compared between Caucasians, Hispanics, and Native Americans.

Result:
Mean recipient age was 9.2 ± 6.09 years. Of the 109 patients, 56(51.4%) were Caucasian, 45(41.3%) Hispanics and 8(7.3%) Native Americans. Forty four percent of Caucasians were on Medicaid compared to 74% of Hispanics and 88% of Native Americans (p=0.007). Matched related donors were used in 28% Caucasians, 26 % Hispanics and 50% Native Americans. Bone marrow stem cells were used as the stem cell source in 62.3% of patients, and conditioning intensity was myeloablative in 90.2% of patients. After a median follow-up of 5 years, cumulative incidence of relapse rates was 29.4% for Caucasians, 51.2% for Hispanics and 62.5% for Native Americans (p= 0.047). Grade II-IV aGVHD rates were 53% in the Caucasians, 48% in Hispanics and 0% in Native

Americans (p=0.0486). In contrast, 2-year overall survival (OS) comparing Caucasian patients to Hispanics and Native Americans was similar 73%, 67%, and 50%, respectively (p=0.38) as was the incidence of cGVHD; Caucasian 37%, Hispanics 23% and Native Americans 14% (p=0.21). In multivariate analysis, race was not significant in the model. However, incidence of cGVHD was independently associated with better relapse rate and OS (p= 0.04).

Conclusion:
Even though we saw racial disparity in relapse rates on univariate analysis, after adjusting for clinical or socioeconomic factors, we do not see any disparities in relapses or survival rates following pediatric allogeneic HSCT for malignancies between Caucasians, Hispanics, and Native Americans. Further sub analysis is ongoing.

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9) Assessing the Prognostic Value of Absolute Lymphocyte Count and Absolute Monocyte Count in Pediatric Neuroblastoma Patients Post Autologous Stem Cell Transplant

Theme: Autologous transplant

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Background:
Neuroblastoma is the most common non-central nervous system solid tumor in pediatrics. Despite intensive multi-modality therapy, the 3-year event free survival of patients with stage IV or high-risk disease is 61%. The rate of lymphocyte recovery following autologous stem cell transplantation (ASCT) has been studied as a prognostic predictor in other disease processes such as multiple myeloma, non-Hodgkin's lymphoma, relapsed/refractory Hodgkin's lymphoma, and breast cancer. However, the importance of the association between lymphocyte recovery and outcome has not been well studied in ASCT in patients with neuroblastoma.

Objective:
This study aims to evaluate the prognostic importance of absolute lymphocyte count (ALC) to absolute monocyte count (AMC) ratio at day 30 and day 100 following ASCT in patients with high-risk neuroblastoma. We hypothesize that early immune reconstitution correlates with improved relapse-free survival.

Methods:
In this retrospective study, we analyzed 28 consecutive patients with stage IV neuroblastoma underwent a single ASCT at Phoenix Children's Hospital between 2010 and 2017. At days +30 and +100 following initiation of high dose chemotherapy (busulfan and melphalan) and auto transplant, absolute lymphocyte blood counts and absolute monocyte blood counts were calculated as percent lymphocytes and percent monocytes from the total white blood cell count.

Results:
The median age was 3.2 years. Prior to transplant about 40% (11) were in clinical remission, 25% (7) had partial remission, and 35 % (20) had very good partial remission. All patients received the

same conditioning chemotherapy, were given peripheral blood progenitor cells, and were followed until death or for a minimum of 2 years post-ASCT. Stage IV neuroblastoma patients with an ALC/AMC ratio ≥1 at Day +30 post-ASCT had a trend toward improved survival, but there was no statistically significant difference in relapse free survival (p=0.0528). When comparing patients with ALC/AMC ratio ≥1 to those with a ratio < 1 at Day +100 post-autologous transplant, there was not a statistically significant difference in OS (p=0.244) or RFS (p=0.223)

Conclusions:
Our result at Day +30, although not significant, likely due to the small power of the study, it trends towards significance. However, there was no correlation between ALC/AMC ratio at Day +100 post single ASCT and relapse free survival in stage IV neuroblastoma patients. This study looked exclusively at patients receiving a single ASCT. Given the survival benefit noted with tandem ASCT, future studies looking at immune reconstitution in this cohort may be warranted.

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10) Impact of CD34+ Cell Dose on Outcome in Children Undergoing Autologous Hematopoietic Stem Cell Transplant for High-Risk Neuroblastoma

Theme: Autologous transplant

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BACKGROUND: Autologous hematopoietic stem cell transplantation (HSCT) is a key component of consolidation therapy for high-risk neuroblastoma. The effect of the CD34+ dose on patient outcomes has not been well established in this clinical setting. In adult autologous transplants, higher CD34+ doses have been associated with improved post-transplant outcomes. However, these higher CD34+ doses may be associated with an increased incidence of post-transplant complications. High CD34+ cell doses may theoretically be either be harmful or beneficial, and it is unknown whether there is an optimal CD34+ cell dose for infusion in high-risk neuroblastoma.

OBJECTIVE: To examine the relationship between CD34+ dose and patient outcomes, including overall survival, (OS) progression free survival (PFS), relapse, non-relapse mortality (NRM), and time to neutrophil engraftment in patients undergoing autologous HSCT for high-risk neuroblastoma.

DESIGN/METHODS: Data on 183 children aged ≤10 years with high-risk neuroblastoma were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR) database. All subjects had received treatment in North America and underwent autologous HSCT between 2008 and 2018. Cox regression models were used to examine for an effect of CD34+ dose on OS, PFS, relapse, and NRM.

RESULTS: The median CD34+ dose infused was 5.2 x10^6/kg (interquartile range 3.9 – 8.8). No association between CD34+ dose and PFS (p=0.09), OS (p=0.25), risk of relapse (p=0.15), or NRM (p=0.18) was noted. Stratification of CD34+ cell dose by quartile did not reveal any statistically significant differences in 3-year PFS (p=0.30), OS (p=0.40), or risk of relapse (p=0.38) between quartiles. The optimal CD34+ cell dose to discriminate neutrophil engraftment was 6.5 x10^6/kg, with a mean time to neutrophil engraftment of 11 days for children receiving a CD34+ dose ≥ 6.5x10^6/kg, versus 13 days for those receiving <6.5 x10^6/kg (p=0.0046). Cell doses < 2.0x10^6/kg or >10.0x10^6/kg did not impact engraftment times. All 16 patients who received a CD34+ cell dose ≤ 2.0x10^6/kg engrafted, with a median time to neutrophil engraftment of 11 days (range 10-39 days) post-transplant.

CONCLUSION: No association was identified between CD34+ cell dose and patient outcomes in children with high-risk neuroblastoma. Although the administration of higher CD34+ doses led to faster time to neutrophil engraftment, it did not affect OS, PFS, NRM, or relapse rates, either positively or negatively. Pediatric transplant physicians should therefore be reassured that the administration of high CD34+ doses does not appear to increase the risk of post-transplant complications, and that low CD34+ doses do not appear to adversely affect survival.

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11) Treating Children, Adolescents, and Young Adults (CAYA) with Refractory Viral Infections in Primary Immunodeficiencies (PID), or Post Solid Organ Transplant (SOT) or Allogeneic Hematopoietic Stem Cell Transplantation (AlloHSCT) with Virus Specific T-Lymphocytes (vCTLs)

Theme: Cellular Therapies

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Background:
Patients with PID and secondary immunodeficiency (SID) following SOT or AlloHSCT have compromised T-cell mediated viral immunity leading to increase in morbidity and mortality due to viral reactivation. Due to limitations of antiviral therapy, further research has gone into the development of virus-specific cytotoxic T-lymphocytes (vCTLs) (Bollard *Blood* 2016). Multiple studies have demonstrated efficacy and safety utilizing the IFN-γ Cytokine Capture System (CCS) using the fully automated CliniMACS Prodigy® device (Miltenyi Biotec) for isolating vCTLs as prophylactic/preemptive treatment or for treating refractory infections (Feuchtinger *Blood* 2010). We created a multicenter viral CTL consortium (VIRCTLC) to treat immunodeficiency patients with vCTLs and have previously demonstrated the safety and efficacy of vCTLs in this population (Flower/Cairo et al, ASTCT 2020).

Objective:
To demonstrate the use of Cytomeglovirus (CMV), Epstein Barr virus (EBV), adenovirus (AdV), and BK virus CTLs manufactured utilizing the CliniMACS Prodigy will be safe and effective in decreasing viral loads in CAYA PID or SID patients with refractory viral infections.

Design/Methods:
A phase II prospective, multicenter, multidisciplinary clinical trial under IND 17449. CAYA patients with refractory viral infections (CMV, AdV, EBV, or BK virus) who met eligibility were consented onto study. Parental donors' peripheral blood mononuclear cells were collected via non-stimulated apheresis. The vCTLs were isolated in the fully-automated IFN-γ CCS by the CliniMACS® Prodigy after incubation with MACS GMP PepTivator® peptide pools. Cell doses were limited to $0.5x10^4$ CD3/kg in HLA mismatched related donors. vCTLs infusions were given every 2 weeks based on responses, for a maximum of 5 infusions.

Results:
Twenty-six patients received vCTLs. Two patients had PID, three patients were SOT recipients, and twenty-one were alloHSCT recipients. Six patients received CMV CTL infusions, 14 received ADV CTLs, three received EBV virus CTLs, and five patients received BK vCTLs. Median number of vCTL infusions was 2 (1-5). Sixteen patients (62%) achieved complete remission (CR) (PCR negative), five achieved partial response (PR) (PCR ≥1 log decrease), three had stable disease (SD), one had progressive disease (PD), one patient died prior to evaluation secondary to multiorgan system failure. No patient has developed grade III/IV acute GVHD, extensive chronic GVHD, an infusion reaction, cytokine release syndrome, or immune effector cell-associated neurotoxicity syndrome secondary to vCTLs.

Conclusion:
Viral specific CTLs are safe in CAYA patients with refractory viral reactivation and manufacturing via the automated CliniMACS Prodigy is reproducible in a timely manner. Accrual is ongoing.

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12) A direct comparison of CAR NK cells and CAR T cells for CD19+ malignancies.

Theme: Cellular Therapies

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Background:
Chimeric antigen receptor (CAR) T cell therapy has shown dramatic success in pediatric acute lymphoblastic leukemia (ALL), however, significant hurdles remain to optimize this therapy. Specifically, CAR T cells depend on the presence of tumor specific surface antigens for cytotoxicity and therapeutic success depends on universal tumor expression of CAR antigens. In addition, allogeneic CAR T cells have not been widely utilized due to the risk of graft versus host disease (GVHD) from donor T cells. NK cells are not antigen specific and allogeneic NK cells have been widely utilized with no significant risk of GVHD. While NK cells and T cells share similar effector functions, there are significant advantages to utilizing NK cells for CAR therapy including the potential for "off-the-shelf" CAR NK products. However, methods for generating CAR NK and CAR T cells differ significantly, and differences in insertion sites and copy number lead to variable expression levels.

Objective:
We used Cas9/RNP to target the CD19 CAR into the AAVS1 safe-harbor locus with AAV-6 to generate CD19 CAR T cells and CD19 CAR NK cells, and compared their cytotoxicity against CD19 expressing tumor cell lines.

Design/Methods:
NK and T cells were isolated from peripheral blood mononuclear cells from the same donor. The cells were transduced with the same CD19 CAR utilizing a combination of Cas9/RNP and AAV-6. NK cells were expanded in culture with IL-2 and irradiated feeder cells expressing membrane-bound IL-21. T cells were cultured in the presence of IL-7 and IL-15. After expansion, we compared cytotoxicity of CAR T cells to CAR NK cells using a calcein cytotoxicity assay against CD19+ cell lines.

Results:
CAR T cell expression for NK cells and T cells after expansion was equivalent (roughly 30%). CD19 CAR NK cells demonstrated superior cytotoxicity against both Raji and CD19+ K562 compared to CD19 CAR T cells. At a 5:1 effector cell to tumor ratio, CAR NK cell average cell lysis was 96% and CAR T cell was 22% against Raji. For K562 with only 20% expression of CD19, CAR NK cell average cell lysis was 86% compared to 4% for CAR T cells.

Conclusion:
We observe that CAR NK cell killing is superior to CAR T cells in this setting, which may be secondary to additional innate NK receptor function against the tumors. We are performing further analysis on cells sorted to purity, including other effector functions and activity against patient-derived targets.

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13) Cryopreserved anti-CD22 and bispecific anti-CD19/22 CAR-T cells are as effective as freshly infused cells
Theme: Cellular Therapies

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Background:
Cryopreservation of CAR-T cells is used for shipping, optimal timing of cell infusions, and storage of subsequent doses. While cryopreservation of leukapheresis product is well established, little data is available about the impact of cryopreserving CAR-T cells after manufacture. Pre-clinical has data demonstrated differences in cytokine production and gene expression in cryopreserved versus fresh cells. [1,2] Mixed results have been reported for clinical efficacy of cryopreserved CAR-T cells. [2,3] Furthermore, it is not clear whether data from one type of CAR-T cell can be extrapolated to other CAR-T products.

Objective:
To compare clinical outcomes between patients who received cryopreserved versus fresh CAR-T cells for treatment of B-cell leukemia or lymphoma.

Design/Method:
We retrospectively reviewed two cohorts of pediatric and young adult patients: those who received anti-CD22 CAR-T and those who received bispecific anti-CD19/22 CAR-T at the NIH Clinical Center. Manufacturing methods were kept consistent within each cohort. Clinical outcomes including *in vivo* expansion, CAR-T associated toxicities, and disease response were compared between groups. Continuous variables were compared using Mann-Whitney U tests and categorical variables using Fisher's exact and Wilcoxon rank-sum tests. Survival estimated with Kaplan-Meier curves was compared using log-rank tests.

Results:
Among 39 patients who received anti-CD22 CAR-T cells, 21 had cryopreserved cells and 18 had fresh infusions. As expected, cryopreserved cells had lower percent viability compared with fresh cells, with dosing based on viable cell counts. There was no difference between fresh and cryopreserved CAR-T cell *in vivo* expansion or persistence at 28 days post-infusion. There was also no difference in inflammatory markers or incidence of cytokine release syndrome (CRS), neurotoxicity, or HLH. The rate of complete response at 28 days and overall survival were the same between groups. Among 19 patients who received anti-CD19/22 CAR-T cells, 11 received cryopreserved cells and 8 had fresh infusions. As above, cryopreserved cells had lower percent viability than fresh cells. Although patients with freshly infused cells had increased *in vivo* expansion and higher ferritin levels, they also had higher baseline disease burden, which likely accounts for this difference. There was no difference in incidence of toxicities. Importantly, there was no difference in disease response or survival between patients who received fresh or cryopreserved bispecific CAR-T cells.

Conclusion:

We found no difference in anti-leukemia effect between infusion of cryopreserved versus fresh CAR-T cells. Future directions include long-term follow-up as well as evaluation of production factors contributing to *in vivo* cell expansion.

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3. Shah et al., *Nature Medicine*, 2020.

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14) Targeting Pediatric Neuroblastoma and Glioblastoma with the combinatorial therapy of IL-21 secretion oncolytic virus and anti-ROR1 CAR NK cells

Theme: Cellular Therapies

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Background:

Children with recurrent and/or metastatic neuroblastoma (NB) and glioblastoma multiforme (GBM) have a dismal event-free survival (<25%) (1). Novel therapies are desperately needed for these poor risk patients. ROR1 is highly expressed on the majority of NB and GBM. Our group has successfully expanded functional and active peripheral blood NK cells (exPBNK) with irradiated feeder cells and electroporated CAR mRNA to exPBNK (2). Oncolytic herpes simplex viruses (oHSVs) are a promising experimental therapy. C134 is a selective replication competent oHSV with enhanced viral gene expression (3).

Objectives:

To determine if C134-based human IL21 expression combined with anti-ROR1 CAR engineered exPBNK cells can efficiently target ROR1$^+$ NB and GBM.

Methods:

ExPBNK cells were expanded with lethally irradiated K562-mbIL21cells as we previously described (1). ExPBNK cells were electroporated with anti-ROR1-CAR mRNA using maxcyte electroporator as we previously described (2). C021 was generated by modifying C134 to express human *IL-21* gene. The supernatants of C134 and C021 (C134+hIL21) were generated as previously described (3). *In vitro* cytotoxicity of anti-ROR1 CAR NK against NB and GBM cell lines were examined at different E:T ratios. IFN-□, granzyme and perforin levels were evaluated

by ELISA assays (1). In vivo anti-tumor effect was examined utilizing human NB tumor xenografted NSG mice (1,2).

Results:
C021 infected NB cells (MOI 0.025) generated hIL-21 in cell supernatants at 24 hours post infection (hpi) and peaked at 72hpi. Combining C134 with exPBNK cell therapy significantly enhanced the NK-mediated killing of NB and GBM cells ($p<0.05$, $p<0.05$). Combinations involving C021(C134+IL21) and anti-ROR1 CAR exPBNK cells had the greatest anti-tumor effect significantly enhancing NB and GBM cell death when compared to C134 + anti-ROR1 CAR exPBNK cell combinations ($p<0.05$, $p<0.05$). C021 addition to enhanced anti-ROR1 CAR exPBNK killing significantly increases IFN-g ($p<0.05$), granzyme B ($p<0.05$) and perforin ($p<0.05$) secretion and significantly upregulated the NK activating marker CD25 ($p<0.05$). Our in vivo animal study showed that C021 and anti-ROR1 CAR exPBNK cell combination reduced tumor burden in human NB xenografted NSG mice compared to untreated group ($p<0.05$) and anti-ROR1 CAR exPBNK treated group ($P=0.056$).

Conclusion:
Our data demonstrated the anti-tumor efficacy of the combination of oHSVs C021 with anti-ROR1 CAR exPBNK cells targeting NB and GBM cells *in vitro* and *in vivo*. (This work is funded by U54 CA232561).

References
Chu/Cairo, JITC, 2021
Chu/Cairo, Cancer Immunol Res, 2015
Cassady, et al, Mol Ther Oncolytics, 2017

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15) Targeting Acute Myeloid Leukemia by the Combination of Expanded Natural Killer Cells and Romidepsin

Theme: Cellular Therapies

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Background:
Acute myeloid leukemia (AML) accounts for approximately 20-33% of all acute leukemias in children, adolescents and young adults, but is associated with a 50% mortality rate. Leap frog advances with high impact are urgently required to significantly improve outcomes in these high-risk AML patients. Since Natural Killer (NK) cells are an essential component of AML

surveillance, and are short- lived when administered ex-vivo, novel combinatorial immunotherapy approaches to clinically enhance NK cell targeting, persistence, and functional activation would significantly enhance AML relapse-free survival. NK therapy has been limited in the past by the low number of active NK in the peripheral blood (PB).
Our group has successfully expanded functional and active peripheral blood NK cells (exPBNK) with irradiated feeder cells to target a variety of pediatric cancers (1). Romidepsin is a histone deacetylase inhibitor and it up-regulates the expression of NKG2D ligands such as MICA/B and induces apoptosis in tumor cells (2).

Objectives:
We aim to investigate if AML cells are sensitive to be killed by ex vivo expanded NK cells and if romidepsin enhances the killing of AML by expanded NK cells.

Design/Methods:
PBNK cells were ex vivo expanded by co-culturing peripheral blood mononuclear cells with lethally irradiated feeder cells (K562-mbIL21-41BBL) as previously described (3). The in-vitro cytotoxicity of expanded NK against AML cell lines (THP1, HEL and KG1a) were evaluated at different E:T ratios as we have previously described (3).

Results:
Expanded NK cells expressed high level of NKG2D (99% expression). THP1, HEL and KG1a cells expressed high level of NKG2D ligands MICA/B (99% expression). As expected, THP1, HEL and KG1a cells are sensitive to be killed by the expanded PBNK cells in a E:T ratio dependent manner which may be mediated through the interaction of NKG2D with MICA/B. THP1, HEL and KG1a cells were also sensitive to be killed by romidepsin. Romidepsin did not significantly affect the expression of MICA/B on these tumor cells. But the combination of romidepsin and the expanded NK cells significantly enhanced the killing of THP1, HEL and KG1a cells than expanded NK cells alone ($p<0.05$, $p<005$, $p<0.05$) or romidepsin alone ($p<0.05$, $p<0.05$, $p<0.05$).

Conclusions:
Our data demonstrated the anti-tumor efficacy of the combination of romidepsin and expanded NK cells in vitro against AML cells. In the future, we will investigate the vivo anti-AML effect of expanded NK with romidepsin utilizing human AML xenografted immunodeficient mice.

Chu/Cairo, Cancer Immunol Res, 2015
Chu/Cairo, Oncoimmunology, 2017
Chu/Cairo, JITC, 2020

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16) Targeting Ewing sarcoma (ES), Osteosarcoma (OS) and Neuroblastoma (NB) with Anti-MCAM Chimeric Antigen Receptor (CAR) Modified Natural Killer (NK) Cells

Theme: Cellular Therapies

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Background

Pediatric patients with metastatic ES, OS and NB have a dismal average 5-year survival (<25%). Novel therapeutic approaches are desperately needed (1). The melanoma cell adhesion molecule (MCAM) is highly expressed in pediatric solid tumors and constitutes a novel target for immunotherapy (2). We previously demonstrated that anti-CD20 CAR NK cells significantly reduced tumor burden, prevented tumor dissemination, and extended survival of treated mice compared to mock NK treatment in a humanized Burkitt lymphoma xenograft mouse model (3). NKTR-255 is an investigational IL-15Rα-dependent, polymer-conjugated, recombinant human IL-15 agonist that retains the full spectrum of IL-15 biology, including expansion of NK cells (4,5).

Objective

Here we developed an anti-MCAM CAR NK cell and investigated its efficacy alone or in combination with NKTR-255 (provided by Nektar Therapeutics) in promoting NK cell cytotoxicity against ES, OS and NB.

Method

Peripheral blood mononuclear cells (PBMCs) were expanded into NK cells ex vivo using K562-mbIL21-41BBL feeder cells in the presence of IL-2. Anti-MCAM CAR NK cells were generated by non-viral electroporation of anti-MCAM CAR mRNA into expanded NK cells.

Results

We found a significantly increased cytotoxicity of anti-MCAM CAR NK cells compared to mock NK cells against ES (A673: 74.7±3.1 vs 58.1±7.6, p=0.009; EWS502: 63±5.6 vs 36.4±3, p=0.008; SKNMC: 83.7±2 vs 64.9±4.6, p=0.04), OS (U2OS: 34.1±10.8 vs 17.3±9.7, p=0.0004), and NB cells (SKNFI: 26.1±3 vs 8.9±6, p=0.01). The enhanced cytotoxicity of the anti-MCAM CAR NK cell is due to specific targeting of MCAM, because CRISPR/Cas9 mediated MCAM knockout diminished the sensitivity of tumor cells to anti-MCAM CAR NK compared to mock NK cells. Furthermore, the combination of NKTR-255 significantly increased the cytotoxic activity of anti-MCAM CAR NK cells against A673 (86±2.8 vs 39±9, p=0.003), EWS502 (46±2 vs 33±6.1, p=0.03), SKNMC (79±2 vs 65±9, p=0.04), U2OS (31±11 vs 19±2, p=0.04) and SKNFI (83±5 vs 68±5, p=0.01) cells. A mechanistic study showed that NKTR-255 treatment enhanced NK cell proliferation and activity. In a preclinical investigation using an orthotopic xenograft mouse model of ES, we found that anti-MCAM CAR NK therapy significantly reduced lung metastasis (42% vs 14%, p<0.05) and prolonged animal survival (0% vs 50%, p<0.05), and NKTR-255 further enhanced these anti-tumor effects of anti-MCAM CAR NK cells (0% lung metastasis and 71% survival).

Conclusion

Our findings demonstrated efficacy of anti-MCAM CAR NK cells alone and/or in combination with NKTR-255 against malignant pediatric solid tumors in vitro and in vivo. Supported in part by U54 CA232561.

1. Nayyar/Chu/Cairo, Front Oncol, 2019
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17) The Impact of Race, Ethnicity, and Obesity on CAR T-cell Therapy Outcomes in Children and Young Adults with B-cell Acute Lymphoblastic Leukemia (B-ALL)

Theme: Cellular Therapies

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Background:
Racial/ethnic minorities and patients with obesity experience worse cancer outcomes following chemotherapy. Whether similar disparities exist for patients receiving chimeric antigen receptor (CAR) T-cell therapy is unknown.

Objective:
To evaluate CAR toxicity and efficacy across racial/ethnic groups and body mass index (BMI) in children and young adults with B-ALL.

Design/Methods:
We retrospectively analyzed complete remission (CR) rates, cytokine release syndrome (CRS) severity, neurotoxicity, and overall survival (OS) stratified by race, ethnicity, and BMI for B-ALL patients treated with CD19, CD22, and/or CD19/22 CAR T-cells on phase I trials at our institute from 2012-2021.

Results:
Among 139 patients (70.5% male), median age was 15.1 years (IQR: 9.6 – 21.2). 77 (55.4%) patients were non-Hispanic white, 40 (28.8%) Hispanic, and 22 (15.8%) non-Hispanic non-white (14 Asian, 5 Black, 3 other/unknown). 41 (29.5%) patients were overweight/obese. 92 (66.2%) had

>5% baseline marrow disease. 50 (36%) received CD19, 71 (51.1%) CD22, and 18 (12.9%) CD19/22 CAR.

CR rates (62.5%, 66.7%, 71.4%, p = 0.61) and neurotoxicity incidence (22.5%, 23.4%, 9.1%, p = 0.33) were similar among Hispanic, non-Hispanic non-white, and white patients, respectively. However, Hispanic patients experienced grade ≥3 CRS at higher rates vs. white patients (32.5% vs. 11.7%, p = 0.006). CR rates (68.9% vs. 63.4%, p = 0.54), incidence of grade ≥3 CRS (19.8% vs. 17.1%, p = 0.71), and neurotoxicity (22% vs. 19.5%, p = 0.75) were comparable between normal weight and overweight/obese patients.

We further interrogated the higher incidence of severe CRS in Hispanic patients. Despite M2/M3 disease being associated with a higher incidence of grade ≥3 CRS vs. M1 disease (23.9% vs. 6.4%, p = 0.01), disease burden between Hispanic and white patients was comparable (p = 0.88). Moreover, overweight/obese Hispanic patients were more likely to experience grade ≥3 CRS vs. overweight/obese white patients (46.2% vs. 0%, p = 0.0006) despite also having similar disease burden.
To evaluate long-term outcomes, we performed OS analysis. Median OS between white vs. non-white (12.8 vs 12.2 months, p = 0.55) and normal weight vs. overweight/obese (11.1 vs. 14.6 months, p = 0.37) patients was similar.

Conclusion:
Our study suggests comparable CAR therapy efficacy for B-ALL across diverse patient populations, albeit with limited representation across racial subgroups. Thus, understanding barriers and improving access to CAR therapy should be prioritized, particularly for patients for whom chemotherapy is less effective. Further study of underlying mechanisms of differential toxicity across demographic groups is warranted.
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18) Hyperinflammation and immune cell dysregulation in a hypomorphic animal model ($C7^{hypo}$) of recessive dystrophic epidermolysis bullosa (RDEB): Immunomodulation by human cord blood derived unrestricted somatic stem cells (USSCs)

Theme: Cellular Therapies

Authors: Yanling Liao[1], Morgan Anderson-Crannage[1], Edo Schaefer[1], Bruno Hochberg[1], Melanie Peters[2], Jian Pan[1] and Michell S. Cairo[1,3,4,5]

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Background:
RDEB is secondary to mutations in the *Col7a1* gene encoding collagen VII (C7) and manifested by life-long dermal blistering, impaired wound healing, persistent inflammation, and mutilating deformities. Our previous studies demonstrated that human cord blood derived unrestricted somatic stem cells (USSCs) secret C7 and suppress TGFβ signaling induced fibrosis in RDEB (Liao/Cairo et al. 2018).

Objective:
To investigate the mechanisms of inflammation and to determine the immunomodulatory effects of USSCs, using a $C7^{hypo}$ mouse model of RDEB.

Methods:
0.2×10^6 USSCs in 20µl PBS were injected intra-hepatically in the newborn $C7^{hypo}$ mice. Complete blood count with differential was measured using hematology analyzer (Zoetis Diagnostics). Cytokines in the plasma and skin lysate were quantitated using BD CBA mouse Th1/Th2/Th17 cytokine kit.

Results:
The $C7^{hypo}$ mice exhibited biomarkers for systemic inflammation, including significantly higher neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios, lower lymphocyte-to-monocyte ratio (LMR), and elevated plasma IL-6, as compared to the wild type (WT) ($p < 0.05$). IL-6, IFN-γ, TNFα and IL-17A were also significantly elevated in the $C7^{hypo}$ paw skin lysate than the WT ($p < 0.05$). While the PLR and LMR were not significantly changed by USSC administration, the NLR was significantly decreased in the USSC treated $C7^{hypo}$ mice (0.77 ± 0.57) as compared to the untreated control (2.52 ± 0.58; $p < 0.05$) and was comparable to the WT (0.17 ± 0.02; $p > 0.05$). In the skin lysate of USSC-treated $C7^{hypo}$ mice, the levels of IL-6, IFN-γ, TNFα and IL-17A were still significantly higher than those in the WT ($p < 0.05$), however, the magnitude of elevation was decreased as compared to the untreated group. More importantly, the skin lysate from USSC-treated mice exhibited a trend of increasing IL-2 and IL-10, both of which have been implicated in the induction of regulatory T (Treg) cells. Immunocytochemical analysis further demonstrated that the paw skin of USSC treated $C7^{hypo}$ mice not only had a

significantly higher relative ratio of CD4:CD8 T cells, but also an increased number of FoxP3$^+$ Tregs than untreated control ($p < 0.05$). Furthermore, USSC administration promoted alternative polarization of macrophages, as demonstrated by increased expression of an anti-inflammatory M2 markers, CD206.

Conclusions:
These preliminary results suggest RDEB is a systemic hyperinflammatory disorder and highlight the immunomodulatory role of cord blood derived USSCs in the treatment for RDEB.

This research was conducted at New York Medical College, Valhalla, NY, USA.

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19) Safety and Efficacy of Dose Escalation of Defibrotide in Hematopoietic Stem Cell Transplantation (HSCT) Recipients with Sinusoidal Obstructive Syndrome (SOS) Refractory to Standard Treatment Doses of Defibrotide

Theme: Disease-Specific, Transplant-Related

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Background:
SOS is a lethal complication (84% mortality) of HSCT, resulting in multi-organ failure (MOF) (Cairo/Cooke et al, Richardson et al, BJH 2020). Endothelial damage within the sinusoids of the liver progresses to a cascade of fibrosis, sclerosis, inflammation, thrombosis, and ischemia, culminating in SOS (Cooke et al, BBMT, 2008). Defibrotide stabilizes endothelial cells in microvascular beds and is FDA approved for the treatment of SOS with renal and/or pulmonary dysfunction (Cairo, et al, BJH 2020). However, only 40-60% of HSCT recipients with SOS survive to Day+100 despite defibrotide treatment (Richardson et al, Blood, 2016). Importantly, patients post HSCT with SOS who obtained a CR following defibrotide have a higher Day +100 OS and median survival vs those who did not obtain a CR (93% vs 37%) 796 vs 68 days (Richardson et al, TCT, 2021). Tripleff et al. (BBMT, 2018) demonstrated the safety of dose escalation of defibrotide to 25 mg/kg/dose (100 mg/kg/day) without evidence of toxicity in HSCT recipients with refractory SOS following standard defibrotide dosing.

Objective:
To evaluate the safety and efficacy of defibrotide dose escalation in HSCT patients who had progressive disease or were refractory (non-CR) to standard defibrotide dosing.

Design/Methods:

Dose escalation of defibrotide proceeded from 6.25 mg/kg/dose to 10, 15, 25 mg/kg/dose q6h in HSCT recipients until CR or DLT. SOS grading were per Cairo/Cooke, et al., BJH, 2020. Response criteria were defined as: CR is Grade 1 or less, partial response is improvement in 1 grade or more in ≥3/6 SOS grading criteria, progressive disease (PD) is progression one grade or more in ≥ 3/6 SOS grading criteria, and stable disease (SD) includes all other patients. Patients also received antithrombin III replacement to maintain activity between 100-120% (Haussmann et al. Haematologica 2006).

Results:
Eight HSCT recipients with refractory/progressive post-HSCT SOS following defibrotide (6.25mg/kg q6hrs): age 8 mo-18y (median 18mo), M/F 3/5, 6 malignant, 2 non-malignant disease. Seven of the eight patients received MAC. All patients had grade 4 SOS prior to initiation of defibrotide dose escalation. Seven patients received hemodialysis during defibrotide. No patient developed hemorrhage during the dose escalation of defibrotide. CR was 62.5%, 12.5% SD and 25% PD. The probability at Day 100 OS in this patient group was 87.5% (CI_{95}: 38.7-98.1).

Conclusions:
Dose escalation of defibrotide to maximum of 100mg/kg/day (25mg/kg q6hrs) was well tolerated in defibrotide refractory HSCT related SOS with improved day 100 OS. A larger cohort will be evaluated to confirm these findings.

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20) Predicting Relapse In Pediatric Patients with Acute Leukemia Undergoing Stem Cell Transplant Using Interpretable Machine Learning—A Proof-of-Concept Study of Applying Machine Learning Beyond "Big Data

Authors: David C. Shyr, Brenna Kelly, Simon C. Brewer

Theme: Disease-Specific, Transplant-Related

Institution: Stanford University School of Medicine, Palo Alto, CA, USA
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Background
Leukemia relapse remains a major cause of mortality after hematopoietic stem cell transplant (HSCT) for patients with acute leukemia. Recent studies have identified donor chimerism as a predictor of relapse in post-HSCT patients with hematologic malignancies, lending to the possibility of meaningful post-transplant relapse surveillance. Machine learning (ML) automates analytical model building, emphasizing pattern recognition and leading to robust predictive models that can be useful in clinical setting such as leukemia relapse. Well suited for "big data," machine learning methods can also be applied to smaller datasets and extract useful information to complement standard statistical analysis. Few examples of this application exist in hematology literatures.

Objective
We present a data analysis study demonstrating how machine learning methods, specifically random forest (RF) classification and local interpretable model-agnostic explanations (LIME),

can reveal the interaction of different risk factors of post-transplant leukemic relapse and obtain robust predictions even with a modest clinical dataset.

Design/Method
Data analysis study of pediatric patients (46 ALL, 33 AML) who underwent HSCT for ALL and AML from 2015 to 2018.

Result
RF produced robust prediction model of post-HSCT relapse in both ALL (sensitivity 85%, specificity 95%) and AML (sensitivity 85%, specificity 69%) which are significantly improved from the baseline models based on inferential statistics (ALL sensitivity 24%, specificity 76%; AML sensitivity 18%, specificity 83%). Variable importance values were estimated using final RF model based on the full dataset, which revealed peripheral blood (PB) CD34 chimerism is the most important post-HSCT predictive factor for ALL in our data set and PB CD3 for AML. Partial dependency plots of both PB CD34 for ALL and CD3 for AML exhibited a threshold effect at 95%, where < 95% confers significant increased relapse risk. LIME analysis/plot illustrated how the RF model makes predictions for a given patient by showing whether the value of a variable decreases or increases the risk of relapse for that patient, highlighting the differential impact of any given variable for the entire cohort vs an individual patient.

Conclusion
ML methods can provide additional information about the entire dataset as well as on the individual patient level, leading to robust predictive power. ML is not only for "big data," but can also be applied to smaller datasets, which may be more appropriate to answer more focused questions, particularly with rare diseases and less common medical challenges. They can provide complementary information to traditional statistical analyses and may offer further insights into existing smaller datasets.

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21) Reduced Intensity Conditioning Stem Cell Transplantation for Young Patients with Diamond-Blackfan Anemia is Safe and Effective
Theme: Disease-Specific, Transplant-Related

Authors: Helena Yu, MD; Eric J. Anderson, MD; Deborah E. Schiff, MD; Nicholas J. Gloude, MD

Institution, city, state, and country: UCSD/Rady Children's Hospital, San Diego, CA, USA

Background:
Hematopoietic stem cell transplantation (HSCT) is a curative option for patients with Diamond-Blackfan Anemia (DBA). Myeloablative conditioning regimens have generally been standard practice, but reduced intensity conditioning (RIC) regimens with HSCT have been used to minimize short and long-term treatment-related toxicities.

Objective:
To perform a retrospective analysis of DBA patients who underwent HSCT with RIC regimen at our institution between 2014 and 2021.

Design/Method:
Case Series

Results:
Four patients underwent an irradiation-free RIC regimen with distal alemtuzumab, fludarabine (150 mg/m2), melphalan (140 mg/m2), and thiotepa (8 mg/kg). Patient 4 additionally received hydroxyurea. All patients were transfusion dependent with iron overload and had failed corticosteroid therapy prior to HSCT. Patient 4 also had autoimmune neutropenia prior to HSCT. Median age at HSCT was 10.5 years (5–17 years). All patients are alive with median follow-up of 20 months (12–72 months). Patient 1 underwent an HLA-matched sibling donor transplant, and patients 2, 3, and 4 underwent HLA-matched unrelated donor transplants. Patient 2 and 3 received bone marrow, and patient 4 received cord blood. Patients 1, 2, and 3 received GVHD prophylaxis with tacrolimus, methotrexate, and abatacept; patient 4 received cyclosporine and mycophenolate mofetil. Median neutrophil engraftment was on day +15 (12–23 days). All patients were transfusion independent by day +100. All patients had >95% donor chimerism at Day +30. Peripheral blood CD3 donor chimerism of patient 3 dropped to 69% at 6 months post-HSCT but is now 94% at 2 years post-HSCT. All patients had >95% CD15 myeloid engraftment at all time points.

No patients developed VOD. Three patients developed aGVHD with maximum grade II, skin stage 3. Two patients developed mild cGVHD, and two patients developed moderate cGVHD. Patient 2 developed chronic GI and skin GVHD, which resolved with tacrolimus and prednisone. This patient was successfully weaned off systemic immunosuppression (IS) on day +303. Patient 1 developed chronic mouth, GI, and liver GVHD at Day +328, which was successfully treated with ruxolitinib. Three patients weaned off IS post-HSCT (median discontinuation on day +281).

Patient 2 was treated successfully with rituximab for EBV viremia before day +100. Patient 4 was treated for adenoviremia with a single dose of cidofovir before day +100.

Conclusion:
HSCT with a RIC regimen was well-tolerated in our cohort. All patients remain transfusion independent and infection-free with excellent donor chimerism at time of last follow-up.

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22) Utility of Cytoreduction prior to Hematopoietic Stem Cell Transplantation in Pediatric Myelodysplastic Syndrome and associated Myeloid Neoplasms: A 10-Year Single Center Experience

Theme: Disease-Specific, Transplant-Related

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[d]Both authors contributed equally.

Background:
Pediatric myelodysplastic syndrome (MDS) and related myeloid disorders are more commonly associated with underlying germline conditions or preceding cancer therapy compared to adult MDS. Allogeneic hematopoietic stem cell transplantation (HCT) is the only potential curative treatment, but nearly half will relapse after HCT. The prognostic impact of proceeding to HCT in complete remission (CR) without measurable residual disease (MRD) and the role of cytoreduction prior to HCT remains controversial.

Objective:
Determine the prognostic impact of pre-transplant cytoreduction and remission status on post HCT outcomes in pediatric patients with MDS and related disorders.

Method:
We performed an IRB-approved retrospective analysis of pre-transplant disease management and clinical outcome for pediatric patients with MDS and related disorders who underwent HCT at Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, USA from 2010-2020.

Result:
63 patients (median age 10 years, range 0-21 years) with idiopathic MDS (n=17), germline MDS (n=13), secondary AML (n=8), myeloproliferative syndromes (n=8) and treatment related myeloid neoplasms (n=17) received an allogeneic HCT. In 26% an underlying germline disorder was identified. Transplant conditioning was primarily busulfan based (n=45) and bone marrow was the primary graft source (n=44). Cytoreduction prior to HCT was performed in 30/63 (n=4 hypomethylating agent, n=25 induction AML chemotherapy, n=1 other). The median time from diagnosis to HCT was 115 days (range 15 – 721days) and did not differ between the groups (p=0.08). Outcomes for patients that received cytoreduction and were MRD negative prior to HCT were superior compared to those with persistent disease after cytoreduction (cumulative incidence of relapse 24-months post-HCT 0.42 (0.15, 0.67) versus 0.6 (0.21-0.85) respectively, p=0.01). Use of cytoreduction prior to HCT was associated with inferior outcome in the overall cohort (cumulative incidence of relapse 24-months post-HCT 0.47 (0.27, 0.65) for those who received cytoreduction versus 0.16 (0.06, 0.31) who did not (p=0.01). However, the subset of patients who received cytoreduction had higher-risk disease characteristics. For those receiving cytoreduction, the median blast percent at presentation was 36% (range 0-95%) compared to those who did not receive cytoreduction (median 0%, range 0-13%, p<0.0001).

Conclusion:
Cytoreduction did not provide benefit in our overall cohort, but its use in children with inherently higher risk disease may have impacted our ability to demonstrate clinical benefit. For patients that received cytoreduction, outcomes were superior if the patient was MRD negative at time of HCT. Larger pediatric studies will characterize the role and optimal approach to cytoreduction on overall outcome post HCT.

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23) An Ex-vivo model for the Evaluation of Unrestricted Somatic Stem Cells (USSCs) Therapy in Acquired Severe Aplastic Anemia

Theme: Disease-Specific, Transplant-Related

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Short Title: USSCs Therapy in Acquired Severe Aplastic Anemia
Key Words: IFN-γ, Acquired Severe Aplastic Anemia, aSAA, STAT 1, CFU, unrestricted somatic stem cells, USSCs, Ex-vivo model.

Financial Disclosure Statement: None.

Background:
In acquired SAA, oligoclonal expansion of dysregulated CD8+ cytotoxic T cells, abnormal function of CD4+ T helper cells, along with elevated production of IFN-γ and TNF-α have been associated with the apoptosis of hematopoietic stem and progenitor cells (HSPC) (Young, N Engl J Med, 2018). Liao and Cairo et al (Cell transplantation, 2014) have demonstrated that cord blood-derived unrestricted somatic stem cells (USSCs) could significantly reverse the abnormal/inverted ratio of CD4:CD8 T cells, induce the number of FOXP3A positive Treg cells and decrease the level of IFN-γ in an animal model of recessive dystrophic epidermolysis bullosa (RDEB). Alternative therapies are in great need for patients with aSAA, since current treatment responses are sub-optimal.

Objective:

To determine the effect of USSCs on HSPC survival and differentiation in an ex vivo culture of aSAA with human CD34+ cells.

Design/Methods:
Human HSPC were cultured with human stem cell factor, FMS-like tyrosine kinase 3 ligand and recombinant human TPO. HSPC alone, with and without IFN-γ and TNF-α, served as controls. USSCs (direct or transwell) were added to the culture**,** HSPC were subsequently harvested and assayed for their survival at day 7 and 14. Annexin-V+/PI+ were referred as late apoptotic cells. Each experimental condition was set up in triplicate. The cells were cultured at 37°C with 5% CO_2. Multi-lineage differentiation capacity was assessed with a selective colony forming units (CFU) assay and compared between experimental groups. Signaling pathways were determined using phosphor-flow-cytometric analysis of pSTAT1.

Results:
The myelosuppressive effect of IFN-γ and TNF-α was significantly rescued (4-fold increase) by the addition of USSCs (transwell) at day 7. At day 28, direct co-culture with USSCs also demonstrated increased CD34+ cell survival ($p<0.001$)**,** from 5 to 35 CD34+ cells/µl. A significantly higher percent of viable cells (73%) was observed among the USSCs treated cells ($P<0.05$), compared to IFN-γ and TNF-α treated cells (63%). Based on the CFU analysis, the CD34+ cells cultured in the presence of USSCs produced more CFU (52, SD±3.7) at day 7 ($p<0.01$) compared to IFN-γ and TNF-α treated cells (16, SD±2.8). In addition at day 14, USSCs demonstrated more BFU ($p<0.05$). Phosphor-flow-cytometric analysis demonstrated a significant decrease in STAT1 in the presence of USSCs ($p<0.05$).

Conclusions:
Cellular therapy, such as USSCs may be therapeutic in the treatment of aSAA. Future studies will need to be done to investigate the exact mechanisms of action and the clinical efficacy of this novel therapy.

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24) Infection rates and Rapid Immune Cell Reconstitution Following Familial Haploidentical (FHI) CD34 Enriched Peripheral Blood (PB) Stem Cell Transplantation (HISCT) with PB Mononuclear Cell Addback in Patients with High-Risk Sickle Cell Disease (SCD)

Theme: Disease-Specific, Transplant-Related

Authors: Talano JA[1], Moore TB[2], Shi Q[3], Weinberg RS[4], Grossman B[5], Shenoy S[6], Chu Y[7], Baxter-Lowe LA[8], and Cairo MS[7,9,10,11,12]
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Background
We previously reported the results of a phase II multicenter transplant trial using haploidentical parental donors for children and adolescents with high-risk Sickle Cell Disease (SCD) achieving excellent survival with exceptionally low rates of graft-versus-host disease (GVHD) and resolution of SCD symptoms.

Objective:
To investigate the rates of infections and immune reconstitution in 20 patients with high risk sickle cell disease who have undergone haploidentical transplantation.

Methods
Comprehensive assessment of immune reconstitution included lymphocyte subsets, plasma cytokines, complement levels, and activation markers were obtained. Incidence of viral, bacterial and fungal infections were recorded.

Results
Myeloid engraftment was robust (100%) at a median of 9 days. NK cell levels were rapidly restored by 30 days. By 60 days, CD19 B cells were normal. CD8 and CD4 T cells levels were normal by 279 and 365 days, respectively. Activated CD4 and CD8 T cells were elevated 100-365 days post-transplant while naïve cells renewal was below baseline. Tregs were elevated 100-270 days post-transplant, returning to baseline levels at one year. At one year, C3 and C4 levels were above baseline and CH50 levels were similar to baseline. The incidence of viral reactivation was CMV =5, EBV= 5, HHV6 =3, and Adenovirus =2. Three fungal infections occurred (Candida =2, Aspergillus fumigatus =1). There were 10 bacterial infections-, Enterobacter cloacae =4, Bacillus =2, Staph coag neg =2, Elizabethkingia menignoseptica =1, and Strep slavarius =1. The cumulative incidence of grades 2 to 4 acute GVHD and late acute GVHD was 6.2% and moderate and/or severe chronic GVHD was 6.7%. The probability of 1-year EFS or overall survival was 90% (95% CI, 64.1%-97.3%) and of 2-year EFS or overall survival was 84% (95% CI, 57.0%-94.4%), and no patient had residual SCD symptoms.

Conclusion
These results suggest that haploidentical transplantation utilizing CD34 enrichment and PB MNC addback resulted in rapid and 100% engraftment with excellent OS and EFS. The fixed T cell addback was protective against significant viral infections but reactivations did occur. There were no primary deaths attributable to infection. The 50% incidence of bacterial infections is significant and should warrant future studies. Extended bacterial prophylaxis may be warranted for this population.

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25) TIGHT BLOOD PRESSURE CONTROL DURING HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH SICKLE CELL DISEASE

Theme: Supportive Care

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Theme: Bone Marrow Transplant, Supportive Care

Background:
Posterior reversible encephalopathy syndrome (PRES) is a serious complication of hematopoietic stem cell transplant (HSCT) characterized by the acute onset of seizures, headache, altered mental status and cortical blindness early post-transplant. It is associated with hypertension (HTN). Children with sickle cell disease (SCD) appear to be especially prone to developing PRES after HSCT with incidences ranging from 21% to 34% observed in major clinical trials of HSCT for SCD.

Objective:
To describe our single institution experience of using tight blood pressure (BP) control in pediatric patients with SCD undergoing HSCT.

Design:
At Phoenix Children's Hospital, all patients with SCD underwent a 24-hour ambulatory blood pressure monitoring prior to HSCT and a baseline for each patient was established. All patients identified as hypertensive began treatment, the rest received first-line treatment of either calcium antagonist followed by angiotensin-converting enzyme inhibitor, a diuretic, or both to achieve systolic BP no greater than 10% of their baseline. We conducted a retrospective chart review from 2010 to 2020, identifying 25 patients who underwent a HSCT for SCD, using a Campath/Flu/Mel conditioning regimen. We reviewed several end organ outcomes including cardiac: HTN, left ventricular mass (LVM); renal: eGFR (calculated by Bedside-Schwartz), use of antihypertensives pre/post-transplant; neurological: incidence of PRES, strokes, and MRI findings pre/post-transplant. Analysis performed included paired T test and measuring the frequency of certain outcomes.

Results:
The average age at transplant was 11.5 years (range: 2-21 years). Indications for transplant included multiple pain crises, frequent acute chest syndrome and strokes. Preexisting HTN was found in 6 patients, 5/6 achieved good control w/ medications, 4/5 required continued treatment post-transplant. Post-transplant, HTN was diagnosed in 12 patients, 10/12 requiring initiation after Campath and 4/12 being weaned off prior to 1-year post-transplant. Pre-transplant, LVM > 95% for age was present in 7/24 patients; post-transplant, only one individual continued to have high LVM ($p < 0.01$). Pre-transplant, 14/24 patients had hyperfiltration w/ eGFR > 135; post-transplant, 11/24 patients experienced continued hyperfiltration ($p > 0.05$). On pre-transplant MRI, 10/24 patients had evidence of prior stroke; 8/10 eventually needed antihypertensive medications, and 9/10 patients had stable disease post-transplant. None of the 24 individuals who underwent tight blood pressure control had PRES post HSCT.

Conclusion:
Our preliminary results suggest that using tight BP control during HSCT is well tolerated, and no patient had PRES. In addition, patients had improvements or stabilization in cardiac, renal, and neurological function at 1-year post HSCT.

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26) Prior COVID-19 Infection and Risk for Developing Endothelial Dysfunction Following Hematopoietic Cell Transplantation

Theme: Supportive Care

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Background:
Endothelial dysfunction underlies many of the major complications following hematopoietic cell transplantation (HCT), including transplant-associated thrombotic microangiopathy (TA-TMA) and sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD). Emerging evidence similarly implicates endothelial cell dysfunction and microangiopathy in severe COVID-19-related multi-system organ dysfunction. Given the overlap in these two illness states, we hypothesize that COVID-19 infection increases the risk of HCT-related endotheliopathies among pediatric and young adult patients.

Objective:
The purpose of this study is to evaluate the relationship between COVID-19 infection and incidence of post-HCT complications mediated by endothelial dysfunction among pediatric and young adult patients.

Design/Method:
This retrospective, multicenter study included patients aged 0-25 years who underwent autologous or allogeneic HCT for any indication between January 1, 2020 and September 21, 2021 and were infected with COVID-19 in either the six months prior to transplant or twelve months following transplant. Clinical variables were collected via review of the medical record. Descriptive statistical analyses were performed.

Results:
Twenty-three total eligible patients were identified. Of those, ten patients were identified who contracted COVID-19 prior to transplant (median age 14.5 years, 80% allogeneic, median date of infection was day -107, range of -73 to -205). Among these patients, 40% developed TA-TMA

and 30% developed SOS/VOD. Thirteen patients were identified who contracted COVID-19 following transplant (median age 16 years, 84.6% allogeneic, median date of infection was day +206, range of +54 to +345). Among these patients, who were notably beyond the highest risk period for development of these endotheliopathies, only 7.7% had TA-TMA and 7.7% had SOS/VOD with these cases pre-dating the diagnosis of COVID-19.

Conclusion:
Among our small group of pediatric and young adult patients who underwent HCT following COVID-19 infection, rates of TA-TMA and SOS/VOD may be higher than rates reported for historical controls. Comprehensive systematic reviews featuring heterogenous populations undergoing autologous and allogeneic HCT cite the incidence of TA-TMA as 12% and pediatric SOS/VOD as 20%. Additionally, patients who contracted COVID-19 prior to HCT may display higher rates of TA-TMA and SOS/VOD than patients who contracted COVID-19 after the typical timeframe these complications arise post-HCT, though statistical significance was unable to be established due to small sample size. Further investigation with larger study groups is warranted to better elucidate this relationship. Overall, our results suggest that enhanced screening for post-transplant endotheliopathies may be warranted for patients undergoing HCT who have a history of COVID-19 infection.

Citations:
Van Benschoten, Transplantation and Cellular Therapy, 2022
Corbacioglu, Bone Marrow Transplant, 2018

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27) A pilot study of gut decontamination and the risk of bloodstream infections during pediatric allogeneic hematopoietic cell transplantation

Theme: Supportive Care

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Background:

Pre-clinical studies suggest that gut decontamination (GD) may protect against acute graftversus-host-disease (aGVHD), although no studies have focused on the potential impact of GD on nonaGVHD illnesses. We recently conducted a randomized phase 2 trial (ClinicalTrials.gov NCT02641236) of GD. We report the results of an exploratory analysis of the impact of GD on the incidence of bloodstream infections (BSI) in pediatric allogeneic hematopoietic cell transplantation (HCT) patients.

Objectives:
(1) Define the Shannon diversity following GD, (2) determine the incidence of BSI in GD and no-GD arms.

Methods:
Patients were randomized to receive the GD regimen (Arm A, n=10) (oral vancomycinpolymyxin B from day -5 through neutrophil engraftment) or not receive GD (no-GD; Arm B, n=10), with the primary objective to characterize the gut microbiota at 2-weeks post-HCT. Serial stool samples were collected from patients in both arms and subsequently underwent shotgun metagenomic sequencing to characterize the gut microbiome. In an exploratory, *post-hoc* analysis, stool metagenomic sequences were compared against the assembled sequence of a BSI isolate for any patient with a BSI in the first 100 days using a population average nucleotide identity (popANI) metric.

Results:
There was no statistical difference between the two arms in Shannon diversity of the gut microbiota at 2 weeks post-transplant for either genus (p=0.80) or species level (p=0.44). Six patients had a total of nine BSI episodes in the first 100 days post-HCT. We observed fewer BSI (1 vs. 5, p=0.048) in the GD vs no-GD arm, respectively. Using strain-specific analysis of BSI-causing bacteria and temporal association with the stool microbiome from patients who developed BSIs, we identified BSI-causing pathogens in 7 of 8 BSI episodes in the gut microbiome in the no-GD arm, including the genus *Staphylococcus* in two patients. The one BSI in the GD arm was not derived from the gut.

Conclusion:
All gut-localized BSIs were found in the non-GD arm suggesting that GD may protect against BSI in HCT patients by decreasing the prevalence or abundance of pathogens that can translocate across the mucosal barrier and subsequently cause gut-derived BSIs. In addition, *Staphylococcus* was found in the gut suggesting the need for an expanded definition of non-mucosal barrier injury (MBI) pathogens in HCT.

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28) Hospital Mandated Restrictions During the COVID-19 Pandemic Alter Hospital Acquired Viral Respiratory Infections During Hematopoietic Stem Cell Transplantation: A Single Center Experience

Theme: Supportive Care

Authors: Perry C. Morocco, M.D., Miranda Foote, M.S.N., P.N.P., Caitlin Cohen, P.N.P., Madan Kumar, D.O., Michele L. Nassin, M.D., M.S., John M. Cunningham, M.D., and James L. LaBelle, M.D., Ph.D.

Submitting Institution: University of Chicago, Comer Children's Hospital, Chicago, IL, USA

Background:
Healthcare systems across the world abruptly changed with the COVID-19 pandemic. At the University of Chicago, strict visitor restrictions were enacted and the use of personal protective equipment was required for patients and staff, reflecting an overall increased institutional awareness of infection preventative measures. It is known that infection control measures, including proper hand hygiene, isolation, and neutropenic precautions, are critical in protecting immunocompromised patients [1], and data is now emerging on how the pandemic affected these measures in various healthcare settings. Recent studies have found that the pandemic has resulted in a 20% decrease in the rates of hospital nosocomial infections [2] and a significant decrease in seasonal respiratory viral infections in adult allogeneic stem cell transplant (SCT) patients, [3].

Objective:
Our goal was to study the incidence of respiratory viral pathogens and transplant-related outcomes prior to and during the COVID-19 pandemic in pediatric SCT patients.

Design/Methods:
A retrospective chart review of patients who underwent SCT at the University of Chicago's Comer Children's Hospital from 7/1/2013-12/19/2021 was conducted. The "pre-COVID-19 era" was defined as 7/1/2013-3/17/2020 and the ''post-COVID-19 era" as 3/18/2020-12/19/2021. The post-COVID-19 era was further subdivided into early, 3/18/2020-2/21/2021, and late, 2/22/2021-12/19/2021, periods based on the institution's loosening of infection control policies. Respiratory viral pathogen (RVP) testing obtained immediately prior to transplant admission and all subsequent RVP testing for that hospitalization was collected. Demographics of all patients was collected, as were outcome measures, including rates of new RVP positivity, death within 100/180/365 days of stem cell infusion, pediatric intensive care unit (PICU) admission, supplemental oxygen requirements, incidence of graft-versus-host disease, and inpatient length of stay.

Results:
We found a significant difference in new RVP positivity during SCT admissions between the early post-COVID era and the pre-COVID and late post-COVID eras, with complete absence of new respiratory viral infections (0/23) versus 17% and 25% positivity respectively ($p=0.027$ and 0.016). The pre-COVID and late post-COVID eras demonstrated similar rates of new RVP positivity ($p=0.36$). Comparison of outcomes in patients with new RVP positivity versus those without, found a statistically higher rates of PICU admission (65.0% to 33.3%, $p=0.013$) and endotracheal intubation (55.0% to 20.0%, $p=0.003$) for allogeneic SCT patients but no differences in autologous SCT patients. There were no differences in mortality between any patient group.

Conclusion:
These findings argue for a continuation of strict protective isolation practices employed during the pandemic for pediatric SCT patients to reduce morbidity.

References:
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[2] Jabarpour, M, et al., Infect Control Hosp Epidemiol, 2021.
[3] De la Puerta R, et al., Bone Marrow Transplant, 2021.

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29) Obesity increases endothelial injury following hematopoietic stem cell transplant

Theme: Supportive Care

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Background
Elevated body mass index (BMI) is characterized as a chronic inflammatory state with endothelial dysfunction. Endothelial injury after hematopoietic stem cell transplant (HSCT) puts patients at risk for complications including transplant-associated thrombotic microangiopathy (TA-TMA). Using a murine model, we hypothesized that elevated BMI in the setting of allogeneic-HSCT (allo-HSCT) predisposes obese mice toward increased endothelial damage.

Objective
To determine if endothelial injury is increased following allo-HSCT *in vivo* and to identify potential targets through proteomic analysis of murine samples from obese mice would which would help in the early identification and risk stratification of TA-TMA among pediatric allo-HSCT.

Methods
C57BL/6J diet-induced obese (DIO) mice and C57BL/6 lean mice were lethally irradiated and injected with $3x10^5$ bone marrow cells from C57BL/6 wild-type donors. Peripheral blood was collected at set time points after transplant for proteomic analysis. Organs were harvested for immunohistochemistry and stained for vascular cell adhesion-molecular (VCAM-1), von Willebrand factor (vWF) and thrombomodulin (TM). Proteomic analysis of obese and lean control plasma samples was performed. Proteins differentially expressed in lean and obese mice were identified and validated in human samples. Examples include vascular endothelial growth factor (VEGF), IL-1β, IL-33, oxidatively modified low-density lipoprotein (OxLDL) and matrix metalloproteinase-9 (MMP-9) were quantified using enzyme-linked immunosorbent assays (ELISA) in consecutive pediatric plasma allo-HSCT samples.

Results

Proteomic analysis of obese and lean murine plasma samples showed differentially expressed proteins including VEGF, IL-1β, IL-33, OxLDL and MMP-9. Elevations in endothelial markers VCAM-1, vWF and TM were observed by IHC in DIO mouse kidney, lung and heart samples compared to control samples on days 14 and 21 from HSCT. Plasma levels of OxLDL were higher in pediatric allo-HSCT recipients with high-risk TMA (median 3297.6 ng/mL) compared to patients without TMA (median 2920.3 ng/mL, p=0.081) Overall IL-1β expression was lower among allo-HSCT patients with high-risk TMA (range 7.77-14.30 pg/mL) compared to allo-HSCT recipients without TMA patients (range 14.06-77 pg/mL,p=0.006).

Conclusions
Expression of VCAM-1, vWF and TM was elevated in transplanted obese mice compared to lean mice demonstrating increased endothelial injury after allo-HSCT. Proteomic analysis revealed increased expression of proteins related to obesity and endothelial injury. OxLDL expression was higher in patients with high-risk TMA and IL-1β expression was lower in patients with high-risk TMA compared to controls. Further experiments are required to determine the significance of these identified markers as potential predictors and prognostic measures of endothelial injury and TMA after HSCT.

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30) IMPACT OF TRIMETHOPRIM/SULFAMETHOXAZOLE PROPHYLAXIS ON ENGRAFTMENT IN PEDIATRIC ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS: A SINGLE CENTER EXPERIENCE

Theme: Supportive Care

Authors: Amanda Lipsitt, Dinesh Keerthi, Ronald Dallas, Jose Ferrolino, Akshay Sharma, Gabriela Maron

Background
Trimethoprim/Sulfamethoxazole (TMP-SMX) is the preferred drug for *Pneumocystis jirovecii pneumonia* (PJP) prophylaxis because of its superior efficacy compared to alternative prophylaxis regimens. However, there are concerns that TMP-SMX can delay engraftment after a hematopoietic cell transplant (HCT) due to its potential myelotoxicity and is therefore generally avoided in pediatric patients in the peri-engraftment period. There is insufficient evidence in the literature on whether TMP-SMX delays engraftment or causes graft failure. Alternative medications commonly used for PJP prophylaxis are less effective and can have unwanted side effects. Additionally, compared to TMP-SMX, most of these medications do not provide coverage against other opportunistic infections such as toxoplasmosis, nocardiosis, listeriosis, and other susceptible bacteria.

Objective
To determine if the use of TMP-SMX for PJP prophylaxis in the peri-engraftment period among pediatric patients delays engraftment or affects graft function.

Design/Method
The medical records of 497 patients under 21 years of age who underwent allogeneic HCT at St. Jude Children's Research Hospital from January 1, 2010 to December 31, 2020 were reviewed.

All received TMP-SMX for PJP prophylaxis during the peri-engraftment period. Of these, 474 patients had recorded time to neutrophil engraftment and 442 patients had recorded time to platelet engraftment.

Results
Majority of the cohort was male (52.5%, n=249) with a median age of 9 years (ranging from 0 to 21 years). Most received an HCT for a malignant disease (n=413: AML=196 and ALL=135). Median overall time to neutrophil engraftment (NE) was 15±12 days and time to platelet engraftment (PE) was 19±22 days. Peripheral blood derived hematopoietic stem cell grafts (n=235) had a median of 11±2 days to NE and 16±15 days to PE. For bone marrow derived grafts (n=222) median time to NE was 20±5 days and to PE was 25±21 days. Graft failure was observed in 15 out of 474 individuals (3.1%).

Conclusion
In this cohort of pediatric HCT patients receiving TMP-SMX during the peri-engraftment period, days to neutrophil and platelet engraftment and the proportion of graft failure are consistent with historic standards (Ogonek, Justyna, et al. *Frontiers in immunology* 7 (2016): 507.). This suggests that TMP-SMX, which is the preferred medication for PJP prophylaxis, does not appear to clinically affect engraftment and may be safely used during the engraftment period.

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31) Incidence of Early Revaccination After Pediatric Allogeneic Hematopoietic Stem Cell Transplant

Theme: Supportive Care

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Background: Infections are a common cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT). Prolonged immune recovery post-HSCT increases the risk of infection and raises concern for poor response to vaccinations. Reimmunization is recommended for all pediatric HSCT patients by transplant and infectious disease organizations[1,2], and individual institutions often develop revaccination guidelines.

Objective: At Vanderbilt Children's Hospital (VCH), the clinical practice guideline (CPG) instituted in June 2015 recommends early initiation (6 months) of reimmunization in immunologically appropriate patients, starting with *Haemophilus influenzae* type B (Hib) and pneumococcal conjugate (PCV13) vaccinations. Therefore, we examined the feasibility of early vaccination for allogeneic HSCT patients and determined the causes of delayed or lack of vaccination.

Methods: A retrospective chart review of the electronic medical record was conducted under an IRB-approved protocol. Data was gathered and entered in a REDCap database, including dates of vaccination, immune reconstitution studies (IgG concentration, T/B cell subsets) and clinical outcomes [e.g., intravenous immunoglobulin (IVIg) administration, graft versus host disease (GvHD), relapse] through 6-month (+/- 30 days) post-HSCT. Early revaccination was defined as Hib and PCV13 administration within 210 days post-HSCT. Patients not meeting this definition were further examined for factors that led to delay or lack of vaccinations. Patients were included if they were alive without underlying disease progression or graft failure 6-months post-HSCT.

Results: Between June 15, 2015 and June 30, 2021, 66 patients met inclusion criteria. Early revaccination occurred in 21/66 patients (32%). Of the 45/66 (68%) that did not receive 6-month vaccinations, the most common reason was concern for impaired immune reconstitution (n=33/45, 73%). Indicators of poor immune recovery included recent IVIg administration (n=15), ongoing immunosuppression (n=24), and poor B cell recovery (n=4); many patients had multiple indications. Other reasons for delay included patient or parent refusal (n=4), prioritization of COVID vaccinations (n=3), scheduling conflicts (n=4), and other (n=1).

Conclusions: Early vaccination occurred in 32% of patients. At 6 months post-HSCT, 50% of patients had poor immune reconstitution resulting in appropriate vaccination delays. However, scheduling conflicts and vaccine hesitancy despite eligibility were small but significant contributors, accounting for 17% of delays. This is a small, single center study but highlights significant challenges with delivery of best practice guidelines. Future directions could include engagement with other institutions regarding best practices to address vaccine hesitancy and to further explore if early revaccination reduces risk of infectious complications post-HSCT.

References:
[1] Tomblyn et al., BBMT, 2009
[2] Rubin et al., Clin Infect Dis., 2014

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32) A New KMT2A-BTK Fusion Oncogene in Pediatric Acute Myeloid Leukemia

Theme: Supportive Care

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Background
Specific subgroups of pediatric AML patients still fare dismal outcomes despite high-risk chemotherapy protocols and hematopoietic stem cell transplantation (HSCT), especially in infants. Chromosomal rearrangement of the Lysine Methyltransferase 2A (*KMT2A*) gene

(11q23) remains the most frequent genotype of infant AML and has been reported in pediatric leukemia with more than 80 fusion partners. The translocation partner of *KMT2A* and coexistent mutations in leukemia cells are both age-specific prognostic factors. Functional mechanisms and targeted therapies are increasingly studied for a few frequent *KMT2A* rearrangements, yet a substantial proportion of *KMT2A* fusions remain poorly or not at all characterized.

Objective
In a pediatric case of monocytic AML, we recently identified a new *KMT2A* fusion partner, the Bruton tyrosine kinase (*BTK*) gene. We aim at further characterizing the *KMT2A-BTK* fusion and the impact of multi-targeted kinase inhibitor sorafenib in the evolution of the disease in this patient.

Design/method
Molecular and biochemical analysis were performed on bone marrow aspirate at diagnosis and throughout the medical follow up. Next-generation sequencing (NGS) was performed on the RNA of the bone marrow leukemic cells. Minimal residual disease (MRD) was measured by flow cytometry and confirmed by nested reverse transcription polymerase chain reaction (nRT-PCR) for tracking of fusion transcript. The patient received three cycles of high-risk AML-type chemotherapy, a tyrosine kinase inhibitor and an allogenic HSCT. In the context of refractory AML, a maintenance therapy with sorafenib was initiated post-HSCT. We performed serial transcriptomic analyses on patient's bone marrow cells at three different timepoints post-HSCT (before and after receiving sorafenib).

Results
We identified a *KMT2A-BTK* fusion and a *FLT3-TKD* collaborating mutation. MRD was not detected with phenotypic assays, although persistently detected by nRT-PCR pre- and post-transplant. Disease monitoring with sorafenib treatment showed complete remission at day 95 post-transplant. We observed an upregulation of specific immuno-modulatory pathways with the addition of sorafenib, compatible with a graft-versus-leukemia (GVL) effect.

Conclusion
Ongoing studies of *KMT2A* rearrangements in AML, especially in infant, are crucial to fine-tune the medical management of these patients and improve the currently poor survival rate. We describe a new *KMT2A-BTK* fusion in pediatric AML. We highlight the importance of NGS techniques and multicenter studies to identify leukemic genetic alterations that can be used for MRD tracking and patient management. We hypothesize that the use of sorafenib in this patient contributed, at least in part, to achieve remission by promoting a GVL effect of the allogenic graft.

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33) Single institution experience with haploidentical HSCT using ptCY for pediatric hematological malignancies.

Theme: Supportive Care

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Background:
Haploidentical allogeneic hematopoietic stem cell transplantation (Haplo-HSCT) using post-transplant Cytoxan (ptCY) for graft vs host disease (GVHD) prophylaxis is a growing subtype amongst all HSCTs for high-risk acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndromes (MDS), mixed phenotypic leukemias (MPAL) and lymphomas. We present here a single institution experience over ten years comparing three groups, namely Haplo-HSCT, matched related donor (MRD-HSCT) and unrelated donor (MUD-HSCT) transplants. Historically Haplo-HSCT was not preferred over MUD-HSCT due to concerns of GVHD and other treatment related complications including viral reactivations.

Objective:
Our goal was to compare all three transplant cohorts with respect to overall survival (OS) outcomes, incidence of graft vs host disease (GVHD); treatment complications such as veno-oclusive disease and CMV reactivation.

Method:
After IRB approval for a retrospective study, we reviewed patient charts for all transplants between 2010 and 2020, 105 patients who received allogeneic HSCT for various hematological malignancies were included in the review, ALL (n = 58); AML/MDS/CML (n = 40), MPAL (n=2) and lymphomas (n=5). The median age was 13 years (0.7 – 23.3 yrs.). Donors were haploidentical for 42, matched related for 34 and unrelated for 29. Donor source was bone marrow (BM) (n=31) and Peripheral blood (PBSC) (n=11) for haplo-HSCT; BM (n=24) and PBSC (n=10) for MRD-HSCT; BM (n=10), PBSC (n=10) and cord blood (UCB) (n=9) for the MUD-HSCT.

Results:
One-year overall survival was for the groups Haplo-HSCT, MRD-HSCT, MUD-HSCT, was 78.6%, 73.5% and 62% and respectively. Acute GVHD grades 1 and 2 were 42.9%, 5.9%, and 41.4%, respectively. Acute GVHD grades 3 and 4 were 9.5%, 8.8% and 10.3% respectively. Chronic GVHD limited were 4.8%, 0% and 0% and respectively. Chronic GVHD extensive were 11.9%, 8.8% and 24.1% and respectively. Veno-occlusive disease was noted in 16.7%, 11.8% and 34.5% respectively. CMV reactivation was noted in 28.6%, 17.6% and 44.8% respectively.

Conclusion:
This single institution retrospective study suggests the potential of Haplo-HSCT as a curative treatment for high-risk hematological malignancies with comparable results to MRD-HSCT and potentially better outcomes than MUD-HSCT. It also highlights the role of ptCY as a viable option for GVHD prophylaxis.
