ASPHO 2019 Conference Paper and Poster Index

Paper Presentations

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Poster Presentations

Odd-numbered posters will present on Thursday, May 2 from 5:30-6:30 pm in the Exhibit Hall.

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Two poster tours will take place in the Exhibit Hall:

- **Even-numbered on Thursday, May 2 from 5:45-6:15 pm**
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Plenary Paper # 2001

POTENTIAL UTILITY OF MRD TO IDENTIFY RELAPSE IN pALL PATIENTS TREATED WITH TISAGENLECLEUCEL

Michael Pulsipher, Xia Han, Maire Quigley, Gabor Kari, Susana Rives, Theodore Laetsch, Gary Myers, MD, Hidefumi Hiramatsu, Gregory Yanik, Muna Qayed, Timothy Driscoll, Michael Boyer, Heather Stefanski, Jochen Büchner, Andre Baruchel, Peter Bader, Lan Yi, Creton Kalfoglou, Harlan Robins, Erik Yusko, Gullu Gorgun, Eric Bleickardt, Stephane Wong, Stephan Grupp

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Background: Detection of minimal residual disease (MRD) is an important predictor of patient outcome following treatment of B-cell acute lymphoblastic leukemia (ALL); importantly, MRD is emerging as a useful tool to detect early relapse, which may fulfill a key previously unmet clinical need.
Objectives: To evaluate the potential of MRD to predict morphologic relapse in pediatric and young adult ALL (pALL) patients.
Design/Method: Bone marrow (BM) and peripheral blood (PB) specimens at screening (pre-tisagenlecleucel infusion), post-infusion, and relapse from two ALL clinical trials (ELIANA [NCT02435849] and ENSIGN [NCT02228096]) were tested using immunoglobulin next-generation sequencing (IgNGS) and flow cytometry (FC). We assessed concordance between two MRD assays to determine which method could support early relapse detection and whether using PB with IgNGS was comparable with BM testing with FC.
Results: IgNGS was performed in 300 samples from 88 patients. 237 samples from 83 patients also had FC MRD results available. Baseline samples, which had high disease burden, showed 100% MRD concordance between both assays. However, post-treatment, where the leukemic burden was dramatically reduced, IgNGS detected a greater number of MRD-positive samples vs FC at each sensitivity level tested (10-4, 10-5, and 10-6). At the highest sensitivity level of 10-6, IgNGS was able to detect 18% more MRD-positive post-treatment samples. IgNGS was able to detect MRD positivity 1-4 months ahead of clinical relapse in a small number of relapsed patients, whether relapse was CD19+ or CD19-. MRD burden in BM was higher than in PB using both FC and IgNGS. In patients with matching data available, IgNGS was able to detect more MRD-positive PB samples than FC MRD-positive BM samples. Patients who were MRD negative by both IgNGS and FC at the end of first month post-infusion had better progression-free survival (PFS) and overall survival (OS) compared with those with detectable MRD. Tumor clonality at baseline and clonal evolution following tisagenlecleucel treatment will be presented.
Conclusion: MRD detection using IgNGS in PB may be used as a surrogate for FC assessment of MRD in BM. Patients who were MRD negative by IgNGS 1 month after infusion had improved PFS and OS vs those with detectable MRD; ongoing studies will provide further information on the applicability of IgNGS MRD detection and its association with long-term outcome in tisagenlecleucel-treated relapsed/refractory pALL patients.Support: Novartis.

Plenary Paper # 2002

LENTIGLOBIN GENE THERAPY IN TRANSFUSION-DEPENDENT B-THALASSEMIA PATIENTS WITH NON-β0/β0 GENOTYPES

Timothy Olson, Mark Walters, Janet Kwiatkowski, Suradej Hongeng, John Rasko, John Porter, Martin Sauer, Adrian Thrasher, Isabelle Thuret, Gary Schiller, Heidi Elliot, Briana Deary, Ying Chen, Ge Tao, Mohammed Asmal, Franco Locatelli, Alexis Thompson

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Background: Although advances in red blood cell (RBC) transfusion and iron chelation have improved the prognosis of patients with transfusion-dependent β-thalassemia (TDT), hematopoietic stem cell (HSC) transplantation is the only curative treatment. LentiGlobin, an investigational gene therapy for TDT, contains autologous CD34+ HSC transduced ex vivo with the BB305 lentiviral vector encoding β-globin with a T87Q substitution.
Objectives: Describe the safety and efficacy of LentiGlobin in patients with TDT (≥100 mL/kg/yr RBCs or ≥8 RBC transfusions/yr) and non-β0/β0 genotypes from the Phase 1/2 Northstar (NCT01745120) study and Phase 3 Northstar-2 (NCT02906202) study using a refined manufacturing process.
Design/Method: HSCs were mobilized using G-CSF and plerixafor, collected though apheresis, and transduced with the BB305 lentiviral vector. Patients received single-agent busulfan myeloablative conditioning, were infused with transduced cells, and followed for safety and efficacy. Statistics are presented as median (min-max).
Results: As of 14 September 2018, 10 and 16 patients with TDT and non-β0/β0 genotypes have been treated in Northstar (follow-up: 36.0 [29.3-48.1] months; age: 16-34 yrs) and Northstar-2 (follow-up: 9.3 [0.7-20.4] months; age: 8-34 yrs; 4 patients ≤12 yrs), respectively. All patients who have >2 months follow-up have achieved neutrophil and platelet engraftment.In Northstar, 8/10 patients with non-β0/β0 genotypes achieved transfusion independence (TI; weighted average hemoglobin [Hb] ≥9 g/dL without RBC transfusions for ≥12 months). Duration of TI was 38.0 (21.2-43.6) months; all responses are sustained. Weighted average Hb during TI was 10.2 (9.3-13.2) g/dL. In patients who achieved TI, liver iron content increased from baseline by a median of 67% and 23% at Month 12 and 24 and then decreased by a median of 9% and 53% at Month 36 and 48, respectively. Iron chelation re-initiation was at 13 (2-16) months.In Northstar-2, 10/11 patients with ≥3 months follow-up stopped RBC transfusions with Hb of 11.1-13.3 g/dL comprising 7.7-10.6 g/dL gene therapy-derived Hb, HbAT87Q, at last visit. Two patients achieved TI and 5/6 patients with ≥12 months follow-up had improved myeloid:erythroid ratios (1:5.6-1:2.2 to 1:1.3-.1:1).The most common non-hematologic grade ≥3 adverse events post-infusion (≥3 patients with non-β0/β0 genotypes in either study) were stomatitis, febrile neutropenia, irregular menstruation, epistaxis, pyrexia, and veno-occlusive liver disease. There were no deaths or clonal dominance.
Conclusion: In summary, 80% of patients with non-β0/β0 genotypes in Northstar achieved TI. Northstar-2 data suggest that patients enrolled in this trial can achieve TI and near-normal Hb. The LentiGlobin safety profile is consistent with myeloablative busulfan conditioning.
Sponsored by bluebird bio.

Paper Session # 2003/Young Investigator Award Recipient

MECHANISMS OF RESISTANCE TO THE TYPE II JAK2 INHIBITOR CHZ868 IN B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Approximately 10-15% of pediatric B-cell acute lymphoblastic leukemias (B-ALLs) harbor CRLF2 gene rearrangements, which confer a poor prognosis. CRLF2-rearranged B-ALLs are addicted to signaling through Janus kinase 2 (JAK2). ATP-competitive (type I) JAK2 inhibitors like ruxolitinib have limited efficacy against these leukemias because other Janus kinases can trans-phosphorylate JAK2 and activate signaling. In contrast, type II inhibitors stabilize JAK2 in the inactive conformation. We previously showed that CHZ868, the first type II JAK2 inhibitor amenable to in vivo use, potently kills JAK2-dependent B-ALL cells, abrogates JAK2/STAT5 signaling, and prolongs overall survival in transgenic and xenograft models of JAK2-dependent B-ALL (1). However, all mice eventually progressed on therapy and succumbed to B-ALL.
Objectives: To study mechanisms of acquired resistance to CHZ868.
Design/Method: Three CRLF2/Jak2 R683G-dependent murine B-ALL cell lines were cultured in escalating doses of drug to generate resistant lines that proliferate in 10 μM CHZ868. Whole exome sequencing (WES), RNA sequencing, and H3K27Ac chromatin immunoprecipitation sequencing (ChIP-seq) were performed on naïve and resistant cell line pairs.
Results: WES revealed JAK2 G993A as a new type II JAK2 inhibitor resistance mutation in 2 of 3 resistant cell lines. When recapitulated in Ba/F3 CRLF2 IL7R JAK2 R683G cells, this mutation confers >10-fold resistance to CHZ868. JAK2 G993A abrogates CHZ868 inhibition of pJAK2 and pSTAT5. This mutation does not confer cross-resistance to the type II JAK2 inhibitor BBT594 and is particularly interesting because G993 is the pre-DFG residue. Most kinases have an amino acid larger than glycine at this position. A 4-methyl group was strategically added to the benzimidazole ring of CHZ868 to increase steric hindrance with the binding pocket of other kinases and improve its selectivity compared to BBT594 (1). When JAK2 G993A is present, the bulkier alanine in the pre-DFG position likely inhibits CHZ868 binding, leading to the observed drug resistance. In the CHZ868-resistant cell line that does not harbor a JAK2 resistance mutation, we identified Ikzf1 alterations and through H3K27Ac ChIP-Seq found that Ets transcription factor binding sites within H3K27Ac peaks were differentially present between the naïve and the CHZ868-resistant cells ($p<10\text{-}80$). Pairing this with RNA-Seq data, we observed complete loss of Erg expression in the resistant cells. This finding was confirmed by qRT-PCR. Work is ongoing to better understand the interplay between ERG transcriptional control and JAK2 independence.
Conclusion: We have identified novel genetic and epigenetic mechanisms that confer resistance to CHZ868. Reference: 1. Wu et al., Cancer Cell, 2015.

Paper Session # 2004/Young Investigator Award Recipient

DISCOVERING NONCODING GENETIC ELEMENTS THAT REGULATE GLOBIN SYNTHESIS

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Background: Sickle cell disease (SCD) causes significant morbidity and mortality in millions of people worldwide. Elevated fetal hemoglobin (HbF) levels alleviate SCD pathology and clinical severity. The expression of HbF varies between individuals, primarily in accordance with genetic determinants. Human population studies have demonstrated that adult HbF levels are influenced by DNA sequence variations in noncoding regions that regulate the production of relevant transcription factors (TFs), such as BCL11A, MYB, and KLF1, and/or in their cognate DNA sequences in the extended β-globin locus. However, the known polymorphisms in these loci account for only approximately 50% of the variation in HbF expression. We hypothesized that the noncoding regions of these genes contain many currently unidentified cis-regulatory modules (CRMs) that regulate HbF expression.
Objectives: To identify and validate novel CRMs in the topologically associating domains of TFs that regulate HbF expression.
Design/Method: Erythroid CRMs can be predicted with high accuracy by the presence of erythroid-specific DNase-hypersensitivity sites, the binding of erythroid TFs, and their physical interactions with target genes. We used these characteristics to predict 311 CRMs for BCL11A, MYB, KLF1, and the β-globin locus. Using a CRISPR/Cas9 genome-editing approach, we designed all possible single-guide RNAs (sgRNAs) within these regions and cloned them into a lentiviral vector library. Human umbilical cord blood–derived erythroid progenitor (HUDEP-2) cells co-expressing Cas9 protein were transduced with the lentiviral library at a low multiplicity of infection. Transduced HUDEP-2 cells were expanded, differentiated, and fractionated into HbF-high and HbF-low populations by fluorescence-activated cell sorting. Integrated sgRNAs were deep sequenced, and an enrichment score was calculated for each sgRNA by comparing the representation of the two cell populations.
Results: We have identified several candidate regulatory loci associated with HbF regulation, the most prominent one being the pseudogene HBBP1. HBBP1 is minimally transcribed but, nevertheless, has one of the most conserved nucleotide sequences in the region. Deleting this pseudogene increases fetal hemoglobin in HUDEP-2 cells, as well as in primary human CD34+ cell–derived erythroblasts.
Conclusion: These experiments suggest that the genomic repertoire of regulatory elements for any gene is much more diverse than previously imagined. We will not only define how these elements interact to “fine tune” the expression of several TFs and their effects on HbF expression but may also lead to novel targets for gene therapy of hemoglobinopathies. These studies will generate a high-throughput approach for identifying previously unknown genomic regulatory elements.

Paper Session # 2005

EMAPALUMAB IN PEDIATRIC PATIENTS WITH PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: SAFETY & EFFICACY

Carl Allen, Franco Locatelli, Michael Jordan, Simone Cesaro, Carmelo Rizzari, Anupama Rao, Timothy Garrington, Julian Sevilla, Maria Caterina Putti, Franca Fagioli, Martina

Ahlmann, Jose-Luis Dapena, Alexei Grom, Fabrizio De Benedetti, Walter Giovanni Ferlin, Maria Ballabio, Cristina De Min

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Background: Primary hemophagocytic lymphohistiocytosis (pHLH) is a rare, genetic, life-threatening syndrome characterized by hyper-inflammation that is mainly driven by high production of interferon (IFN)γ, leading to the development of fever, splenomegaly, cytopenias, and coagulopathy. Because mortality remains high with existing induction regimens, there is a need for improved therapy for pHLH.
Objectives: To address the need for improved therapy for pHLH, emapalumab, a human monoclonal antibody that targets and neutralizes IFNγ, was developed. Results of a clinical trial (NCT01818492) using emapalumab in pediatric patients with pHLH were reported.
Design/Method: This open-label study included 34 patients aged ≤18 years who were diagnosed with pHLH based on genetic confirmation, family history, or the presence of ≥5 of the 8 HLH-2004 diagnostic criteria. Data analysis included all patients or a subset of 27 patients who had failed previous conventional HLH therapy prior to study entry. Emapalumab (1 mg/kg, every 3-4 days, with the potential to increase to 10 mg/kg) was administered concomitantly with dexamethasone (5-10 mg/m²/d, then weaning) until the start of hematopoietic stem cell transplantation (HSCT). The primary end point was overall response rate (ORR) at the end of treatment as assessed by pre-defined parameters consistent with HLH disease. Primary analysis used an exact binomial test to determine whether the ORR exceeds the null hypothesis of 40%. The data cutoff date applied was July 20, 2017.
Results: Baseline disease was consistent with pHLH abnormalities, based on HLH-2004 diagnostic criteria. ORR was 65% and 63% for all patients or patients who failed conventional therapy, respectively, which were both higher than the null hypothesis of 40%. The percentage of patients who proceeded to HSCT was 65% and 70% in the 2 groups. Emapalumab infusions were well tolerated, with 27% of patients experiencing mild to moderate infusion-related reactions. Safety events observed included HLH manifestations, infections, or toxicities due to other administered drugs. One patient had an infection caused by pathogens potentially favored by IFNγ neutralization (disseminated histoplasmosis) that resolved.
Conclusion: This is the first prospective HLH study that reports response rates based on objective pre-defined criteria. Emapalumab controlled HLH activity with a favorable safety and tolerability profile such that a majority of patients proceeded to HSCT. Based on these results, emapalumab was approved by the FDA to treat patients with pHLH with refractory, recurrent, or progressive disease, or intolerance with conventional HLH therapy. This study was sponsored by Novimmune SA.

Paper Session # 2006

MODELING IKZF1 LESIONS IN B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA REVEALS POTENTIAL THERAPEUTIC TARGETS

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Background: In B-ALL, deletions and mutations of the gene IKAROS family zinc finger 1 (IKZF1) are associated with an increased risk of relapse. IKZF1 encodes the IKAROS protein, which is a master lymphoid regulatory transcription factor and chromatin remodeler. In B-ALL, entire gene deletions or intragenic deletions can occur. One of the most common IKZF1 perturbations in B-ALL is a 50-kilobase intragenic deletion of exons 4-7, resulting in the expression of the IK6 dominant-negative isoform. Mechanistic studies of these deletions are needed, as available data rely on clinical statistical associations, RNA interference, viral overexpression of IK6, and mouse models.
Objectives: To investigate the functional differences among IKZF1 lesions, and elucidate potential therapy targets through the precise modeling of these lesions in human clonal cell lines.
Design/Method: Using CRISPR/Cas9 we ablated IKAROS expression using sgRNAs targeting early exons of IKZF1 in Nalm6 and REH B-ALL cells (IKZF1(-/-)). We also used a novel CRISPR/Cas9 homology-directed repair strategy to generate clonal cell lines expressing IK6 under control of the endogenous promoter (IKZF1(IK6/+)). We treated clonal cells with a panel of chemotherapeutic agents used to treat B-ALL, and calculated IC50 values after 48-72 hour treatment. We performed RNA-sequencing to determine gene expression profiles, and xenografted engineered cells into NOD scid gamma (NSG) mice.
Results: Compared to IKZF1-wild type, Nalm6 IKZF1(-/-) and IKZF1(IK6/+) clones exhibited resistance to most chemotherapeutic agents tested, but profound resistance to dexamethasone was found only in IKZF1(-/-) cells. Both IKZF1 lesion types resulted in more rapid engraftment in NSG mice and reduced survival time, but more pronounced hepatic infiltration with IKZF1(IK6/+) cells, consistent with a more infiltrative disease phenotype. Gene expression analysis revealed that B-ALL cells with IKZF1 lesions are characterized by a stem cell-like gene expression signature, upregulation of FLT3, and dysregulation of JAK/STAT pathway. When these cells were treated with JAK1/2 inhibitor ruxolitinib, no difference in sensitivity was observed compared to the IKZF1-wild type; however, closer analysis of RNAseq data revealed JAK3, STAT3, and STAT5 most dysregulated.
Conclusion: Using isogenic human B-ALL cells engineered to harbor specific IKZF1 lesions, we identified notable differences in drug response and in vivo dynamics between IKZF1(-/-) cells and IKZF1(IK6/+) cells. This implies that delineation of the exact IKZF1 status at diagnosis may be informative in determining the most effective therapeutic regimen. Additionally, we identified a number of potentially targetable vulnerabilities in IKZF1(-/-) B-ALL cells that warrant investigation for the treatment of this poor prognosis subset of patients.

Paper Session # 2007

PROGNOSTIC DETERMINANTS IN CHILDHOOD T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA: RESULTS OF DFCI 05001

Melissa Burns, Andrew Place, Kristen Stevenson, Alejandro Gutierrez, Suzanne Forrest, Lynda Vrooman, Marian Harris, Sarah Hunt, Jane O'Brien, Barbara Asselin, Uma Athale, Luis Clavell, Peter Cole, Kara Kelly, Caroline Laverdiere, Jean-Marie Leclerc, Bruno Michon, Marshall Schorin, Jennifer Welch, Traci Blonquist, Donna Neuberg, Stephen Sallan, Lewis Silverman

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Background: While outcomes for pediatric T-cell acute lymphoblastic leukemia (T-ALL) are relatively favorable, there are few widely accepted prognostic factors, limiting the ability to risk-stratify treatment intensity.
Objectives: To assess the prognostic significance of early T-precursor (ETP) subtype, end-induction minimal residual disease (MRD), and mutational status of known genetic drivers on outcome in children with T-ALL treated on DFCI ALL Consortium Protocol 05-001.
Design/Method: Between 2005-2011, 97 patients (aged 1-18 years) with T-ALL were enrolled on DFCI 05-001. Total duration of therapy was 24 months from date of complete remission (CR) (defined as fewer than 5% marrow blasts at end of induction); patients with initial induction failure were removed from protocol treatment. End-induction MRD was assessed by RT-PCR in those achieving CR but not used to risk-stratify therapy. ETP status was retrospectively determined by review of diagnostic flow cytometry in 95 cases. 90 cases with sufficient diagnostic DNA were retrospectively evaluated by targeted next generation sequencing (NGS) for oncogenic mutations.
Results: The 5-year event free survival (EFS) and overall survival (OS) for T-ALL patients was 82% [95%CI 73-88%] and 89% [95%CI 81-94%], respectively. ETP phenotype, identified in 17 patients (18%), was associated with induction failure (35% vs. 5%; p=0.002) and inferior 5-year EFS (54% [95%CI 25-76%] vs. 88% [95%CI 79-94%]; p=0.001), but not inferior 5-year OS (82% [95%CI 54-94%] vs. 92% [95%CI 83-96%]; p=0.16). High end-induction MRD ($\geq$ 0.001), identified in 15 of 58 (26%) evaluable patients, was associated with inferior disease free survival (DFS) (69% vs.95%; p=0.012). NGS analyses identified 107 mutations within known genetic drivers of T-ALL in 59 patients sequenced. Recurrently mutated genes/pathways included NOTCH1 (47%), FBXW7 (20%), PI3K (13%), RAS (8%), Hedgehog (8%), Polycomb Repressive Complex 2 (4%), and JAK (3%) signaling pathways. Activating NOTCH1 mutations were associated with non-ETP phenotype (51% vs.17%; p=0.031), low end-induction MRD (60% vs.20%; p=0.015), and superior 5-year OS (98% [95%CI 84-100%] vs. 82% [95%CI 68-91%]; p=0.020). The 5-year DFS for non-ETP patients with NOTCH1 mutations and low end-induction MRD (n=25) was 100%. Conversely, pathogenic mutations within the PI3K pathway were associated with an inferior 5-year DFS (73% [95%CI 37-90%] vs. 94% [95%CI 84-98%]; p=0.009) and OS.
Conclusion: For T-ALL patients treated on DFCI 05-001, ETP phenotype, end-induction MRD, and activating mutations within NOTCH1 and the PI3K pathway were prognostically relevant, supporting possible incorporation of these factors into risk classification in future trials.This study was partially supported by a grant from Enzon Pharmaceuticals.

Paper Session # 2008

GAP JUNCTION INTERFERENCE INCREASES APOPTOSIS IN ALL CELLS AND AUGMENTS EFFECTS OF ANTIMETABOLITES

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Background: Acute lymphoblastic leukemia cells have an intimate interaction with nonmalignant stromal cells in the marrow microenvironment. In vitro nonmalignant cells prevent

apoptosis of acute lymphoblastic leukemia cells. Cell-cell contact is required for this effect. The mechanisms of this stromal support are not fully known. We have recently demonstrated that ALL cells and stromal cells exhibit bidirectional exchange of intracellular molecules. Gap junctions are formed between cells in a variety of tissues. They are composed of connexin proteins and form intercellular channels through which ions and small molecules can pass.
Objectives: Our objective was to test the hypothesis that gap junction function contributes to the antiapoptotic support that nonmalignant stromal cells provide to acute lymphoblastic cells.
Design/Method: We have a well-developed in vitro experimental model in which nonmalignant human bone marrow stromal cells are cocultured with human acute leukemia cells. The ALL cells are primary human ALL cells that have undergone one round of in vivo expansion as patient derived xenografts in NSG mice. ALL cell viability at various times after coculture was measured by flow cytometry. We assessed gap junction presence by Western blot in stromal and leukemia cells. We interfered with gap junction function using either peptide blockade using GAP27 peptide (with scrambled peptides as controls) or with carbenoxolone (a small molecule that interferes with gap function function in vitro and in vivo). In chemotherapy studies we assessed the in vitro antileukemia effects of 6-MP, methotrexate, dexamethasone and vincristine in the presence or absence of carbenoxolone.
Results: (1) Contact with stromal cells induced connexin 43 protein (the primary component of gap junctions) in acute leukemia cells as assessed by Western blot. (2) Gap junction blockade with GAP27 peptide in stromal cell-leukemia cell cocultures decreased ALL cell survival compared to control peptides. (3) Interference with gap junction function by addition of carbenoxolone to stromal cell-leukemia cell coculture reduced ALL cell survival. (4) In combination carbenoxolone increased the antileukemia effects of 6-MP and methotrexate. The magnitude of the effect varied between the 6 ALLs studied.
Conclusion: Acute lymphoblastic leukemia cells form gap junctions with nonmalignant marrow stromal cells. Interference with gap junction function increases leukemia cells apoptosis and may enhance the activity of antimetabolite drugs against leukemia cells.

Paper Session # 2009

HYDROXYUREA LOWERS TRICUSPID REGURGITANT JET VELOCITY IN CHILDREN WITH SICKLE CELL ANEMIA

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Background: Elevated tricuspid regurgitant jet velocity (TRV) ≥ 2.5 m/sec is a known predictor of disease severity in individuals with sickle cell anemia (SCA): it is associated with decreased exercise capacity in children and early mortality in adults. TRV increases with age, but it remains unclear if initiation of disease modifying therapy (DMT) in childhood can prevent the progressive elevation of this biomarker
Objectives: To determine the longitudinal effect of DMT, hydroxyurea and chronic transfusion therapy (CTT) on TRV elevation to high risk status (TRV ≥2.5 m/sec), and identify the hematological factors associated with such TRV elevation.
Design/Method: Children aged 5-18 years with SCA were enrolled in the Long-Term Effects of

Erythrocyte Lysis Trial (ELYSIS, NCT 00842621) at St Jude Children's Research Hospital. Prospective measurement of TRV by 2D-echocardiogram was performed at steady state (≥ 4 weeks from illness, transfusion, hospitalization), and then repeated two years later. Markers of hemolysis were obtained concurrently.
Results: 182 participants with HbSS or HbSβ0thalassemia, mean age 10.6 years (SD 3.62), were followed longitudinally. Of those, 91 were treated with DMT (66 with hydroxyurea and 25 with CTT) both at baseline and at the 2-year evaluation, while 55 had never received any DMT, and 36 participants were untreated at baseline but initiated hydroxyurea during the 2-year follow-up period after the initial echocardiogram. Among those who received hydroxyurea (102 participants), the prevalence of TRV ≥2.5m/sec decreased significantly from 37.3 % to 21.6% in the follow-up period, p =0.015. This was not seen with CTT (baseline 52% and 2-year 48%, p=1.0) or among participants who did not receive any DMT (baseline 30.9% and 2-year 32.9%, p=1.0). A linear mixed model was used to determine the association between the TRV trend and hematological parameters. Among participants who initiated hydroxyurea, a 1.0 g/dL increase in hemoglobin was associated with a 0.054 m/sec decrease in TRV (p=0.048). Among participants on continuous hydroxyurea therapy, a 1.0 x 10e9/L increase in absolute reticulocyte count was associated with a 0.8 m/sec increase in TRV (p=0.045).
Conclusion: Hydroxyurea therapy may mitigate TRV progression in children with SCA. While the improvement in anemia seen after initiating hydroxyurea may drive the initial decline in TRV, this trend appears to be more influenced by the reduction in hemolysis with its continuous use. Prospective studies should evaluate whether continuous use of hydroxyurea can prevent progressive TRV elevation into adulthood, where it has been identified as a predictor of early mortality.

Paper Session # 2010

NOVEL NEXT-GENERATION SEQUENCE BASED ASSAY FOR NON-INVASIVE PRENATAL TESTING OF SICKLE CELL DISEASE

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Background: Over 300,000 infants are born with sickle cell disease (SCD) every year worldwide, including at least 1,000 in the US. Prenatal diagnosis by amniocentesis or chorionic villus sampling is available; but high cost, invasiveness, and risk of miscarriage limit their use. Recently, non-invasive prenatal testing (NIPT), by genetic analysis of the cell-free fetal DNA (cffDNA) present in maternal blood, has become commonplace for aneuploidies. Yet, no NIPT for SCD or other hemoglobinopathies have been commercialized to date. We have developed and optimized an NIPT for SCD by assessing the relative mutation dosage of fetal SCD and beta-thalassemia DNA through a novel molecular counting strategy using NGS.
Objectives: The primary objective of this study is to evaluate the performance of a novel NIPT for sickle cell disease.
Design/Method: The SCD NIPT assay and associated custom bioinformatics analysis were performed on cfDNA obtained from a training cohort of non-pregnant compound heterozygotes for SCD. The SCD NIPT assay was then performed on a validation cohort of pregnant women with either SCD or sickle cell trait (SCT). The accuracy of the SCD NIPT was evaluated by

comparison with newborn screening results.
Results: Non-pregnant individuals with genotype HbSE, HbSC, or HbS/beta-thalassemia were included as a training cohort to establish the precision and accuracy of the assay for measuring HbS allele fraction from cfDNA. As expected, the HbS allele fraction in these individuals was 0.500 (standard deviation = 0.011, n = 26), and there was no detectable fetal fraction in these samples. Both training and validation cohort results matched the theoretical limit of detection set by the number of cell-free HBB DNA molecules in plasma. The precision and accuracy of the HBB assay on cfDNA were then used in conjunction with >1000 pre-clinical samples (mixtures of sheared SCT and SCD genomic DNA) to determine analytical sensitivity >98% and specificity >99%, even in the absence of paternal DNA.
Conclusion: We have developed an assay for NIPT of sickle cell disease. The results obtained to date indicate that the assay reliably detects fetal SCD status when the fetal fraction is as low as 5%, the same limit as aneuploidy NIPT. Several Phase I/II and III trials for curing SCD or beta-thalassemia using autologous gene-editing of stem cells are currently in progress. SCD NIPT could be particularly useful for deciding to bank umbilical cord blood as a source of stem cells for future gene-editing cures. Supported by a grant from BillionToOne, Inc.

Paper Session # 2011

GABAPENTIN FOR PAIN IN SICKLE CELL DISEASE: RESULTS OF A RANDOMIZED PHASE II CLINICAL TRIAL

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Background: Pain in sickle cell disease (SCD) can have a significant neuropathic component. Therapies targeting neuropathic pain have not been extensively studied in this setting. We report results of a randomized controlled trial evaluating utility of gabapentin for acute vaso-occlusive crisis (VOC) pain.
Objectives: The primary objective was to evaluate efficacy of gabapentin when added to standard therapy for acute VOC pain. Main outcome was as >33% reduction in pain scores between presentation (baseline) and assessment at 3 hours post-study drug administration. The secondary objective was to compare opioid consumption as morphine equivalent dose (MED, mg/kg) between baseline and 3 hours, in the gabapentin versus placebo groups.
Design/Method: This was a phase II double-blind placebo-controlled study. Patients with SCD, ages 1 to 21 years, presenting with VOC pain were enrolled and randomized to receive either a single oral dose of gabapentin, 15 mg/kg or placebo in addition to standard treatment. Pain scores and opioid requirement were compared between treatment arms.
Results: Ninety patients (35 females, 59 males) were randomized, 45 in each arm. Forty-two and forty-four participants were evaluable in gabapentin and placebo arms, respectively. Pain scores at presentation were similar for both groups, mean (standard deviation/SD) 7.8 (1.8). In gabapentin arm, 67.5% (n=27) patients experienced >33% decrease in pain from presentation to 3 hours post treatment versus 59.5% (n=25) in placebo arm (p=0.23, Z-test). The overall mean (SD) MED (mg/kg) was 0.16 (0.10), with no significant difference between gabapentin (median 0.12, SD: 0.09) and placebo arms (median 0.13, SD: 0.11) (p = 0.897, Wilcoxon rank sum test).

Absolute decrease in pain scores from baseline to admission or discharge from acute care was higher in gabapentin (median 1.0, SD: 3.1) as compared to placebo arm (median 0.5, SD: 2.3), but not significant (p=0.38, Wilcoxon rank sum test). However, for patients with HbSS genotype absolute pain decrease was significantly greater in gabapentin (mean 5.9, SD: 3.5) versus placebo arm (mean 3.6, SD: 3.3) (p = 0.03, t-test).
Conclusion: Although not significant, a greater proportion of patients achieved clinical improvement in pain when gabapentin was added to standard therapy. Gabapentin also resulted in greater decrease in pain scores, particularly in patients with HbSS. Thus, gabapentin can be a useful adjunct to standard management, particularly for patients with HbSS, who generally have a more severe phenotype and often with neuropathic pain features. Future studies with larger cohorts are needed to confirm these findings.

Paper Session # 2012

QUALITY OF LIFE IS THE MOST IMPORTANT INDICATION FOR SECOND-LINE ITP TREATMENT IN CHILDREN

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Background: Guidelines for treatment of patients with newly-diagnosed immune thrombocytopenia (ITP) give clear indications for initiation of pharmacologic treatment versus close observation. After initial diagnosis, however, no evidence-based guidance exists regarding decision to treat, and second-line therapies (treatments other than steroids, IVIg, or anti-D-globulin) are started for many reasons besides bleeding. ICON1 is a prospective, observational, longitudinal cohort study of 120 children from 21 centers initiating second-line treatments for ITP.
Objectives: Evaluate reasons pediatric hematologists treat children with ITP with second-line therapies.
Design/Method: At study entry, clinicians were given a list of 12 potential reasons the patient required a second-line treatment. They were asked to choose all that applied and to rank the top three reasons. For continuous measures, t-tests were used to compare characteristics of patients with and without a particular reason for starting second-line treatment. For categorical measures, Fisher's exact test was used to compare these groups.
Results: Quality of life (QOL) was the most frequently cited reason for starting a second-line therapy, with clinicians choosing it as a reason to treat in 88/120 (73%) patients. Thirty-two (27%) ranked QOL as the most important reason, with no difference across patient age, gender, race, or ethnicity. Sixty-eight (57%) listed QOL among the top 3 reasons for treating, but surprisingly there was no difference reported in baseline HRQoL, using the Kids ITP Tool, in those children in whom QOL was ranked versus unranked. Additional highly-ranked reasons to start second-line treatment included frequency of bleeding symptoms (n=50, 42%) and severity of thrombocytopenia (n=47, 39%). Patients for whom severity or frequency of bleeding was a

treatment indication were more likely to have newly-diagnosed or persistent ITP vs chronic ITP (66% vs 34%, p=0.0008 and 58% vs 42%, 0=0.028, respectively). In contrast, patients for whom sports participation was a treatment indication (n=36) were more likely to have chronic ITP (69% vs 31%, p=0.028). Despite data showing a low rate of serious bleeding in children with ITP, parent anxiety (ranked in 26%), physician anxiety (13%), and patient anxiety (8%) are still relatively common reasons for initiating treatment.
Conclusion: Perceived QOL is the most frequently selected reason pediatric patients start second-line therapies for ITP. Consequently, understanding the effect of treatments on QOL is critical for this patient population. Although bleeding symptoms may primarily dictate the decision to treat in newly-diagnosed patients, a variety of factors influence the decision to treat later in the disease course.

Paper Session # 2013/Early Career Travel Stipend Award Recipient

BCL2-INHIBITOR RESPONSE IN NEUROBLASTOMA: BIOMARKERS AND THERAPY RESISTANCE

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Background: Apoptosis evasion is a cancer hallmark, which is regulated through the interactions of the Bcl2-family proteins at the mitochondria. Survival proteins such as Bcl2 and Mcl1 bind stress-activated BH3 proteins (like Bim, Puma and Bid), to prevent them from activating the obligate executioner proteins Bak and Bax and provides a survival advantage. Neuroblastoma (NB) is a highly lethal childhood tumor in which therapy resistance contributes to treatment failure.
Objectives: We used mitochondrial profiling and co-immunoprecipitation (co-IP) to define NB survival dependencies and develop biomarkers to predict response to Bcl2-inhibitors (BCL2i) such as venetoclax and newer Mcl1 inhibitors (MCL1i).
Design/Method: NBs stress response "set-point" was defined through mitochondrial profiling by interrogating isolated mitochondria with diverse BH3-only proteins. This allows us to classify survival mechanisms as Bcl2- or Mcl1-dependent. The former have Bim sequestered by Bcl2 (confirmed by coIP) and a dominant mitochondrial response to BikBH3, the latter have Bim bound to Mcl1 (Bim:Mcl1 by coIP) and a dominant NoxaBH3 response. All NBs tested have co-expression of Bcl2 and Mcl1, yet rely on a single functionally dominant survival protein.
Results: Bcl2-dependent NBs are highly sensitive to BCL2i's (venetoclax- BCL2i; navitoclax-BCL2i/BCLXi/BCLWi) with IC50s <<1 uM, while resistance is noted as predicted in Mcl1-dependent NBs (IC50> 2uM). The MCL1i, S63845, had no activity against Bcl2-dependent NB as expected, but also had no single-agent activity against Mcl1-dependent NB. However, S63845 markedly sensitizes Mcl1-dependent NBs to BCL2i's (shifting IC50>1 log in all tested using a non-cytotoxic S63845 concentration). Ongoing mechanistic work tests a hierarchical model in which Bcl2 can sequester Bim displaced from Mcl1 (by an MCL1i), sensitizing a previously Mcl1-dependent NB to a BCL2i. In contrast, Bim displaced from Bcl2 by a BCL2i (in a Bcl2-dependent NB) does not bind Mcl1 but engages Bak/Bax to induce death. To measure Bim:Bcl2

and Bim:Mcl1 as predictive biomarkers we are developing proximity ligation assays (PLAs) for use with FFPE-tumor slides. NB xenografts of defined survival dependency are being used to optimize these assays.
Conclusion: NBs response to Bcl2-family inhibitors demonstrated heterogeneous survival dependencies predicted by functional profiling assays. We propose a hierarchical binding model where Bim:Bcl2 binding predicts BCL2i monotherapy sensitivity. Mcl1-dependent NBs are resistant to MCL1i' as a single agent but combining an MCL1i with a BCL2i achieves synergistic cytotoxicity. Lastly, development of clinically-relevant biomarker assays to define Bim binding will allow stratification of patients in clinical trials with Bcl2-family inhibitors.

Paper Session # 2014

THE CLINICAL APPLICATION OF MOLECULAR TESTING IN PEDIATRIC SOLID TUMORS: AN INSTITUTIONAL EXPERIENCE

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Background: Studies on the genomic analysis of pediatric tumors have identified approximately 40% of pediatric tumors with possible actionable alterations, generating a series of precision medicine trials and a handful of FDA approved targeted therapies for pediatric patients. However, there is limited guidance for the application and integration of molecular profiling data into daily clinical practice in pediatrics. These studies have primarily utilized large scale, genome wide screening applications thus limiting use at many centers due to cost and availability of testing, and complicated by increased number of variants of unknown significance for which clinical significance is unclear. The feasibility of incorporating these larger scale studies into daily practice has yet to be addressed.
Objectives: Demonstrate the utility of a precision medicine program primarily using a clinically available targeted gene panel focusing on genomic alterations known to be associated with cancer.
Design/Method: Retrospective review of pediatric solid tumor patients with molecular testing performed at diagnosis or recurrence using OmniSeq Comprehensive, a targeted sequencing panel; or, when clinically indicated, a broader panel from Foundation Medicine. All results were reviewed at a multi-disciplinary Pediatric Molecular Tumor Board. Clinically useful findings were defined as those that aided in diagnosis, prognosis or with which there was an associated potential targeted therapy.
Results: We analyzed 61 pediatric solid tumor samples collected from July 2016 to October 2018, with 84% (51/61) tested by OmniSeq Comprehensive. A subset with primarily CNS tumors, had analysis by a Foundation Medicine panel due to inclusion of additional genes relevant to tumor subtype classification, diagnosis or prognosis. Of the samples analyzed 51% (31/61) had a clinically useful finding, and 41% (25/61) led to a recommendation for off-label use of a FDA approved targeted therapy, or had a targeted therapy available within an open clinical trial. Forty-percent (10/25) of patients with an available agent were started on a targeted therapy and 50% (5/10) (8% of the entire cohort) had improvement in disease.
Conclusion: Application of molecular testing utilizing a targeted gene panel in combination with

a broader scale assay when clinically indicated is feasible and produces a similar rate of actionable mutations compared to results from published series utilizing extensive sequencing approaches including whole genome and whole exome sequencing. In this small series, a targeted panel is an effective method of identifying actionable mutations in the majority of solid tumors and led to initiation of clinically relevant single agent therapy in multiple patients.

Paper Session # 2015

ENHANCING TUMOR DIRECTED T CELLS WITH AN INTERLEUKIN-7 SIGNAL MODULATOR

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Background: The adoptive transfer of tumor targeted T cells for cancer offers the potential for cure, without the long term toxicities associated with standard therapies. However, while T cells have produced impressive results in patients with hematologic malignancies, these successes have not been replicated in solid tumors. T cells likely fail to expand, persist and maintain their function for sufficient time to eliminate solid tumors, which lack costimulatory molecules and growth-promoting cytokines, and instead produce an array of inhibitory ligands. While our previous clinical studies have shown that chimeric antigen receptor (CAR)-modified T-cells directed to the tumor antigen GD2 are safe and can produce complete tumor responses in neuroblastoma patients with a low tumor burden, even third generation GD2.CARs fail to persist for long enough to eliminate disease in most patients.
Objectives: To overcome current limitations of T cell expansion and persistence in the immunosuppressive tumor microenvironment by augmenting cytokine signaling/polarization.
Design/Method: To tackle these problems, we have developed a constitutively active IL7 receptor (C7R) to provide the proliferative and survival advantages of IL7 signaling.
Results: C7R-modified GD2.CAR T-cells were able to expand, persist and eliminate systemic neuroblastoma in murine models, in which unmodified GD2.CAR T-cells failed. In vitro studies showed that C7R-modified, but not unmodified GD2.CAR T-cells could repeatedly kill tumor cells in serial coculture assays and resist immunosuppressive components of the tumor microenvironment, such as myeloid-derived suppressor cells and PD-L1 and TGFβ. Further IL7 is a homeostatic cytokine that improves survival of circulating T-cells and in our studies C7R upregulated anti apoptotic molecules like BCL2 and downregulated FAS and CASP8 in nanostring analyses. In preclinical testing C7R did not produce autonomous proliferation of mature T cells in the absence of cognate tumor antigen or costimulation. Incubating the C7R-transduced T cells in the presence of clinically relevant concentration of the JAK inhibitor ruxolitinib resulted in ablation of tonic STAT5 phosphorylation and concomitant decrease in T-cell expansion to the level of control T cells. C7R also dramatically enhanced the antitumor functions of EphA2-specific CARs in an orthotopic brain tumor model and of EBV-specific T-cells targeting lymphoma via native T-cell receptors.
Conclusion: Modification of T cells with an IL-7 cytokine signal leads to improved anti-tumor efficacy in preclinical models of neuroblastoma, EBV associated lymphoma and brain cancers.

This approach will now be evaluated in a clinical trial for patients with refractory or relapsed high-risk neuroblastoma.

Paper Session # 2016/Early Career Travel Stipend Award Recipient

EPIGENOME SCREENING IDENTIFIES TRANSCRIPTIONAL ELONGATION AS THERAPEUTIC VULNERABILITY IN DIPG

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Background: Mutations in the histone 3 (H3) gene (H3K27M) are the eponymous drivers in diffuse intrinsic pontine gliomas (DIPGs) and other diffuse midline gliomas (DMGs), aggressive pediatric brain cancers for which no curative therapy currently exists. Despite this recognition, the ability to therapeutically target the dysregulated epigenetic milieu imparted by the H3K27M mutation has remained elusive.
Objectives: In order to identify specific epigenetic dependencies which arise as a consequence of the H3K27M mutation, we performed shRNA screens targeting genes classified as epigenetic or chromatin-associated molecules in patient-derived cell lines representing multiple pediatric brain cancers. This identified AFF4, the scaffold protein of the super elongation complex (SEC), as a dependency unique to H3K27M-mutant DIPG cells. The objective of this work is to define the unique mechanistic relationship between the H3K27M mutation and SEC-mediated transcription and to determine whether targeting this dependency via inhibition of CDK9, the catalytic subunit the SEC, might be employed as a therapeutic approach in DIPG.
Design/Method: We performed a functional shRNA screen using 4188 total shRNAs targeting 408 genes classified as epigenetic or chromatin-associated molecules in an array of medulloblastoma, ependymoma, atypical teratoid/rhabdoid tumor, and DIPG patient-derived cultures. We interrogated the role of AFF4 in H3K27M-mutant DIPG using an shRNA lentiviral approach and employed RNA-seq-based gene set enrichment analysis to delineate differentiation programs under AFF4 regulatory control. We utilized ChIP-seq to examine the mechanistic link between H3K27M mutation status and observed AFF4 overexpression. Finally, we use a combination of RNA- and ChIP-seq to examine the effects of CDK9 pharmacologic inhibition on regulatory transcriptional pausing and assess the anti-tumor effect both in vitro and in vivo.
Results: We find that SEC member proteins are highly expressed in DIPG as a direct consequence of the H3K27M mutation and that this relative abundance overcomes repressive transcriptional regulation in order to suppress differentiation and promote self-renewal of DIPG tumor stem cells. We find that CDK9 is sensitive to pharmacologic inhibition by the drug atuveciclib and that CDK9 inhibition in DIPG restores regulatory transcriptional pausing, promotes cellular differentiation, and leads to potent anti-tumor effect both in vitro and in orthotopic mouse xenograft models.
Conclusion: Together, these studies present a rationale for further exploration of SEC inhibition as a promising new therapeutic approach to this intractable disease.

Paper Session # 2021

LEUCINE FOR THE TREATMENT OF TRANSFUSION DEPENDENCE IN PATIENTS WITH DIAMOND BLACKFAN ANEMIA

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Background: Diamond Blackfan anemia (DBA) is a rare, inherited bone marrow failure syndrome characterized by anemia, congenital anomalies and a predisposition to cancer. Patients usually present during infancy or early childhood, but can present in adulthood. In the majority DBA is due to a mutation in a small or large ribosomal protein (RP) subunit leading to RP haploinsufficiency. Treatments for the anemia of DBA include red cell transfusions (with iron chelation), corticosteroid therapy or stem cell transplantation. One report found one complete erythroid response after the use of the branched chain amino acid L-leucine in 6 select patients. Leucine supplementation enhances ribosome biogenesis and mRNA translational efficiency. Mouse and fish models of DBA respond to L-leucine with amelioration of anemia.
Objectives: The primary objectives were to determine the feasibility of administering L-leucine in subjects with DBA who are red cell transfusion-dependent and to determine the efficacy of L-leucine to produce a hematologic and growth response. The secondary objective was to determine the safety profile of L-leucine.
Design/Method: The Phase I/II study had an anticipated accrual of 50 subjects in 12 sites. A dose of 700 mg/M2 orally three times per day for 9 months was used. Inclusion criteria included age > 2 years, the diagnosis of DBA and transfusion dependence with adequate kidney and liver function. Response was evaluated at 9 months with Complete Response (CR) defined as no further transfusions required and Hb >9; Partial Response (PR): Hb <9 gm/dL with an increase in reticulocyte count; and No Response (NR): no change in Hb or reticulocyte count. Growth percentiles were evaluated at baseline and at completion of treatment and the growth velocity change was calculated.
Results: The study opened in 7/2014 and closed in 2/2017; 55 patients consented; 12 screen failures; 43 patients evaluable. There were 21 males; the median age was 10years 4months. No untoward side effects were attributable to L-leucine. Two patients had a CR and 5 patients had a PR with elevated retic counts. Ten of the 22 patients with growth potential and complete data had an average increase of 8%ile in growth velocity, independent of the hematologic response at the end of treatment.
Conclusion: L-leucine resulted in an erythroid response in 16% of patients. It was well-tolerated and safe in patients with DBA and resulted in an increase in growth velocity in some patients. Higher doses should be well-tolerated in future studies and may lead to more responses.

Paper Session # 2024

SEPTIC SHOCK (SS) INCIDENCE IN NATIONAL ALL & AML COHORTS USING ADMINISTRATIVE & CLINICAL TRIAL DATA

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Background: Infections cause significant morbidity and mortality during leukemia therapy; however, clinical trial reporting is incomplete (Miller 2016 JCO). Using administrative data to identify SS could improve incidence estimates.
Objectives: We hypothesized daily resource utilization (RU) codes indicating vasopressor exposure could identify SS and be used to estimate incidence and timing in national acute lymphoblastic (ALL) and myeloid leukemia (AML) cohorts.
Design/Method: We previously validated a retrospective ALL cohort using Pediatric Health Information System (PHIS) data (Fisher 2014 Med Care). We also merged Children's Oncology Group (COG) AML trials AAML0531 and AAML1031 with PHIS (Li 2015 PLOS One). Concurrent PHIS pharmacy codes for any 2 vasopressors or norepinephrine or dobutamine alone were used to define SS. Dopamine or epinephrine alone required blood culture or antibiotics codes ±3 days. Epinephrine alone with asparaginase ±3 days was considered anaphylaxis. Vasopressors were captured ≥7 days from first chemotherapy until the first of: 30 days before relapse, 10 days before transplant, 3 years from diagnosis (ALL) and end of therapy (AML). For ALL, we approximated NCI risk using age and anthracyclines in Induction. We validated events using manual chart reviews of all Children's Hospital of Philadelphia (CHOP) patients with ALL (2004 - 2013) and AML (2008 - 2015). PHIS SS occurring ±14 days from chart-defined SS were considered true positives.
Results: PHIS vasopressor RU identified 35/38 events among 360 patients with ALL (sensitivity 92%, PPV 45%). If events were compared to any sepsis regardless of severity, PPV increased to 88%, suggesting strict SS definitions may miss fluid-responsive shock. Of 38 CHOP patients with AML in the PHIS/COG cohort, PHIS vasopressor RU identified 6/6 events (sensitivity 100%, PPV 35%). Comparing events to any sepsis improved PPV to 76%. Overall 3-year SS incidence for the entire PHIS ALL cohort (N=10,163) was 12.4%. Infants, age ≥ 10 years, and anthracyclines in Induction had significantly higher SS rates. Most events occurred within 6 months from diagnosis, when therapeutic intensity is highest. High-risk patients were more likely to experience multiple events with a second peak ~8 months from diagnosis, corresponding to Delayed Intensification. Overall on-therapy incidence for 697 COG AML patients identified in PHIS was 33%. Patients ≥15 years or with end-Induction minimal residual disease experienced higher SS rates.
Conclusion: Unlike previous ICD9 code-based approaches, vasopressor RU identifies patients with SS with precise timing, augmenting incomplete clinical trial data. This method could identify at-risk patients who may benefit from intensified surveillance or prophylaxis.

Paper Session # 2025

NELARABINE ABROGATES RELAPSE RATES IN CNS-3 T-ALL: A REPORT FROM CHILDREN'S ONCOLOGY GROUP AALL0434

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Background: AALL0434 included a 2 x 2 pseudo-factorial randomization using an augmented BFM regimen. Patients were randomized to receive escalating dose Capizzi methotrexate plus pegaspargase (CMTX) or High Dose MTX (HDMTX) and intermediate (IR) and high-risk (HR) patients were randomized to receive or not receive six 5-day nelarabine (Nel) courses. IR/HR CNS1/CNS2 patients received 1200 cGy cranial radiation (CRT). CNS3 patients received 1800 cGy CRT, were non-randomly assigned to HDMTX arms and took part in the Nel randomization. Low-risk patients received no CRT and did not participate in the Nel randomization. We have reported that both CMTX and Nel improved event-free survival (EFS).
Objectives: To assess outcomes of AALL0434 T-ALL patients based on CNS status at diagnosis.
Design/Method: A review of T-ALL patients enrolled on AALL0434 was performed. CNS status was assigned at diagnosis using microscopy and/or clinical features.
Results: From 2007-2014, 1550 T-ALL patients were enrolled and evaluable for analyses, including 1128 (72.8%) CNS1, 306 (19.7%) CNS2 and 116 (7.5%) CNS3. Five-year EFS rates for CNS1, 2, and 3 were 85.2%, 83.1%, and 71.4% respectively (p=0.0007) and overall survival (OS) rates were 90.4%, 89.2%, and 83.1% (p=0.0438). Five-year disease free survival (DFS) rates for Arm C (HDMTX without Nel) differed by CNS status: CNS1 87.2%, CNS2 80.0%, and CNS3 70.2% (p=0.0006), but 5-year DFS for Arm D (HDMTX+Nel) showed no statistically significant differences in outcome based on CNS status (p=0.35): CNS1 85.1%, CNS2 80.0%, and CNS3 93.1%. Nelarabine significantly improved DFS of CNS3 patients who received HDMTX (p=0.02): 93.1% with Nel (n=29) vs. 70.2% without (n=71). The 5-year cumulative incidence of isolated CNS relapse was significantly associated with CNS status: CNS1 1.0%, CNS2 4.2%, and CNS3 11.0%; p< 0.0001. However, there were no differences in 5-year DFS between CNS1 and CNS2 treated with CMTX (89.7% vs. 92.9%, p=0.17) or CMTX+Nel (91.8% vs. 89.9%; p=0.62).
Conclusion: CNS3 T-ALL patients treated on AALL0434 demonstrated increased risk of isolated CNS relapse and inferior EFS, despite receiving 1800 cGy CRT and additional CNS-directed chemotherapy. Strikingly, for CNS3 patients receiving HDMTX and CRT, the addition of Nel dramatically improved DFS and OS, producing outcomes similar to those for CNS1 and CNS2 patients. For AALL0434 patients receiving the superior CMTX arms, with or without Nel, outcome did not differ based on CNS1 vs. CNS2 status. Because most of these patients received 1200 cGy CRT, it is unclear if CNS1 vs. CNS2 status will impact outcome without CRT.

Paper Session # 2026

CURRENT CANCER SURVIVORSHIP PRACTICES: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

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Background: Due to advances in treatment, the 5-year overall survival rate for childhood cancer is >80%, leading to greater than 360,000 survivors of childhood cancer <40 years of age in the United States (US). These survivors require lifelong monitoring for chronic health conditions, poor mental health, neurocognitive deficits and subsequent malignancies due to their previous cancer and its treatment. A 2007 survey described the variability of survivor care within Children's Oncology Group (COG) institutions; however, little is known about current survivor care delivery.
Objectives: To describe current survivor services provided by COG institutions in the US.
Design/Method: A 190-question online survey was distributed to 201 US COG institutions over a 3-month period in 2017. Descriptive statistics were used to describe survivor services.
Results: Representatives from 119 (59.2%) institutions completed the survey. Of these, 97.4% of institutions reported they provide pediatric cancer survivor care either in a specialized late effects program (75.6%) or a general pediatric oncology clinic (21.8%). 88.2% of institutions provided survivors with a copy of their cancer treatment summary and 59.7% provided a written account of pertinent findings from their survivor visit. Only 34.1% of institutions provided survivorship services over the lifespan; other institutions either reported having an upper age limit (40.0%) or transitioning survivors outside the pediatric center when survivors are ready (25.9%). A pediatric oncologist was involved in survivor care at 90.5% of institutions and primary care was involved at 10.2%. Other disciplines involved in survivor care at the institutions included social work (78.2%), nursing (69.5%), psychology/neuropsychology (63.0%) and nutrition (45.7%). Treatment summary preparation time ranged from an average of 40 minutes (range 0-180) for survivors of low-grade Wilms tumor to 120 minutes (range 15-480 minutes) for survivors after stem cell transplant. While a majority of institutions reported having a specialized late effects program, only 29.8% reported that >75% of eligible patients were seen in a late effects clinic. Philanthropic support was received by institutions to support personnel (43.2%) and enable clinical care (35.3%) for survivors. The most prevalent reported barriers to survivor care were lack of dedicated time for program development (57.0%) and insufficient funding for program support (40.0%).
Conclusion: The majority of COG institutions have dedicated care for pediatric and young adult survivors of childhood cancer; however, at most institutions <75% of eligible patients access this care. Research regarding more efficient technology-based strategies is needed to ensure all survivors have the opportunity to receive appropriate and equitable care.

Paper Session # 2027

INTRA-ARTERIAL CHEMOTHERAPY FOR RETINOBLASTOMA: A 7-YEAR SINGLE INSTITUTION EXPERIENCE

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Background: Retinoblastoma (RB) is the most common primary intraocular malignancy in children. For several decades, systemic chemotherapy has historically been the mainstay of eye-preserving RB treatment. However, advancements in intra-arterial chemotherapy (IAC) technique over the last decade have dramatically enhanced eye salvage rates, particularly in more advanced cases.
Objectives: To define disease characteristics, treatment outcomes, and therapy-related complications in RB patients treated primarily with IAC at a single referral center.
Design/Method: Retrospective analysis of patients diagnosed with RB and treated with primary IAC at the Bascom Palmer Eye Institute, Sylvester Comprehensive Cancer Center, and Jackson Memorial Hospital between January 2012 and December 2018.
Results: Twenty-eight patients (17 males, 11 females), 15 with bilateral disease and 13 with unilateral disease (6 left eyes and 7 right eyes) were included in this study. The mean age of diagnosis was 9.44 months (standard deviation was 7.17 months). Patients ranged in age from 1 month to 24 months at diagnosis. Five patients had a family history of RB (17.9%). Leukocoria (64.3%) and strabismus (39.3%) were the most common presenting sign of disease prior to diagnosis. International RB Classification was group A (2 eyes), B (4 eyes), C (12 eyes), D (15 eyes) and E (10 eyes). A total of 95 sessions of IAC were performed (mean 3.39 session per patient, standard deviation 1.87), including melphalan alone (15 sessions), melphalan and topotecan (6 sessions), melphalan and carboplatin (11 sessions), and melphalan, carboplatin, and topotecan (63 sessions). There was no statistically significant differences between groups and number of IAC sessions performed. Overall survival rate was 100%. Results also demonstrate that IAC is associated with hematologic complications. Hematologic parameters were followed post administration of IAC. 67.7% of IAC cycles were associated with moderate-degree neutropenia (mean ANC 0.77k/uL, standard deviation 0.39k/uL). 67.7% of IAC were also complicated by anemia (mean hemoglobin 9.30g/dL, standard deviation 1.11g/dL) and 15.1% of the cycles were complicated by thrombocytopenia (mean platelet count 107k/uL, standard deviation 42.9k/uL).
Conclusion: Intra-arterial chemotherapy is an effective therapy for RB, particularly when considering patients with high-grade disease. While not affecting overall survival rate, clinicians should be vigilant in monitoring patients for systemic hematologic complications, particularly neutropenia and anemia.

Paper Session # 2028

THE SHWACHMAN DIAMOND SYNDROME REGISTRY: HEMATOLOGIC COMPLICATIONS

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Background: The Shwachman-Diamond Syndrome Registry (SDSR) was established in 2008 with the goal of understanding the natural history and biology of SDS to improve lives of people with SDS.

Objectives: The SDSR has enrolled 220 patients with biallelic SBDS mutations or SDS-Like features.
Design/Method: Longitudinal data has been collected for 176 patients with median follow-up of 10.7 (0.3-52.8) years.
Results: Biallelic SBDS mutations were noted in 129 patients, and biallelic DNAJC21 or ELF1 mutations or heterozygous SRP54 mutation in one patient each respectively. Clinical characteristics and outcomes of patients with biallelic SBDS mutations were examined. AML developed in 5 patients and MDS in 11 patients at a median age 37.9 years (19.5-47.3) and 10.7 years (1-45) respectively. No solid tumors were diagnosed. 21 individuals have undergone stem cell transplantation. Overall survival was 91%, with deaths mainly caused by myelodysplasia (MDS) (n=3) and acute myeloid leukemia (AML) (n=4). One individual with MDS died of hepatic failure unrelated to MDS. Cytopenias were almost universal (98.8%) and often intermittent, with neutropenia the most frequent in 98.8%, anemia in 16.5% and thrombocytopenia in 45.3%. Bone marrow evaluations were available in 98, with 88.2% demonstrating marrow hypoplasia. Notably, marrow hypoplasia was progressive, with average marrow cellularity of 74% in patients <1 year (n=13), 45% in children 1-19 years (n=277), and 38% in adults 19-43 years (n=38). Discordance between marrow cellularity and cytopenias was noted in some cases, and a systematic analysis of marrow cellularity and blood counts is ongoing. Marrow dysmorphologies were common, present in 40.9%, 49.5%, and 28% of the erythroid, myeloid and megakaryocyte lineages respectively. Thirty-three percent (n=30/89) developed clonal abnormalities at median age of 8.67 years (0.3-38.9). The most common clonal abnormalities were iso(7q) (n=4) and del(20q) (n=13). Notably, iso7q clones were transient while the majority of del20q clones were persistent. Progression to MDS occurred in one patient with a history of iso(7q) and one with del(20q).Evidence to guide optimal surveillance strategies for leukemia predisposition syndromes is lacking. The SDSR revealed wide variation in clinical practice amongst local hematologists including: no surveillance for well-appearing patients, intermittent blood counts, or marrow exams of variable frequency with inconsistent testing of cytogenetics and FISH. Some patients were not followed by hematology because they looked well until they presented with AML.
Conclusion: Additional clinical and laboratory studies are underway to provide evidence-based guidelines and to develop more sensitive tests for optimal surveillance of patients with predisposition to myeloid malignancies.

Paper Session # 2029

CHARACTERISTICS AND OUTCOMES OF UNPROVOKED VENOUS THROMBOEMBOLISM IN THE PEDIATRIC POPULATION

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Background: In adults, unprovoked venous thromboembolism (VTE) is associated with high risk of recurrence after stopping anticoagulation. Unprovoked VTE is less common in pediatric patients and there is minimal data describing characteristics and outcomes of this population.
Objectives: To describe the characteristics and outcomes of unprovoked VTE in pediatric

patients followed at our center.
Design/Method: We performed a retrospective analysis of a prospectively maintained institutional thrombosis database. We identified all patients with an unprovoked VTE followed at our center over a 10-year period (2009-2018). Patients were managed according to published guidelines. A thrombophilia evaluation was performed in all patients. Relevant data extracted from the database were summarized using descriptive statistics. We compared unprovoked VTE patients with and without a major thrombophilia - defined as inherited deficiency of antithrombin, protein C, or protein S, or antiphospholipid antibody syndrome. Data were compared using the Mann-Whitney U test or Fisher exact test as appropriate. Hazard ratio (HR) for recurrent VTE and 95% confidence interval (CI) were estimated using the Log-rank test. A two-tailed p-value less than 0.05 was considered significant.
Results: During the study period, 32 patients developed 46 unprovoked VTEs (including 14 recurrent VTEs in 9 patients). The median age was 16.6 years and 18 (56%) were males. Embolic events occurred in 22 patients (69%) [pulmonary embolism (PE) (21) and embolic stroke (1)]. All patients with unprovoked VTE received anticoagulation with 17 remaining on indefinite anticoagulation. Additional therapies included catheter-based interventions (6), systemic thrombolysis (4) and surgical thrombectomy (2). Anticoagulation-related major and/or clinically-relevant non-major bleeding was seen in 5 patients (16%) and minor bleeding was seen in 7 patients (22%). Chronic complications included post-thrombotic syndrome in 9 patients (28%) and chronic thromboembolic pulmonary hypertension in 3 patients (9%). Of the 32 patients with unprovoked VTEs, 13 (40%) were found to have major thrombophilia [antiphospholipid antibody syndrome (6) and inherited natural anticoagulant deficiency (7)]. Patients with major thrombophilia were largely similar in characteristics to patients without major thrombophilia except for a significantly higher frequency of PEs (68% vs. 24%, $p<0.01$). At median follow-up of 3.8 years, the risk of recurrent VTE was not significantly higher in patients with major thrombophilia (HR 1.7, CI 0.5-5.3, $p=0.8$).
Conclusion: Pediatric patients with unprovoked VTE represent a high risk group with suboptimal outcomes. Patients with major thrombophilia had higher frequency of PE but not higher recurrence risk. Multicenter, prospective studies are needed to develop more optimal evidence-based risk stratified management approaches.

Paper Session # 2030/Early Career Travel Stipend Award Recipient

3RD PARTY VST ARE AN EFFECTIVE THERAPY FOR THE TREATMENT OF BK-VIRUS REACTIVATION AFTER TRANSPLANT

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Background: BK virus is a commonly acquired childhood virus, with a seroprevalence in adults approaching 90%. Following primary infection, the virus resides in uroepithelial cells in a latent state. Viral reactivation commonly occurs during periods of immunocompromise. Following allogeneic hematopoietic stem cell transplantation (HSCT), reactivation occurs in greater than 50% of patients, with symptoms including hemorrhagic cystitis, renal injury, viremia and disseminated disease. Antiviral medications such as cidofovir and leflunomide are expensive and

have significant toxicity profiles without significant response rates. Viral specific T-lymphocytes (VSTs) are a form of manufactured cellular therapy whereby T-cells from healthy donors are engineered to recognize target viral epitopes and kill viral infected host cells.
Objectives: Describe our institutional experience treating patients with BK virus disease using partially HLA-matched VSTs from third-party healthy donors.
Design/Method: VSTs with activity against multiple viruses, including BK virus, were manufactured using peripheral blood mononuclear cells pulsed with viral peptide pools. Patients were eligible for our ongoing institutional phase I/II study if they had BK viremia or symptomatic BK viruria. VSTs could be given no earlier than 28 days following HSCT.
Results: 12 patients have been enrolled and treated with VSTs for BK virus. 10/12 patients were referred from outside institutions. The degree of HLA match ranged from 2/10-6/10 with a median of 5/10. 11/12 patients had allogeneic HSCT and 1/12 was on immunosuppression following solid organ transplantation. Patients were eligible to receive repeat infusions on a monthly basis and a total of 17 infusions in the 12 patients have been performed. Response was determined by improvement in viremia by quantitative PCR and/or symptomatic improvement in genitourinary symptoms. A positive clinical response was seen in 10/10 evaluable patients and 13/14 infusions. One patient was non-evaluable due to the need for high dose, lymphodepleting steroids shortly after infusion for the development of ARDS attributed to an aspiration event while another was non-evaluable due to the recent timing of cellular infusion. No acute infusional toxicity was seen with any infusion and there was no de novo graft-vs-host disease (GVHD) attributable to VST infusion.
Conclusion: Third party "off the shelf" partially HLA-matched VSTs are a highly efficacious therapy for the management of BK reactivation in patients with profound immunocompromise. No new GVHD was seen in this cohort who received partially HLA-matched VSTs and using a bank of third party donors allows for rapid turn-around from time of symptom onset to infusion of cellular therapy.

Paper Session # 2031

INHIBITION OF NEMO-LIKE KINASE IMPROVES ERYTHROPOIESIS IN MODELS OF DIAMOND BLACKFAN ANEMIA

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Background: Diamond Blackfan Anemia (DBA) is a congenital pure red cell aplasia with associated physical abnormalities such as microcephaly, absent or malformed thumbs, and cleft lip and/or palate, and an increased risk of cancer. Approximately 70% of patients with DBA have mutations in ribosomal protein genes, of which RPS19 and RPS11 account for over 25% and 5% of cases, respectively. Current therapies for DBA, including serial transfusions, steroids, and stem cell transplantation, have undesirable side effects.Nemo-like Kinase (NLK) is chronically hyperactivated in RPS19- and RPL11-haploinsufficient murine and human models of DBA, as well as erythroid progenitors from patients with DBA. NLK expression is relatively high in

hematopoietic stem cells regardless of ribosomal insufficiency, but once progenitors differentiate, NLK expression is dramatically reduced in all non-erythroid lineages. A region in the NLK 3'UTR is recognized by microRNA miR181; miR181 is significantly upregulated in all non-erythroid committed progenitors and accounts for the loss of NLK in these lineages. Better understanding NLK's role in disease pathogenesis is likely to facilitate the development of needed targeted treatments.
Objectives: To study the effects of NLK hyperactivation and pharmacological inhibition on erythropoiesis in DBA.
Design/Method: In order to understand the potential effect of NLK hyperactivation on all hematopoiesis, the miR181 binding site was mutated in megakaryocyte and other myeloid precursors by CRISPR/Cas9. To further study the role of NLK in erythropoiesis in the context of DBA, shRNA targeting NLK was used in an RPS19-insufficient human model. Finally, an independent, high-throughput kinase inhibitor screen was performed to identify compounds that both inhibited NLK kinase activity and increased erythroid progenitor expansion in RPS19-insufficient Kit+ murine cells.
Results: Mutation of the miR181 binding site in megakaryocyte and other myeloid lineages resulted expansion defects similar to erythrocytes in DBA (80.5% and 76% reductions relative to controls, respectively). In an RPS19-insufficient human model, shRNA silencing of NLK increased erythroid expansion by 2.2-fold. The inhibitor screen identified SB431542 and SD208, two known TGF-beta inhibitors, that increased erythroid expansion in murine (3.1- and 5.4-fold) and human (3.2- and 6.3-fold) DBA models with no effect on normal erythropoiesis. Similar results were observed in three DBA patient-derived CD34+ progenitors, with 2.3-, 1.9-, and 2.1-fold increases in CD235+ erythroblast generation compared to untreated.
Conclusion: Aberrant NLK hyperactivation underlies the erythrocyte expansion defect seen in DBA, and NLK inhibition helps restore normal erythropoiesis. NLK holds promise as a potential treatment target that avoids the side effects seen with current therapies.

Poster # 001

MAP KINASE PATHWAY ACTIVATION AS BIOMARKER FOR MEK INHIBITION IN PEDIATRIC B-LYMPHOBLASTIC LEUKEMIA

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Background: The prognosis for children with B ALL who relapse remains poor largely due to the challenges of treating drug resistant leukemic blasts. Prior studies show that Ras pathway mutations are common in relapsed B-ALL and activation of the mitogen activated protein kinase/extracellular signal related kinase (MAPK/ERK) pathway is a primary driver of drug resistance at relapse even in cases without Ras mutations.
Objectives: To determine whether MAPK/ERK pathway activation at diagnosis may be a predictive and prognostic biomarker.
Design/Method: Eighty one diagnostic bone marrow samples from patients with B-ALL

obtained from the Children's Oncology Group were plated in serum-free media with and without 1uM Trametinib (MEK 1/2 inhibitor) for 4 hours. Samples were left unstimulated or stimulated with phorbol-12-myristate 13-acetate (PMA) for 15 minutes followed by fixation with 4% paraformaldehyde and permeabilization with 95% methanol. Samples were stained for caspase 3, CD10, phosphorylated ERK and phosphorylated AKT, processed on the BDLSRII HTS cytometer and analyzed with FlowJo software. The median fluorescent intensity of phosphorylated ERK was measured for viable leukemic blasts (defined as CD10 positive and caspase 3 negative). MAPK activation was defined by the fold change in pERK MFI for untreated cells with PMA stimulation vs. without stimulation. Inhibition index was defined as the MAPK activation (as defined above) minus the fold change in pERK MFI for trametinib treated cells with vs. without PMA divided by the MAPK activation.
Results: A wide range of MAPK activation levels were observed in patient samples (median 1.26, range 0.7-4.4). Eleven percent of samples showed activation levels with ratios >2. Inhibition index ranged from -92.4 to 83.8, median 23.7. There was a significant correlation between the degree of MAPK activation and inhibition ($r = 0.64$, $p = 0.0001$). All of the samples with MAPK activation ratios >2 displayed significant inhibition (>35%). Of note, there was a subset of patients with low MAPK activation (25%) that also showed >35% inhibition. For those with outcome data (n=57), there was no difference between activation (mean of 1.32 vs. 1.39, p=0.62) or inhibition (mean of 21.79 vs. 14.56, p=0.46) in patients who relapsed (n=18) vs. those in remission, respectively.
Conclusion: We conclude that while MAPK activation alone, as measured by phospho-flow cytometry, correlates with inhibition, the inhibition index is the most appropriate predictive biomarker to potentially select patients that might respond to MAPK inhibitors. Based on our data, MAPK activation is not a prognostic biomarker.

Poster # 002

RUNX1 AMPLIFICATION IN EGYPTIAN PEDIATRIC PATIENTS WITH PRECURSOR-B ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Intrachromosomal amplification of chromosome 21 (iAMP21) is a rare chromosomal abnormality that occurs in about 2% of pediatric patients with B-cell precursor acute lymphoblastic leukemia (BCP-ALL). It is defined as three or more additional copies of RUNX1signals on a single abnormal chromosome 21 (a total of five or more RUNX1signals per cell). Recently, it started to be considered a high-risk chromosomal abnormality.
Objectives: To determine the frequency and clinical characteristics of iAMP21 in Egyptian pediatric patients with BCP-ALL and to assess its prognostic significance.
Design/Method: Pediatric patients less than 18 years old with BCP-ALL, who were treated at Children Cancer Hospital Egypt (57357-Hospital) from the year 2009 to 2011 on St. Jude total study XV protocol, were retrospectively screened with ETV6/RUNX1-specific fluorescent in situ hybridization (FISH) probe for the presence of iAMP21.
Results: A total of 518 patients were studied and iAMP21 was found in 9 patients, 1.74%. The

male to female ratio for iAMP21 patients was 1.25. Their median age was 6.7 years, most patients (8/9) had an age <10 years and the median white blood cell count at presentation was 6.2 x 10^3/mL. None of the patients had Pro-B immunophenotype. About 44% of the patients with iAMP21 had slow early response to induction treatment compared to 17% in the group without iAMP21 (p =0.031). Patients with iAMP21 had lower 5-year relapse-free-survival (RFS) compared to patients without iAMP21 (66.7±15.7% v 84.7±1.7%; respectively, p=0.205). Among iAMP21 patients, those with negative minimal residual disease (MRD) at the end of the induction and received intermediate risk treatment did not relapse, while 2 out of the 5 patients; who received less intensified therapy on low-risk arm; relapsed despite MRD negativity at the end of the induction.
Conclusion: The presence of iAMP21 was associated with slow early response to induction treatment and was likely to have lower RFS compared to patients without iAMP21. Patients with iAMP21 and negative MRD at end of induction had inferior outcome when treated on low-risk arm compared to intermediate-risk arm. This study suggests that all patients with iAMP21 should receive intensive chemotherapy regimen regardless of their MRD level at end of induction, however, it is limited due to small number of patients and further study on a larger population is needed.

Poster # 003

IMPACT OF MINIMAL RESIDUAL DISEASE AT END CONSOLIDATION IN STANDARD RISK B-LYMPHOBLASTIC LEUKEMIA

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Background: Minimal residual disease (MRD) at the end of induction (EOI) is strongly correlated with outcome in pediatric B-lymphoblastic leukemia (B-ALL). Additionally, patients with NCI high-risk (HR) B-ALL who have EOI MRD ≥0.1% that persists at ≥0.01% at end of consolidation (EOC) have very poor outcomes. Their 5-year disease-free survival (DFS) is only 39%±7% compared to 79%±5% in HR patients who have EOC MRD <0.01%. However, the impact of EOC MRD is not known for NCI standard-risk (SR) B-ALL.
Objectives: Describe DFS and overall survival (OS) in patients with SR B-ALL with EOI MRD ≥0.01% and EOC MRD ≥0.01% compared to patients with EOC MRD <0.01%.
Design/Method: We assessed DFS/OS in SR B-ALL patients enrolled on the Children's Oncology Group classification study, AALL08B1, who reported EOI MRD ≥0.01% and EOC MRD ≥0.01% determined by multi-parameter flow cytometry performed in COG central reference labs or COG-approved labs. DFS/OS were estimated using the Kaplan-Meier method starting from EOC, and curves compared using the log-rank test.
Results: Of 8,614 non-Down syndrome, non-Ph+, SR B-ALL patients who had EOI MRD available, 1,534 (17.8%) were positive at a threshold of ≥0.01%. The 5-year EFS of EOI MRD positive patients was 85.3%±1.6% versus 94.2%±5% for EOI MRD negative patients (P <0.0001). Of the 1,534 patients who were EOI MRD positive, 368 (24%) reported EOC MRD,

of which 25 (6.8%) had MRD ≥0.01%. The 3-year DFS for SR patients who were EOI MRD positive and EOC MRD positive was 81.9%±17.4%, versus 92.6%±2.3% for those who were EOI MRD positive but EOC MRD negative (P =0.0265). OS for patients who were EOC MRD positive was 90.3%±12.6% versus 96.9%±1.5% for EOC MRD negative patients (P =0.18). The 3-year cumulative incidence of isolated bone marrow (BM) relapse was 18.2%±8.6% for the EOC MRD positive group versus 2.9%±1.2% for EOC MRD negative cohort (P <0.001). Analysis of other relapse subtypes was limited by small numbers.
Conclusion: Patients with NCI SR B-ALL who are EOI and EOC positive have significantly inferior DFS and greater risk for isolated BM relapse compared to those who clear their MRD by EOC. However, these outcomes are substantially better than those of HR B-ALL patients who are EOI and EOC MRD positive. Together, these data support that novel approaches to EOC MRD-positive SR B-ALL are warranted but do not justify the use of hematopoietic stem cell transplant or other cellular based immunotherapies for these patients.

Poster # 004

MINIMAL RESIDUAL DISEASE IN PERIPHERAL BLOOD DURING EARLY INDUCTION PHASE IN CHILDHOOD B PRECURS ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Minimal residual disease (MRD) in childhood acute lymphoblastic leukemia (ALL) during the early stages of therapy may have significant impact on outcome.
Objectives: To study the prognostic significance of MRD by flow-cytometry in peripheral blood (PB) after 1 week of multiagent induction treatment in childhood B-precursor ALL.
Design/Method: This study included 359 newly diagnosed pediatric B-precursor ALL patients treated at the Children's Cancer Hospital-Egypt. Patients were risk stratified and received risk directed therapy according to the total study XV protocol adopted from St. Jude Children Research Hospital.PB-MRD was measured by flow-cytometry on day 8 in 128 patients and on day 12 in 231 patients as they received 4 days of prednisone pre-phase.
Results: The median follow-up of patients who are alive in complete remission was 54.8 months (range, 32 to 85).The 5-year event free survival (EFS) and relapse free survival (RFS) of all patients with day 8 or day 12 PB-MRD <0.01% was 89.3±3% and 92.9±2.7% respectively (n=126); 83.1±3.8% and 87.3±3.5% for MRD 0.01-<0.1%, respectively (n=104); 70.4±4.2% and 78.7±4% for MRD ≥0.1%, respectively (n= 129). (p=0.001, and p=0.007, respectively).For provisional low risk (LR) patients, the 5-year EFS and RFS was 92.7±3% and 94.5±2.8%; respectively for PB-MRD <0.01% (n=101), 83±4.3% and 87.5±3.9%; respectively for PB-MRD 0.01 -<0.1% (n=79), on the other hand it was 72.3±4.9% and 79.6±4.6%; respectively for PB-MRD ≥0.1% (n=91), (p=0.001 and p=0.007, respectively).Provisional LR patients with ETV6-RUNX1 or hyperdiploid (DNA index ≥1.16) and PB-MRD <0.01% had 5-year EFS 96.4±2.6% (n=75) compared to 82.6±8.2% for other provisional LR with PB-MRD <0.01% but lacking favorable cytogenetic features (n=26) (p=0.021).
Conclusion: Early induction PB-MRD by flow-cytometry constitutes an early prognostic index

for children with B-Precursor ALL and can help in identification of a subgroup of patients provisionally classified as low-risk ALL with either favorable DNA index or ETV6-RUNX1 having an excellent outcome that can be cured with limited therapy.

Poster # 005

OBESITY AS A RISK FACTOR FOR PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA: A COG REPORT (AALL17D2)

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Background: Obesity is a known risk factor in many adulthood cancers, but its role in childhood cancer development is unknown. Increases in the incidence of both childhood acute lymphoblastic leukemia (ALL) and obesity in childhood have been observed over the past three decades.
Objectives: We sought to identify whether obesity measured at diagnosis is a risk factor for childhood ALL.
Design/Method: Demographics, anthropometrics and disease characteristics from children and young adults (aged 1-30 years) diagnosed with ALL between 2004-2017 and treated on Children's Oncology Group (COG) frontline treatment protocols with available pre-treatment anthropometric data (n=4775) were compared to National Health and Nutrition Examination Survey (NHANES) controls (n=30,107). Underweight, normal weight, overweight, or obesity were defined using standard CDC age- and sex-based pediatric and adult definitions for body mass index (BMI). Multivariate logistic regressions were performed, adjusting for sex, race/ethnicity, age, socioeconomic status and obesity status, to assess associations between BMI classification and ALL.
Results: ALL patients (72% B-ALL, 28% T-ALL) were more likely to be male (62%), 58% were non-Hispanic white, 9% non-Hispanic black and 24% identified as Hispanic. Five percent had underweight, 58% normal weight, 17% overweight and 20% obesity. Using normal weight as the reference group, higher BMI classifications were found to be associated with ALL diagnosis (overweight, OR=1.10, 95% CI 1.00-1.20, p=0.046; obesity, OR=1.15, 95% CI 1.05-1.25, p=0.002), as was underweight (OR=1.74, 95% CI 1.48-2.03, p=<0.0001). When stratified by ALL immunophenotype, association with obesity was only observed in B-ALL (OR=1.24, 95% CI 1.13-1.46, ptrend<0.0001). When stratified by sex, association with obesity was only observed in males (OR=1.26, 95% CI 1.13-1.40, ptrend<0.0001).
Conclusion: This is the first study, to our knowledge, to show associations between pre-treatment overweight or obesity and ALL, specifically among males and B-cell immunophenotype. This study also confirmed the association between underweight and newly diagnosed ALL. Detrimental physiologic effects of ALL may influence the association between BMI status and newly diagnosed ALL (i.e. underweight at time of diagnosis). However, the association between obesity and ALL needs to be further investigated, and may suggest a role for underlying mechanisms of obesity (inflammation, environmental exposures, or other genetic susceptibility) in ALL pathogenesis. Interestingly, the association between male sex and obesity suggests there may be a role for sex hormones, particularly estrogen. Further analyses are needed

to elucidate whether other ALL disease characteristics may be associated with pre-treatment childhood BMI.

Poster # 006

EFFECT OF SLCO POLYMORPHISMS ON HIGH-DOSE METHOTREXATE CLEARANCE IN HEMATOLOGIC MALIGNANCIES

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Background: High-dose methotrexate (HD MTX) is a critical component of treatment for pediatric acute lymphoblastic leukemia (ALL) and other malignancies. While highly effective, HD MTX regimens have a risk of significant toxicities and require inpatient serial drug level monitoring through clearance. There is substantial interindividual variation in HD MTX clearance which has important clinical implications: slow clearance increases risk for toxicity, while rapid clearance may decrease efficacy and increase risk for relapse. Organic anion transporting polypeptides (OATPs; SLCO) are critical to the uptake and disposition of many drugs. OATP1B1, -1B3 (hepatic), and -1A2 (kidney, blood:brain barrier) transport MTX and are known to have common function-altering polymorphisms in humans.
Objectives: The primary aim of this study is to determine the contribution of genetic variation in SLCO genes to the clearance of HD MTX in patients with ALL or lymphoblastic lymphoma. The secondary aim will examine the relationship between these polymorphisms and toxicities and patient outcomes.
Design/Method: This is an observational study involving patients treated on a COG pediatric oncology protocol using HD MTX. Targeted genotyping using a Sequenom-based assay was conducted for key polymorphisms in drug disposition genes in the MTX disposition pathway, including SLCO. Clinical information (including serial MTX levels) is obtained from the electronic medical record. BioVU, Vanderbilt's DNA repository linked to a de-identified version of the medical record, is also being utilized. Primary endpoint is MTX clearance (using pharmacokinetic modeling). Secondary endpoints are incidence/severity of MTX-induced toxicities (mucositis, neutropenia, hepatotoxicity) and patient outcomes (survival, relapse). Linear regression modeling will be used for analysis of the primary endpoint, and logistic regression modeling will be used for analysis of the secondary endpoints.
Results: Genotyping and clinical data have been obtained on 109 patients with ALL or lymphoblastic lymphoma. Median age at first dose of HD MTX is 10.4y (range 0.7-38.6y). Adult patients in the BioVU system were included if they were treated according to a COG pediatric protocol. Preliminary analysis of the effect of the key SLCO1B1 polymorphism rs4149056 (521T>C) in 80 patients who received HD MTX at 5 g/m2 shows significantly higher 24-hour MTX levels in patients with at least one copy of the variant allele compared to wild-type ($p=0.05$). Pharmacokinetic modeling is underway to determine methotrexate clearance and association with genetic variation in MTX drug disposition genes.
Conclusion: MTX levels in children and young adults with ALL or lymphoblastic lymphoma receiving HD MTX (5 g/m2) are associated with SLCO1B1 genetic variation.

Poster # 007

HISPANIC CHILDREN ARE AT INCREASED RISK OF DELAYED METHOTREXATE CLEARANCE AND SEVERE NEPHROTOXICITY

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Background: Methotrexate is a crucial chemotherapeutic agent used to treat children with acute lymphoblastic leukemia (ALL). As methotrexate is excreted nearly exclusively by the kidneys, high dose methotrexate-related severe nephrotoxicity, as defined by the Ponte di Legno consensus criteria, is a serious potential complication of treatment.
Objectives: To evaluate risk factors for patients who experience delayed methotrexate clearance and severe nephrotoxicity.
Design/Method: A retrospective chart review was performed over a ten-year period at Texas Children's Cancer Center and The University of Texas Health Science Center at San Antonio (UTHSCSA). Charts of all known patients diagnosed with acute leukemia, T or B Cell, who received high dose methotrexate were evaluated. Data collected included methotrexate clearance values, time to clearance of methotrexate, creatinine values that corresponded with methotrexate clearance values, and baseline creatinine values prior to methotrexate infusions. Patient demographics evaluated included age, sex, and ethnicity.
Results: For the Texas Children's Data Analysis there were 287 patients receiving their first high dose methotrexate infusion. The mean time to clearance of the cohort was 75 hours. Ethnicity showed a significant association with delayed clearance. The mean time to clearance of Hispanic patients was 83 hours compared to the mean clearance time of 66 hours found in Non-Hispanic patients (student's t-test, $p=0.02$). Both groups were not different in terms of age, T Cell ALL to Pre-B Cell ratio, or male to female ratio. Of the 4% of patients with greater than 200 hours to clear, 100% were Hispanic. The UTHSCSA Hispanic population (28 of 33 children) had a mean clearance time of 94 hours versus 68 hours for Non-Hispanic patients.In addition, 7 patients in the Texas Children's Cohort met the Ponte di Legno criteria to have severe nephrotoxicity, 100% were Hispanic. Patients with severe nephrotoxicity had a mean hospital stay of 16 days, 71% experienced mucositis, and most required significant electrolyte replacement.
Conclusion: There is a select population of Hispanic children who are at increased risk of delayed methotrexate clearance and severe nephrotoxicity with their first high dose methotrexate infusion. These sequelae lead to significant morbidity and warrant further evaluation at a genetic level to define if there is a genetic variation predisposing these children to adverse events with HDMTX. Until this is known, physicians should consider initiating protective efforts in Hispanic patients with their first infusion, such as increasing hydration, rather than waiting for these children to experience a first delay.

Poster # 008

PRE-B ACUTE LYMPHOBLASTIC LEUKEMIA AMONG HISPANIC CHILDREN

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Background: Hispanics are the largest minority group in the US. Literature confirms Hispanics have the highest incidence of acute lymphoblastic leukemia (ALL) and poorest outcomes compared to other racial and ethnic groups.
Objectives: Characterize and compare Pre-B ALL among Hispanics and Caucasians.
Design/Method: Retrospective chart review was performed at Children's Mercy Hospital from 01/01/2014- 10/31/2018. Data was analyzed using descriptive statistics and the Fisher Exact test.
Results: One hundred-ten patients with Pre-B ALL were eligible for study. Patients with Trisomy 21 and infant ALL were excluded. Sixty-two percent of patients were Caucasian (n=68), Hispanics 20%, (n= 22) African Americans 12% (n=13), multiracial 4% (n=4), Asian 2% (n=3). Patients classified as multiracial that stated some element of Hispanic ancestry (n=3/4) were included as Hispanic in the data analysis (n=25). Males represented 64% and 56% of the Hispanic and Caucasian cohorts respectively. Median age at diagnosis for each group was similar (Hispanics 5 years and Caucasians 4 years). Among Caucasians and Hispanics, high-risk Pre-B ALL by National Cancer Institute criteria represented 38.2% and 24% of cases respectively. Minimal residual disease (MRD) at the end of induction chemotherapy was present in 40% of Hispanics and 28% of Caucasians (p=0.265). Higher rates of MRD were found among Hispanics with standard risk ALL (47%) than Caucasians (28%) (p=0.102). All patients were treated per the standard of care arm or on-study with Children's Oncology Group protocols. Hispanics were more frequently moved from standard to high risk therapy compared to Caucasians (57.8% vs 40.4% respectively) (p=0.205) due to MRD or unfavorable cytogenetics as indicated by protocol or current clinical standards. Favorable cytogenetics (ETV6-RUNX1 and trisomy 4, 10, 17) were found more frequently in Caucasians. There was no difference between the two groups in terms of unfavorable cytogenetics.
Conclusion: Hispanics with standard-risk ALL had higher trends of end of induction MRD compared to Caucasians and over half of the Hispanics with standard-risk ALL required intensified therapy with a high-risk protocol after end of induction evaluation. Our Hispanic cohort was small and likely attributed to the lack of statistically significant differences between the two groups. Hispanic patients with end of induction MRD that received intensified therapy remain in remission. As the Hispanic population increases in the US, focused population studies will be required to better understand and stratify ALL in this minority group in order to continue to decrease ethnic disparities and improve outcomes.

Poster # 009

IMATINIB & HIGH-DOSE METHOTREXATE CAUSE KIDNEY INJURY AND DELAYED METHOTREXATE CLEARANCE IN PH+ ALL

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Background: Philadelphia chromosome-positive (Ph+) B-cell acute lymphoblastic leukemia (B-ALL) is a high-risk subtype of pediatric ALL occurring in 3-5% of patients. Imatinib is an oral

tyrosine kinase inhibitor (TKI) targeting the BCR-ABL1 fusion oncoprotein which defines this leukemia. When added to an intensive Berlin-Frankfurt-Munster (BFM) chemotherapy backbone, imatinib significantly improved event-free survival in pediatric patients with Ph+ ALL from 35% to 70%.1 Methotrexate (MTX), a component of BFM chemotherapy, has multiple drug interactions which can result in profound MTX-induced toxicity. However, there are no formal drug interactions listed between HD-MTX and TKIs, and limited information on potential pharmacokinetic interactions. Importantly, current pediatric protocols do not give warning that concomitant administration of TKIs with HD-MTX may result in serious renal toxicity or provide recommendations to withhold TKIs during HD-MTX treatment. Here we report serious acute kidney injury (AKI) and delayed MTX clearance in four pediatric patients with Ph+ ALL treated concomitantly with HD-MTX and imatinib.
Objectives: Describe the clinical complications which result from the interaction between HD-MTX and imatinib
Design/Method: Case series and review of the literature
Results: Four pediatric patients with Ph+ B-ALL, median age 12 (range, ages 4-19) years, treated at two institutions (Children's Hospital of Wisconsin and Wolfson Children's Hospital) according to Children's Oncology Group protocol AALL0031, developed Grade 3 AKI (CTCAE v4) during their 1st cycle of HD-MTX while on imatinib. This was characterized by elevated creatinine (range, 35 to 325% increase from baseline); significantly delayed MTX clearance (range, 7 to 14 days post-MTX administration) which required aggressive intravenous hydration and increased leucovorin rescue and resulted in the development of Grade 3 mucositis and prolonged hospitalization (range, 7 to14 days). Two of the four patients received emergent glucarpidase due to severity of their renal dysfunction (creatinine increases of 235% and 325%) and elevated 36-hour MTX levels of 17.64 umol/L and 36.9 umol/L respectively, (goal <3 umol/L). For subsequent HD-MTX cycles, imatinib was withheld in all four patients and creatinine levels remained normal for age, MTX clearance times improved (range, 2 to 6 days) and they developed mild mucositis (Grade 1/2) with fewer days of hospitalization (range, 2 to 6 days).
Conclusion: We identified significant renal toxicity when imatinib was given concurrently with HD-MTX. For pediatric patients with Ph+ ALL receiving imatinib, we recommend withholding imatinib during HD-MTX infusions, until the MTX has cleared, to help mitigate the risk of AKI, delayed MTX clearance, and significant morbidities.

Poster # 010

CONTINUATION OF TYROSINE KINASE INHIBITORS AFTER CHEMOTHERAPY IN PH+ ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Standard of care therapy for children with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) now includes a combination of tyrosine kinase inhibitors (TKI) and chemotherapy, with or without hematopoietic stem cell transplantation (HSCT) depending upon treatment response and availability of an appropriate transplant donor. Whether and for how long to continue TKI after completion of chemotherapy is not known.

Objectives: To describe the use of TKI after completion of chemotherapy for Ph+ ALL, including prophylactic use (no detectable BCR-ABL by polymerase chain reaction [PCR]), preemptive use (detectable BCR-ABL by PCR) and last known disease status (relapse, remission).
Design/Method: We performed a single institution retrospective case series. Potential cases were identified by searching the Stanford Translational Research Integrated Database Environment for patients diagnosed with ALL at age ≤ 29 years who received a TKI, and charts were reviewed to include only those with Ph+ ALL who completed all planned treatment with chemotherapy plus TKI, without HSCT in first complete remission (CR1).
Results: We identified ten patients (all < 21 years at diagnosis) who had completed all planned treatment with chemotherapy plus TKI, without HSCT in CR1. Of these, 6 of 10 (60%) stopped TKI at the end of chemotherapy, while 4 of 10 (40%) continued on TKI prophylactically. Three of the four subsequently stopped TKI between 11 months and 6 years after completion of chemotherapy: one relapsed 11 months after stopping prophylactic TKI, and two resumed TKI preemptively due to detectable BCR-ABL PCR that developed while off TKI. Three patients in CR1 remain on TKI indefinitely as of last follow up (two for preemptive treatment, one for prophylaxis). Among the six patients who stopped TKI at the end of chemotherapy, four relapsed and two remain disease free in CR1 as of last follow up. Among all five patients who relapsed, one died of disease, three remain in CR2 at 6 months, 9 months, and 4.5 years following HSCT, and one is currently receiving relapse therapy.
Conclusion: At a single institution, there is variability in practice patterns related to continuation of TKI following completion of chemotherapy for pediatric Ph+ ALL. Larger studies are needed to characterize prophylactic and preemptive TKI use in pediatric patients with Ph+ ALL in order to determine risks, benefits, and best practices. Funding Support: This project was supported by the Stanford Maternal and Child Health Research Institute (MCHRI); the primary author is the "Rosa A. Wann and Marjorie Shannon Fellow".

Poster # 011

HIGH VS. LOW-INTENSITY BRIDGING CHEMOTHERAPY WHEN AWAITING CAR-T THERAPY: A POPULATION-BASED STUDY

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Background: Chimeric antigen receptor T-cells (CAR-T) have emerged as a promising treatment for children with relapsed/refractory acute lymphoblastic leukemia (ALL). While CAR-T outcomes have been published, little data exist on how to manage patients for the months between T-cell collection and CAR-T infusion. Unlike stem cell transplant (SCT), successful outcomes for children with high disease burden pre-CAR-T have been demonstrated. Thus, traditional high-intensity chemotherapy for relapsed ALL that aims to minimize disease burden but carries significant morbidity may not be the best option for pre-CAR-T populations.
Objectives: To compare our population-based experience in using high vs. low-intensity

chemotherapy regimens to bridge patients in terms of toxicity, inpatient days, and success in reaching CAR-T infusion.
Design/Method: All Ontario children referred to Sickkids (the provincial pediatric referral centre for cellular therapy) between 2014-2018 for first T-cell collection with intent to proceed to CAR-T therapy were included and followed until CAR-T infusion, decision to pursue alternative therapy, or death. Bridging regimens were classified as low vs. high intensity based on likelihood to cause >7 days of neutropenia. Disease and outcome variables were compared between high vs. low intensity regimens.
Results: The cohort included 32 patients with median age of 9.7 years at the time of first T-cell collection [interquartile range (IQR) 6.0-12.3]. The median number of previous relapses was 2 (IQR 1-2); 14 (44.0%) had undergone prior SCT. The vast majority (28, 87.5%) were successfully bridged to CAR-T therapy with a median time to infusion of 81 days (IQR 60-105). Two patients experienced manufacturing failure and pursued SCT instead, 1 died of toxicity, and 1 was still awaiting infusion at the end of the study period. Low-intensity bridging regimens were used following collection for 19 (59.4%) patients, most often based on low-dose intravenous methotrexate or maintenance therapy. Common high-intensity regimens included high dose cytarabine, or anthracycline. Patients receiving high-intensity therapy did not have more aggressive disease prior to bridging treatment (as indicated by peripheral blasts, previous relapses, prior SCT). Patients receiving initial high-intensity regimens experienced more microbiologically documented infections and inpatient days. Excluding patients experiencing manufacturing failure or awaiting CAR-T, the likelihood of receiving CAR-T did not vary [high - 11/12 (91.7%) vs. low - 17/17 (100%); p=0.41].
Conclusion: In heavily pre-treated patients, initial low-intensity chemotherapy had a very high likelihood of successfully bridging children to CAR-T infusion, and was associated with lower rates of toxicity. Low-intensity regimens should be the first line option in this population.

Poster # 012/Early Career Travel Stipend Award Recipient

ACUTE KIDNEY INJURY AFTER CD19-TARGETED CAR T CELL THERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: CD19-targeted chimeric antigen receptor (CAR) T cell therapy for acute lymphoblastic leukemia (ALL) is associated with potentially severe toxicities. Acute kidney injury (AKI) is a commonly reported toxicity, but has not yet been systematically evaluated.
Objectives: We sought to describe AKI incidence, severity, outcome, and risk factors in the first 30 days after CTL019, a CD19 CAR T cell therapy, for pediatric ALL.
Design/Method: We studied patients treated with CTL019 through two clinical trials (NCT01626495 and NCT02906371) at Children's Hospital of Philadelphia between 2012-2018. Demographic, laboratory and pharmacy data were automatically extracted from the electronic medical record using an EPIC data query tool. The primary outcome was AKI, defined using the Kidney Disease: Improving Global Outcomes criteria. Stage 1 (serum creatinine (SCr) >= 1.5

times the baseline) was classified as mild AKI. Stage 2 or 3 (SCr >=2 times the baseline) were classified as severe AKI. Renal recovery was defined as improvement in SCr to within 1.5 times baseline by day +30. Log-binomial regression was used to estimate risk ratios for the association of cytokine release syndrome (CRS) and other patient characteristics with AKI.
Results: We analyzed 125 patients with 3231 creatinine values. Median age was 11.2 (range: 1.4-29.1) years at infusion; 57.6% were male, 72% were Caucasian, and 82.4% were non-Hispanic. AKI developed in 26 patients (21.0%; 95% CI, 14.5-28.9), severe AKI developed in 15 patients (12%; 95% CI, 7.3-19.1), and 3 patients (2.4%; 95% CI, 0.7-7.3) required renal-replacement therapy. Among those with AKI, 22 (88%; 95% CI, 66.7-96.4) recovered renal function by day +30. Patients with Grade 3/4 CRS had a 4.9 times greater risk of developing AKI (95% CI, 2.4-9.9; p<.001) and a 10.3 times greater risk of developing severe AKI (95% CI, 3.1-34.3; p<.001) than patients with no or Grade 1/2 CRS. The median time to CRS start, AKI onset, and maximum SCr was 2, 7 and 9 days after infusion, respectively. Neither history of hematopoietic cell transplant nor demographic characteristics were associated with AKI.
Conclusion: In the first 30 days after CTL019 infusion, 21% of patients developed AKI, but most recovered renal function by day +30. AKI was strongly associated with Grades 3 and 4 CRS and developed at a median of 5 days after the start of CRS. Additional analyses will compare the trajectories of CRS biomarkers and tumor lysis labs with creatinine trajectories in order to elucidate mechanisms of renal injury and identify opportunities for intervention.

Poster # 013

ZUMA-4 PHASE 1: KTE-X19, AN ANTI-CD19 CAR T CELL THERAPY, IN CHILDREN AND ADOLESCENTS WITH R/R B-ALL

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Background: KTE-X19, formerly KTE-C19, is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy. Early clinical experience with KTE-X19 in children and adolescents with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) is promising. Here, we present end of Phase 1 results from ZUMA-4.
Objectives: Evaluate the safety and efficacy KTE-X19 in pediatric and adolescent patients with R/R B-ALL.
Design/Method: In this dose-finding study, patients aged 2–21 years with R/R B-ALL (Ph+ allowed) and >5% bone marrow (BM) blasts received either 2 or 1×10^6 CAR T cells/kg following conditioning chemotherapy. The primary endpoint was incidence of dose-limiting toxicities (DLTs). Secondary endpoints included complete remission (CR) rate (CR and CR with incomplete hematologic recovery [CR+CRi]) and overall survival (OS). KTE-X19–formulation was optimized in a second 1×10^6 dose group using a lower infusion volume (40-mL versus 68-mL).
Results: As of 10/11/2018, 24 patients (median age 13 years [range 3-20]; 42% ≥3 prior regimens; 29% primary refractory disease; 25% R/R post-alloSCT; 37% [range 0–100%] median

pre-conditioning BM blast count) received KTE-X19. The median follow-up was 13.2 months. Four patients received a targeted 2×10^6 cells/kg with no DLTs in evaluable patients (n=3). Patients were then enrolled at a targeted 1×10^6 cells/kg to improve the overall safety profile: 11 received the 68-mL formulation, and 9 received the 40-mL. Overall, the most common Grade ≥3 AEs were hypotension (50%) and anemia (33%). Rates of Grade ≥3 neurologic events were 25%, 36%, and 11% in the 2×10^6, 1×10^6 (68-mL), and 1×10^6 (40-mL) groups, respectively, and rates of Grade ≥3 cytokine release syndrome were 75%, 18%, and 22%. Overall, there were 3 Grade 5 AEs that were unrelated to KTE-X19. All but 2 patients in the 40-mL, 1×10^6 group were evaluable for efficacy with ≥2 months of follow-up. The CR+CRi rate was 100%, 64%, and 71% in the 2×10^6, 1×10^6 (68-mL), and 1×10^6 (40-mL) groups, respectively, with 25%, 71%, and 100% of CR+CRi patients in ongoing response as of the data cut-off, and 75%, 73%, and 86% of all patients had undetectable minimal residual disease. Median OS was not reached for either 1×10^6 group and was 8 months for the 2×10^6 group. CAR T cell expansion was observed in all dose/formulation groups.
Conclusion: Children and adolescents with R/R B-ALL achieved high MRD-negative remission rates with a manageable safety profile and promising efficacy after a single dose of KTE-X19. Phase 2 of ZUMA-4 is ongoing at the 40-mL, 1×10^6 cells/kg dose.

Poster # 014

HYPERGLYCEMIA REQUIRING INSULIN DURING INDUCTION THERAPY IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Hyperglycemia is a known complication of induction therapy for childhood Acute Lymphoblastic Leukemia (ALL). However, its impact on clinical outcomes is unclear.
Objectives: To investigate the impact of hyperglycemia requiring insulin during induction therapy on morbidity and mortality in children with ALL during and following induction therapy.
Design/Method: We used the Pediatric Health Information System (PHIS), an administrative electronic database of children's hospitals in the U.S. We included patients between 1 and 21 years of age admitted between 2004 and 2011 with ALL undergoing induction chemotherapy (identified by medication charges during admission for vincristine, Peg-asparaginase/L-asparaginase, and dexamethasone or prednisone). These patients were divided into two cohorts (i) those who received insulin and, (ii) those who did not require insulin during induction therapy. Patients were followed for 4 years from induction chemotherapy for outcomes data.
Results: A total of 6,213 patients from 30 children's hospitals met inclusion criteria. Of these, 543 patients (8.7%) received insulin during their admission for induction chemotherapy. Patients who required insulin during induction chemotherapy had an older mean age (11.26 years vs 6.16 years), a lower mean income (p=0.02) and were more likely to be NCI high risk (p=0.001), have Trisomy 21 and had a longer average length of stay during induction (p<0.001 for both). Patients who required insulin during induction were also found during follow-up to have a significantly increased risk of developing osteonecrosis, relapsed leukemia and bone marrow transplantation (all p<0.001), as well as a significantly increased risk of mortality both during induction therapy

and following induction (p<0.001). During the follow-up period, patients who required insulin had a greater average number of hospital readmissions (5.85/patient vs 5.39/patient, p<0.001). Hospital encounters in patients with a history of insulin use were more likely to be complicated by sepsis (p<0.001) or candidiasis (p=0.002) and were more likely to require ICU utilization (p<0.001). Logistic regression adjusting for age, NCI risk group and steroid type demonstrated that insulin use was associated with increasing odds of mortality during induction (OR 7.79, p<0.001), ICU admission during induction (OR 2.65, <0.001) and readmission for an infectious episode during follow-up (OR 1.16, p=0.007).
Conclusion: Hyperglycemia requiring insulin during induction chemotherapy is associated with an increase in infectious complications, resource utilization, and mortality in pediatric patients with ALL. Further studies are needed to assess the impact of optimal management of hyperglycemia on these outcomes in this population.

Poster # 015

HYPERGLYCEMIA AND ADVERSE OUTCOMES IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA/LYMPHOMA PATIENTS

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Background: Hyperglycemia is associated with adverse outcomes in various adult cancer populations including increased infection, sepsis, relapse/progression of disease, mortality, and length of stay. Pediatric acute lymphoblastic leukemia (ALL) and lymphoma (ALLy) patients are of particular interest, as steroids and asparaginase are critical components of therapy and have a known association with hyperglycemia. While a few studies have evaluated the occurrence of hyperglycemia during induction chemotherapy for pediatric ALL, the literature on this area is scant and focuses on transient hyperglycemia. The incidence of, risk factors for, and impact of ongoing abnormal glycemic control in pediatric AYA patients is unclear, and further research exploring this potentially this modifiable risk factor for increased morbidity and mortality is necessary.
Objectives: This study aims to retrospectively determine the incidence, risk factors, and timeline of abnormal glycemic control in the pediatric ALL/ALLy population and to characterize the relationship between abnormal glycemic control and adverse outcomes in this population.
Design/Method: Records for 229 pediatric and young adult patients, age 0-26 years (6.0 median y/o at diagnosis, 53.7% male), who underwent treatment for ALL/ALLy from 2010–2014 at Children's Hospital Colorado were retrospectively reviewed. The primary outcomes are hyperglycemia (mean glucose ≥140mg/dL) in induction and time-to-infection (serious bacterial infection, invasive fungal infection, viremia). A multivariable logistic regression will be used to identify predictors of hyperglycemia in induction. The effect of glucose on time-to-infection will be assessed using a multivariable Cox regression model. Secondary analyses will investigate the effect of glucose on additional outcomes, including overall survival.
Results: 17.5% patients experienced mean glucose ≥140mg/dL during at least one cycle of chemotherapy, with induction having the highest proportion of patients with hyperglycemia (12.7%). The mean proportion of glucose values ≥140mg/dL was 21.0%. There was an average of 23 glucose measurements per patient in induction and mean glucose values ranging from 71.5-

290.1mg/dL (median:110.1mg/dL, IQR:23.6mg/dL). Analyses of risk factors for hyperglycemia during induction are forthcoming, but are hypothesized to include increased age, overweight/obese body habitus, and Hispanic ethnicity. Analyses of the association between measures of glycemic control and time-to-infection are planned.
Conclusion: Hyperglycemia occurs in the pediatric ALL/ALLy population with a significant number of patients being affected. As in other populations, mild to moderate increases in mean glucose may represent biomarkers for heightened risk of infection, critical illness and mortality. Moreover, malglycemia may be causal in these associations. Continued exploration of these relationships and the potential for intervention is necessary.

Poster # 016

ORAL MERCAPTOPURINE ADHERENCE IN PEDIATRIC ALL: A SURVEY STUDY FROM THE DFCI ALL CONSORTIUM

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Background: Poor adherence to oral 6-mercaptopurine (6-MP) during acute lymphoblastic leukemia (ALL) therapy, identified in 33% of patients on Children's Oncology Group (COG) clinical trials, is associated with increased relapse risk. Factors impacting adherence include age, race/ethnicity, household structure, income, parental education, and pill-taking routine. Rates and risk factors for 6-MP non-adherence in the context of non-COG ALL regimens have not been investigated. Dana-Farber Cancer Institute (DFCI) ALL Consortium protocols utilize 14-day pulses of 6-MP and intravenous methotrexate throughout maintenance therapy in repeating 3-week cycles. This differs from continuously dosed 6-MP, oral methotrexate and repeating 4-week chemotherapy cycles in COG trials, which may require less frequent family contact with the medical team. Survey-based adherence reporting, while known to underestimate non-adherence as compared to the gold-standard Medication Event Monitoring System (MEMS) caps, may be more practical in the non-trial setting and is thus appropriate for exploratory research.
Objectives: To describe the rate of parent-reported 6-MP non-adherence and barriers to adherence in the context of DFCI ALL Consortium-based therapy.
Design/Method: Eligible families (child age 1-18 years) receiving therapy on, or as per DFCI 11-001 were consented to participate in a cross-sectional survey during Continuation phase at four U.S. DFCI Consortium sites (February 2015 –March 2017). The Adherence Survey was adapted from Bhatia et al (J Clin Oncol, 2012) and assessed self-reported sociodemographic variables, medication-taking behaviors, chemotherapy comprehension, food insecurity, and 6-MP adherence. Patients were considered adherent if they reported taking 14 days of 6-MP during their prior cycle, all others were considered non-adherent.
Results: Sixty-two families completed the Adherence Survey of whom 56 (90%) had evaluable self-report adherence data. Characteristics of these evaluable families included 29% Hispanic, 25% non-English speaking, 25% with highest maternal education high school or less, and 34% low socioeconomic status as assessed by food insecurity. Nine (15%) were non-adherent to 6-MP and 10 (18%) reported difficulty remembering to administer all medications. Twenty-three

percent reported that it was “not easy” to follow 6-MP administration guidelines related to dairy intake. Fifty-seven percent expressed interest in receiving educational resources about 6-MP; 39% suggested that printed calendars would help with adherence.
Conclusion: Fifteen percent of families reported 6-MP non-adherence in the context of a DFCI ALL Consortium regimen. Given known underreporting associated with survey-based adherence measures, additional research on medication-taking behaviors and chemotherapy comprehension is needed. Prospective investigations of oral chemotherapy adherence using MEMS caps in the open DFCI ALL Consortium trial is ongoing.

Poster # 017

PARENTS PERSPECTIVE ON MEDICATION ADHERENCE AND MHEALTH AS A POTENTIAL INTERVENTION IN CHILDHOOD ALL

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Background: Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer. 6-Mercaptopurine (6-MP) is a critical component of maintenance therapy in ALL. Adherence to 6MP remains suboptimal and lower adherence rates are associated with increased risk of relapse. mHealth has been efficacious at improving adherence behaviors in children, adolescents and young adults with other chronic health conditions; however, limited research has addressed parents reported barriers to adherence and interest in mHealth.
Objectives: To assess parents reported barriers to adherence, access to personal technology, and preferences for a smartphone app as a behavioral intervention to improve 6-MP adherence.
Design/Method: A cross-sectional survey was administered in an outpatient oncology clinic via REDCap from November 2017 through December 2018 in Chicago, IL, USA. Study measures included modified Morisky Adherence Scale 8-items (©MMAS-8), visual analogue scale (VASdose), and adherence barriers survey.
Results: Eighteen parents participated (83% female, 61% White, mean±SD age 37±7.23 years). Parents reported the most common reasons for non-adherence being lack of social support (67%), forgetfulness (28%), and lack of understanding of ALL treatment regimen (17%). Using ©MMAS-8, parents reported 6-MP adherence (mean±SD) of 7.3±1.1 with 9 (50%) reporting low/moderate adherence (<8). Using VASdose, parents reported 6-MP adherence (mean±SD) of 97.5±5.3% with only one (6%) reporting low adherence (<95%). The number of adherence barriers inversely correlated with adherence level using ©MMAS-8 (rs=–0.21) and VASdose (rs=–0.1), suggesting higher 6-MP adherence in parents with fewer barriers.All participants (100%) owned smartphones, mainly iPhones (72%), and most owned iPad tablets (89%) and laptops (83%). The majority were comfortable using smartphones (94%). Most had unlimited plans for text messaging (94%) and data (67%), and all (100%) had fast Internet connection. Parents were interested in having the ability to review laboratory results (100%), daily 6-MP reminders (83%), 6-MP tracking (89%), monthly steroids reminders (67%), positive-reinforcement messages (61%), clinic visit reminders (83%), and education about ALL (89%) and ALL medications (94%). Using cumulative ranking of the proposed smartphone app features, ability to review laboratory results was ranked first most frequently, followed by

medication reminders, education about ALL medications, and medication log.
Conclusion: Parents of children with ALL provided valuable insight into barriers for adherence and preferred features for a smartphone app. Parent's Access to mobile technology and interest in using mhealth features aimed at promoting medication adherence suggest potential for a smartphone app as a behavioral intervention to optimize adherence to 6-MP in children with ALL.

Poster # 018

FEASIBILITY OF ADHERENCE MONITORING IN A MULTI-CENTER THERAPEUTIC CLINICAL TRIAL FOR PEDIATRIC ALL

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Background: Poor adherence to oral 6-mercaptopuine (6-MP), a key component of therapy in childhood acute lymphoblastic leukemia (ALL) is associated with relapse (Bhatia et al, JCO, 2012). To date, no studies have examined adherence to dexamethasone, liquid medications, or to medication during early phases of ALL therapy. The Dana-Farber Cancer Institute ALL Consortium is currently conducting the first embedded investigation of adherence to both 6-MP and dexamethasone in a multi-center trial for childhood ALL, DFCI 16-001. Objectives are to (1) determine adherence to liquid and tablet 6-MP and dexamethasone, (2) assess adherence during both the first and second years of therapy (3) identify sociodemographic predictors, including household material hardship, of non-adherence, (4) examine how non-adherence impacts disease-free survival. The trial is actively enrolling patients at seven sites in the U.S. and Canada.
Objectives: To present interim results describing the acceptability and feasibility of measuring adherence to liquid and tablet formulations of both 6-MP and dexamethasone using Medication Event Monitoring System (MEMS) caps and self-report surveys in a multicenter clinical trial of children and adolescents with ALL.
Design/Method: Parents of patients (1–18 years) are approached for Adherence study enrollment prior to Consolidation II (approximately 4-6 months after starting treatment). Adherence is monitored for three consecutive cycles during Consolidation II (nine weeks), and for three cycles during Continuation (second year of treatment) using MEMS caps, which record the date/time of bottle opening. Prior to MEMS monitoring, participants complete a face-to-face Health Literacy screen, and a demographic survey. At the end of each monitoring phase, parents complete an adherence survey.
Results: As of December 2018, 60/86 (70%) eligible patients who were approached consented to participate. Common reasons for declining participation are: pillbox use (20%) and comfort with current medication-taking routine (23%). Of enrolled patients, 50% have finished the first monitoring period, 50% are still in Consolidation II (being monitored), and <1% have reached timepoint eligibility for Continuation monitoring. Of those consented, three have withdrawn consent citing increased burden of medication-taking with MEMS caps; two report MEMS leakage with liquid medicines.
Conclusion: Monitoring adherence to 6-MP and dexamethasone in children during ALL therapy

is feasible and thus far, parents have been receptive to the study objectives. Successful monitoring relies on close collaboration between study sites, clinical care teams, research staff, and pharmacists. Feasibility concerns include recruitment of patients who use pillboxes, participant retention, and management of MEMS caps with liquid medications. Assessment of oral chemotherapy adherence is ongoing.

Poster # 019

INHIBITION OF FIRST PASS METABOLISM IN CHILDHOOD LEUKEMIA/LYMPHOMA: MERCAPTOPURINE AND ALLOPURINOL

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Background: 6-Mercaptopurine (6-MP) is a thiopurine drug used in combination during maintenance therapy for acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LLy). The anti-leukemic effect of 6-MP is driven by the active metabolite 6-thioguanine nucleotide (6-TGN), and can be hepatotoxic due to the metabolite 6-methyl mercaptopurine nucleotide (6-MMPN). The hepatotoxicity often results delays in 6-MP treatment with potential to increase the risk of relapse. Allopurinol alters the metabolism of 6-MP to decrease 6-MMPN levels and increase 6-TGN levels. We report eight cases of 6-MMPN related hepatotoxicity
Objectives: 1. To describe the clinical and laboratory features of 6-MMPN related hepatotoxicity. 2. To describe therapeutic methods altering 6-MP metabolism to increase 6-TGN levels. 3. To describe the effect of allopurinol dosing on lab values and metabolites.
Design/Method: Eight children in maintenance chemotherapy with presumed 6-MMPN induced hepatotoxicity were identified. A retrospective review was performed of their clinical/laboratory presentation as well as therapeutic intervention and resultant lab findings and metabolite levels.
Results: Six children had ALL and two had LLy. There were five girls and three boys. All had normal thiopurinemethyltransferase (TPMT) phenotype and/or genotype. All children had elevated liver enzymes, two with significant elevation of direct bilirubin. Elevated 6-MMPN levels were subsequently identified during maintenance therapy ranging from cycle 1 day 57 to cycle 7 day 57. 6-MMPN mmol/8x10E8 rbc ranged from 11,388-46,294 (>5,700 leading to hepatotoxicity). Three children were not treated with allopurinol, two of which were on baseline 6-MP dosing of 56% and 72%. Five children were treated with allopurinol with doses ranging from 1mg/kg-10mg/kg daily (50mg/m2-300mg/m2) and 6-MP dosing was decreased by 50% as well. Liver enzymes and 6-MMPN level then decreased in all. Three children who initially received >100mg/m2 of allopurinol developed subsequent myelosuppression. This resolved with 50% dosing of allopurinol. Therapy was continued with resolution of hepatotoxicity and myelosuppression as well as normalization of 6-MMPN and 6-TGN metabolites.
Conclusion: TPMT phenotype/genotype alone are not predictive of hepatotoxicity in maintenance therapy. Future treatment protocols should consider recommending screening for purine metabolites in children who experience recurrent hepatotoxicity. Allopurinol at doses >100mg/m2 results in significant myelosuppression even with dose reduction of 6-MP. Future studies are needed to look at the prevalence of 6-MMPN hepatotoxicity as well as to optimize alteration of metabolism.

Poster # 020

HYPERSENSITIVITY AND SILENT INACTIVATION WITH GENERIC PEGYLATED L-ASPARAGINASE IN CHILDREN WITH ALL

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Background: Pegylated asparaginase (PEG-Asp) is an integral component of acute lymphoblastic leukaemia (ALL) chemotherapy. Hypersensitivity and silent inactivation are known to occur with this immunogenic drug and inadequate asparagine depletion is reported to be associated with poorer survival.
Objectives: To report incidence of hypersensitivity and silent inactivation with generic PEG-Asp along with monitoring of asparaginase activity.
Design/Method: This prospective observational study, included 68 patients <18 years of age with ALL treated with generic PEG-Asp (Emcure) as part of our Institutional ALL protocol (based on ALL BFM-95 backbone) between January 2016 and December 2018. Two doses of PEG-Asp at 1500 IU/m2 were administered as 2-hour infusion intravenously, two weeks apart on days 8 and 22 of induction (Ia) and re-induction (IIa) phase of therapy. Patients were monitored for hypersensitivity and known asparaginase related toxicites and graded as per Common Terminology Criteria for Adverse Events version 4.03. Serum asparaginase activity levels were recorded using medac Asparaginase-Aktivitäts-Test, 0, 7 and 14 days after each dose (day 8,15,22,29,36 of Ia and IIa). Therapeutic level of asparaginase activity was defined as >100 IU/L and silent inactivation as levels <20 IU/L. Study was conducted after appropriate informed consent/assent and approval from the Institutional Ethics committee. The data was analyzed with the software package SPSS, version 20.1 (Chicago,IL).
Results: Serum samples were available for 68 (Ia) and 66 (IIa) of the consenting patients enrolled in the study. The mean asparaginase trough levels (14 days after PEG-Asp) were 216+/-72 and 206+/-42 IU/L during Ia and IIa respectively. Clinical hypersensitivity (grade 2 or more) occurred in 1/68 and 3/66 patients and silent inactivation among 0/68 and 2/66 patients during Ia and IIa respectively. Therapeutic drug levels were achieved among 67/68 (98%) patients in phase Ia and 62/66 (93%) during IIa. One patient who developed grade 2 hypersensitivity during IIa had adequate therapeutic levels. The incidence of other asparaginase toxicities were similar to those previously reported by us and others. There were no toxic deaths. The two year event free survival was 87%. This study from India reports incidence of silent inactivation with generic PEG-Asp in a population ethnically different from the west.
Conclusion: Use of generic PEG-Asp during Ia phase of ALL induction therapy was associated with adequate trough levels in almost all patients. During reinduction there was a low (7%) though significant incidence of clinical hypersensitivity or silent inactivation warranting therapeutic drug monitoring during IIa for optimizing therapy.

Poster # 021

IMPACT OF CHILDHOOD CANCER DRUG WASTAGE ON PEDIATRIC ONCOLOGY PROGRAMS IN ONTARIO, CANADA

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Background: Cancer drug wastage occurs when less than the entire contents of a parenteral drug within a single dose vial are administered to a patient. There are no known analyses of cancer drug wastage in pediatric oncology or reports that quantify differences in cancer drug wastage between adults and children.
Objectives: The objectives were to quantify the financial impact of drug wastage of pegaspargase (Oncaspar) in pediatric cancer and compare with recent reports of other single-dose vial cancer drugs used in adults in a publicly funded healthcare system (Ontario, Canada).
Design/Method: A cross-sectional study was conducted over six-months (09/2013–02/2014) investigating the extent of pegaspargase wastage among children with acute lymphoblastic leukemia or lymphoblastic lymphoma treated in one of five pediatric oncology programs in Ontario. Pegaspargase was the focus, as it is a single-dose vial drug that was the largest contributor to pediatric chemotherapy expenditures and had undergone significant price increases.Dose level data were prospectively collected for each pegaspargase dose delivered, without any alteration in routine pharmacy or clinical practice. We recorded clinical diagnostic features, date of drug administration, total dose and amount of wastage. Furthermore, we documented whether wastage mitigation was possible (e.g. sharing vials on the day of treatment), the treating center, and whether the dose was administered to a patient enrolled on a clinical trial.To calculate the proportion of drug wasted, we determined the number of vials required to fill a single dose. Categorical variables were compared between doses with wastage and no wastage using Chi-square tests. The total annual wastage cost in Canadian dollars (CAD) was estimated, adjusted to the 2017 Canadian pegaspargase cost.
Results: Over the six-month period, 223 doses of pegaspargase were administered. The estimated provincial annual cost of pegaspargase wastage in 2017 is $887,000 CAD or a striking 38.3% of the total cost paid in province for the drug. Pegaspargase wastage in children is significantly higher than recent reports of other single-dose vial cancer drugs used in adults in Ontario (1-2% of total drug costs; Leung, JOP, 2017).
Conclusion: Wastage accounts for a large proportion of the cost of pegaspargase in pediatric patients. In agents with major pediatric indications, smaller vial sizes that reflect patient size variations across the spectrum of pediatrics may significantly mitigate the burden of waste. Cancer drug reimbursement strategies used by publicly or privately funded health systems must consider the significantly higher proportion of drug costs due to wastage in pediatric oncology.

Poster # 022

RAPID DESENSITIZATION PROTOCOL FOR PEGASPARGASE FOLLOWED BY THERAPEUTIC ASPARAGINASE LEVELS

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Background: Asparaginase, an integral component of therapy for acute lymphoblastic leukemia (ALL), is associated with hypersensitivity reactions in 5% to 45% of patients. Patients who receive an inadequate course of planned asparaginase therapy due to side effects or silent inactivation have inferior outcomes. Hence, maximizing delivery of asparaginase therapy is important. Most pediatric ALL protocols use pegaspargase upfront. Hypersensitivity is a frequent complication of asparaginase therapy, and the occurrence of such a reaction is strongly associated with the development of anti-asparaginase antibodies leading to reduced or absent asparaginase activity. In this scenario, discontinuation of pegaspargase and substitution with Erwinia asparaginase is preferred. Once hypersensitivity has occurred, current consensus discourages using the same formulation with premedication/desensitization protocols due to concern that these measures may decrease clinical symptoms but do not prevent inactivation of asparaginase by antibodies, thus leading to ineffective treatment of leukemia and poorer outcomes. As the pharmacodynamic goal of asparaginase therapy is complete asparagine depletion, an asparaginase activity threshold of 0.1 IU/ml has been used to define therapeutic activity levels. No desensitization protocols have described subsequent measurement of asparaginase activity above therapeutic threshold.
Objectives: To describe a desensitization protocol for clinical asparaginase hypersensitivity in three children with ALL with subsequent demonstration of adequate asparaginase activity.
Design/Method: Case series
Results: Three children with precursor B-cell ALL developed grade 3 or higher clinical hypersensitivity to pegaspargase. As Erwinia was not available, a desensitization protocol was developed. Patients were premedicated with Prednisone, Cetirizine, Ranitidine and Monteleukast. Pegaspargase 2500 IU/m2 was divided into three fractions (1:100, 1:10 and 1:1 dilution). The fractions were infused over approximately 60 minutes with increasing rate of infusion every 15 minutes. Patients were monitored in the PICU with no adverse events. Asparaginase activity levels checked 7-10 days after administration were greater than 0.1 IU/ml (0.390 IU/ml, 0.600 IU/ml and 0.274 IU/ml). All patients tolerated a second administration of the desensitization protocol and pegaspargase. Asparaginase activity checked for two of these children 7 days after second administration remained above 0.1 IU/ml (0.287 IU/ml and 0.505 IU/ml).
Conclusion: This case series is the first describing safe use of a pegaspargase desensitization protocol with subsequent measurement of asparaginase activity above therapeutic threshold. Many countries have limited availability of Erwinia asparaginase. United States of America is experiencing a shortage. This approach could bolster confidence in safe and effective use of available formulations of asparaginase which are essential for ALL treatment.

Poster # 023

EVALUATION OF ASPARAGINASE INFUSION VARIABILITY OFFERS BACKGROUND FOR QUALITY IMPROVEMENT INITIATIVE

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Background: Pegylated L-Asparaginase (PEG) is an important component of treatment for acute lymphoblastic leukemia. Reactions to PEG occur in up to 10% of patients. Distinguishing

between hypersensitivity reactions and infusion related reactions is important in determining whether the medication should be discontinued, but difficult due to overlap in symptoms. When PEG is discontinued secondary to a hypersensitivity reaction, Erwinia asparaginase is substituted. This alternative has a shorter half-life, requiring six doses of Erwinia for each dose of PEG. This modification significantly increases the number of clinic visits, cost of treatment and decreases quality of life for patients and families.
Objectives: To describe the current PEG reaction rates at Connecticut Children's Medical Center and to develop guidelines for safer PEG administration and more standardized approach to hypersensitivity and infusion-related reactions.
Design/Method: Information regarding the patients, drug administration and complications were extracted from the electronic medical record of all patients who received PEG or Erwinia between June 2017 and June 2018.
Results: During the study data period, PEG was infused 81 times, for 29 patients, all with hematologic malignancies. Adverse reactions occurred during 10 (12.3%) infusions. Seventy percent of patients that had a documented PEG reaction experienced GI symptoms and 40% had skin reactions. Infusion time ranged from 60 to 190 minutes, with 2 infusions stopped early due to reaction. No Common Terminology Criteria for Adverse Events (CTCAE) scores were recorded. Four patients were switched to Erwinia due to reaction. A total of 101 doses of Erwinia were administered and reactions occurred during 6 (6%) infusions. For a single patient, a dose of PEG cost $14,405.66, compared to $112,707.12 for one cycle of Erwinia treatment (6 doses).
Conclusion: Preliminary data revealed a slightly higher rate of reaction during PEG infusions compared to previous studies. There was variability in the treatment of these reactions and in choosing to switch to Erwinia. Documentation of adverse reactions was highly subjective. Infusion rates were variable, even among infusions for the same patient. A multidisciplinary project group has been assembled to address these issues. A quality improvement research project is underway and aims to standardize infusion rate, grading and documentation of reactions, establish clear guidelines for switching to Erwinia therapy and to create an institutional clinical pathway for management of anaphylaxis. We hope this will increase the safety of PEG infusion and limit conversion to a more time-intensive and expensive therapy.

Poster # 024

MINIMIZING DRUG WASTE AND OPTIMIZING COST EFFECTIVENESS OF BLINATUMOMAB IN A TERTIARY CARE CENTER

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Background: Blinatumomab (Blincyto®) received accelerated approval for the treatment of Philadelphia chromosome-negative relapsed or refractory B cell precursor acute lymphoblastic leukemia (ALL) in 2014 with expanded approval in 2018 for minimal residual disease (MRD) positive pediatric and adult patients with B-cell precursor ALL. Each package of blinatumomab comes with 35 micrograms (mcg) of medication and 10 milliliters (mL) of stabilizing solution. Recommended blinatumomab dosing for relapsed/refractory B cell ALL is 5 mcg/m2/day (maximum 9 mcg/day) for is the first seven days then to escalate to 15 mcg/m2/day (maximum 28 mcg/day) for the remainder of a 28 day cycle. Each 48 hour bag of blinatumomab requires 5.5

mL of stabilizing solution with the specified amount of medication including 30 mL of overfill to account for medication remaining in the tubing and is given an 8 day expiration date.
Objectives: The objective of our study was to minimize medication waste and optimize the cost effectiveness of blinatumomab by preparing multiple bags at one time.
Design/Method: Prior to initiating a new patient on blinatumomab, the pediatric pharmacist created a table calculating the amount of drug and stabilizer required for each bag and determined which packaging the medication and stabilizer would be obtained from. The medication was billed to the patient on a microgram basis allowing preparation of multiple patients with one vial and further minimizing waste if more than one patient was receiving blinatumomab therapy at a time.
Results: With batch preparation of bags, patients receiving 9 mcg/day for the first 7 days and 28 mcg/day for days 8 – 28, only 20 vials were required compared to 26 vials leading to a cost savings of $22,244.58 per patient. The total cost savings of five pediatric patients receiving blinatumomab was $118,637.79.
Conclusion: In patients receiving blinatumomab therapy, consolidating vials and stabilizing solution for multiple patients or batch preparation for one patient, is a safe and viable cost mitigation strategy.

Poster # 025

SAFE AND EFFICACIOUS USE OF BLINATUMOMAB IN A CHILD WITH ALL AND A HISTORY OF LIVER TRANSPLANTATION

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Background: Post-transplant malignancy is a potential sequelae of solid organ transplantation (SOT). Various chemotherapies have been used in these patients with attention paid to outcomes of the transplanted graft. Review articles have identified potential toxicities associated with various chemotherapies in the setting of previous SOT, but not all therapeutics have been studied. The recent evolution of targeted therapies has made tremendous advances in cancer treatment but also raises new questions in more complex patients. With the emerging use of targeted therapies and immunotherapies as salvage regimens as well as upfront options for various malignancies we need evidence of ability to tolerate these treatments among both our standard patients as well as some of our more complicated and fragile patients. This includes patients receiving chronic immunosuppression in the setting of SOT. We report a case of a patient with a history of liver transplantation who subsequently developed pre B-cell leukemia that failed conventional treatment and required Blinatumomab, a monoclonal antibody directed at both CD19 on precursor B-cells as well as CD3 on cytotoxic T cells, to achieve remission and ultimately proceed to hematopoietic stem cell transplantation (HSCT).
Objectives: This case report is to demonstrate that in patients with a history of SOT the use of directed CD19 therapy with Blinatumomab can be safely used without demonstrated impact on the transplanted graft.
Design/Method: Single subject case report
Results: The patient being discussed was status post liver transplantation and was able to tolerate two cycles of Blinatumomab to achieve an MRD negative remission which allowed for a

matched sibling HSCT. During the course of Blinatumomab the patient had transient elevations of AST and ALT and a peak total bilirubin of 2.7. Otherwise synthetic function was normal throughout both cycles with no evidence of graft rejection. He then proceeded through HSCT without any issues related to sinusoidal obstruction syndrome (SOS) or liver GVHD and now over 100 days out is doing well.
Conclusion: B-cell directed therapies have safely been used in treatment of B-cell driven malignancies in patients with history of SOT through use of agents such as Rituximab, but newer agents have either had detrimental effects including graft failure or have not been described in the literature. Our case encourages safe and efficacious use of CD19 directed therapy with Blinatumomab in patients with a history of SOT which allows for another possible agent to be used in treatment of B-cell driven malignancy in these patients.

Poster # 026

FEASIBILITY OF POVERTY SCREENING IN A MULTI-CENTER THERAPEUTIC CLINICAL TRIAL FOR PEDIATRIC ALL

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Background: Poverty-associated disparities are well-described at the population level in childhood cancer. The impact of poverty on outcome in the clinical trial setting is not known, and systematic poverty measurement is not standard in pediatric oncology clinical trials. Household material hardship (HMH)–defined as food, housing, or energy insecurity—is a parent-reported poverty measure amenable to screening and intervention and has been identified as prevalent in a single-center pediatric oncology study. The Dana-Farber Cancer Institute (DFCI) Acute Lymphoblastic Leukemia (ALL) Consortium is currently conducting the first embedded investigation of HMH in a multi-center therapeutic trial for de novo childhood ALL, DFCI 16-001. This ancillary HMH study aims to identify the association between HMH and event-free and overall survival for children treated on DFCI 16-001. The trial is actively enrolling patients at 7 U.S. and Canadian sites.
Objectives: To present interim results describing the feasibility of poverty screening in a multi-center clinical trial and preliminary frequency of HMH in a cohort of children enrolled on the DFCI 16-001 ancillary HMH study.
Design/Method: Eligible families (child age <18 years) are offered opt-in consent for the HMH study at time of trial enrollment. Participating families complete a face-to-face HMH survey at 4 time-points (T0-T3) throughout 2-years of therapy. Analyses utilize baseline (T0) HMH survey data collected within 32 days of trial-enrollment. Survey domains include: demographics, food, housing, energy (utilities), income, home environment, stress and neighborhood. Families are considered to have HMH if they screen positive for at least 1 of 3 unmet basic needs (food, housing, energy) utilizing a previously published HMH instrument associated with inferior health outcomes in general pediatrics.
Results: As of November 2018, 104/123 (85%) eligible patients consented to the opt-in ancillary HMH study. One hundred (96%) HMH-enrolled families completed T0 of whom 100% provided

complete HMH data and 94% provided income. Thirty-four families reported at least one T0 HMH; 22% housing, 21% food and 13% energy insecurity. Eighty families have reached the first follow-up timepoint (T1), of whom 73 (91%) completed the T1 survey with 100% complete HMH data.
Conclusion: Systematic poverty screening is feasible in a multi-center therapeutic clinical trial as demonstrated by high participation, minimal attrition and high data-capture. Preliminary multi-center data indicate that approximately 1 in 3 (34%) children with newly diagnosed ALL live in households with unmet basic needs at time of clinical trial enrollment. Investigation of a relationship between HMH and disease outcome is ongoing.

Poster # 027

IDENTIFYING RELAPSE AND HSCT INCIDENCE IN A NATIONAL PEDIATRIC ALL COHORT USING ADMINISTRATIVE DATA

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Background: Administrative data have been used to identify relapse and hematopoietic stem cell transplant (HSCT) in leukemia populations. Published approaches are limited to relapses occurring after cessation of therapy; however, a substantial portion of pediatric ALL relapses occur on therapy.
Objectives: We hypothesized HSCT and early and late relapses could be detected accurately in a pediatric acute lymphoblastic leukemia (ALL) cohort using pharmacy billing and ICD9 codes. We present our methods, validated at two large freestanding children's hospitals, and incidence estimates of relapse and HSCT as first events in a national cohort.
Design/Method: Electronic medical records (EMR) were reviewed for patients with de novo ALL at the Children's Hospital of Philadelphia (CHOP; 2004-2013) and Texas Children's Hospital (TCH; 2007-2013). We performed a stepwise review using our previously validated Pediatric Health Information System (PHIS) ALL cohort (Fisher 2014 Med Care). Patients with ICD9 relapse codes (204.02); age <1 year; HSCT codes; intensive chemotherapy >day 365; doxorubicin in the first 30 days; or chemotherapy billing consistent with relapse were selected for manual review. We reviewed these patients' daily inpatient pharmacy codes for chemotherapy patterns consistent with relapse. HSCTs were identified using ICD9 procedure codes and conditioning patterns. Events were captured until five years from diagnosis or last day of PHIS data. Events matching within 30 days for relapses and 7 days for HSCTs were considered true positives. We estimated 5-year relapse and HSCT incidences for the entire PHIS cohort.
Results: PHIS codes identified 40/46 relapses (sensitivity 86.95%, PPV 97.6%) in 362 CHOP patients. All 39 EMR HSCTs were identified (sensitivity/PPV 100%). PHIS codes identified 28/30 TCH relapses (n=317) at any time and 23 (sensitivity 76.7%, PPV 82.1%) within 30 days. 31/32 HSCTs were identified (sensitivity 96.8%, PPV 100%). Among the entire PHIS ALL cohort (N=10,163), 10% experienced relapse and 7% HSCT. Mean time to relapse was 26.8 months. Most infant relapses occurred by 18 months, while standard-risk patients relapsed later

(31.4 months). Mean time to transplant was 18 months, with standard-risk patients' later mean (25 months) suggesting most occurred after relapse. High-risk patients were more likely to undergo HSCT in the first 6 months. Black, Hispanic, infant, and publicly insured patients had higher relapse and HSCT rates.
Conclusion: We present novel, accurate approaches to identify relapses and HSCTs using administrative data. Our method is labor-intensive and requires disease-specific clinical expertise; however, unlike prior reports, this approach captures on-therapy relapses in children, irrespective of clinical trial enrollment.

Poster # 028

VITAMIN D DEFICIENCY IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA/LYMPHOMA: RESULTS OF DFCI 11-001

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Background: Children and adolescents with acute lymphoblastic leukemia (ALL) are at risk for skeletal toxicities. The impact of Vitamin D (VitD) status on skeletal toxicity risk and the role for VitD supplementation during ALL therapy are not defined.
Objectives: We aimed to determine the prevalence of VitD deficiency in children/adolescents with ALL or lymphoblastic lymphoma (LL). We explored the feasibility of VitD supplementation within a multi-institutional trial and the relationship between VitD status and skeletal toxicity (fracture and osteonecrosis).
Design/Method: Between 2012-2015, patients aged 1-21 years with newly-diagnosed ALL/LL were eligible for DFCI 11-001. 25-hydroxyvitamin D levels were assessed (diagnosis, end-induction, start of continuation, and therapy conclusion). Patients were classified by VitD level as deficient (<20 ng/mL), insufficient (20-29 ng/mL), sufficient (30-79 ng/mL), or high (≥80 ng/mL). Guidelines for VitD supplementation (starting end-induction) were weekly ergocalciferol (50,000IU) for 6 weeks or daily cholecalciferol (5,000IU) for 8-12 weeks for deficiency, and daily ergocalciferol (600-1000IU) or cholecalciferol (600IU) for 3 months for insufficiency, with calcium supplementation. Fracture and symptomatic osteonecrosis were prospectively reported.
Results: Of 239 patients enrolled on DFCI 11-001, 188 consented to VitD assessment, with samples obtained from 176 patients at diagnosis, 157 end-induction, 117 continuation-start and 41 off-therapy. At diagnosis, 54 (31%) of assessed patients were deficient, 81 (46%) insufficient, and 40 (23%) sufficient. At end-induction, 80 (51%) were deficient, 51 (32%) insufficient, and 26 (17%) sufficient with median level 19.8 (range 5.5-61.9). At continuation-start, 21 (18%) were deficient, 31 (26%) insufficient, and 63 (54%) sufficient, with median level 31.9 (range 4.2-94). Thirty-four of 80 (42%) end-induction deficient patients received supplementation; 11 of 25 attained sufficient level at continuation-start (9 without continuation-start measurement). On multivariable analysis, older age (≥10 years at diagnosis) was associated with deficiency at diagnosis (OR 1.20, 95% CI 1,11, 1.29, p<0.001). Canadian sites had a lower proportion of

deficient patients (despite higher latitude). Season-of-measurement and ethnicity were not significant predictors. VitD deficiency at diagnosis and/or end-induction (early-deficiency) was not associated with increased incidence of subsequent osteonecrosis (p=0.68) or fracture (0.43), nor was deficiency at continuation-start. In age-stratified analysis, no difference was observed in osteonecrosis based on Vitamin D status.
Conclusion: The majority of childhood ALL/LL patients had VitD deficiency or insufficiency at diagnosis and end-induction. Attaining sufficient VitD levels was feasible but challenging in the context of ALL-directed therapy. Although no differences in skeletal toxicity were observed based on VitD status, power was limited, and further investigation is needed.

Poster # 029

GAIT PARAMETERS AND QUALITY OF LIFE DURING AND AFTER ACUTE LYMPHOBLASTIC LEUKEMIA THERAPY

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Background: Children treated for Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL) can develop neuropathy and myopathy with subsequent gait abnormalities due to vincristine and steroid treatment. Previous studies have analyzed temporal and spatial gait parameters in children during and after treatment for ALL/LL but no studies have assessed the utility of an electronic evaluation system versus observational gait analysis in this population. In addition, there are no studies evaluating quality of life (QoL) from both the patient and parent perspectives as it relates to gait parameters.
Objectives: Our primary objective was to characterize temporal and spatial gait parameters of children with ALL/LL receiving and after completing chemotherapy. Our secondary objective was to assess QoL in relation to changes in gait parameters.
Design/Method: Participants age 2-27 years old were recruited to complete an evaluation at one of 12 different time points throughout or after therapy. Gait parameters were evaluated with a clinical gait assessment (global gait score (GGS)) and using the GAITRite® electronic evaluation system. GAITRite® data was compared with gender and age matched normative data. All participants, age 5 or older, and a parent for all participants completed a PedsQL questionnaire. The relationships between patient and parent reported QoL, GGS and the GAITRite parameters were analyzed.
Results: One hundred and seven participants completed gait and QoL evaluations at one of 12 time points. Preliminary analysis for the QoL objective found modest but consistent negative correlations between GGS and QoL total functional domain scores for both subjects (r=-0.29, p=0.0066) and parents (r=-0.24, p=0.0134). Similar negative correlations were found between GGS and the QoL physical function domains of participants (r=-0.28, p=0.0102) and parents (r=-0.26, p=0.0085). Among GGS component scores (walking, running, hopping and stairs), significant reductions in parent-reported QoL physical functional domain scores were found for walking (t-test: p=0.0375) and running (p=0.0063). A significant decrease in QoL total functional domain scores was also observed among participants with a hopping deficit (p=0.0245). Analyses of the complete data set regarding gait parameters and quality of life will

be finalized and ready for presentation at time of the ASPHO conference.
Conclusion: A significant and consistent relationship exists among gait deficits and QoL functional domain scores for both parents and participants who are receiving or completed therapy for ALL/LL. Additionally, this relationship may only exist for certain components of gait and varies between parent and patient. Further conclusions are pending analysis of the full data set.

Poster # 030

PROGNOSTIC IMPACT OF OPHTHALMIC EVALUATION IN NEWLY DIAGNOSED CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Ocular abnormalities (OA) in pediatric patients with acute lymphoblastic leukemia (ALL) are common and occur both at diagnosis (retinal hemorrhages) and later in treatment (cataracts). The frequency, predictors and prognostic impact of OA in the context of contemporary ALL treatment is not well characterized.
Objectives: To determine the relationship between OA at diagnosis and prognosis, and to investigate risk factors for the development of cataracts, in pediatric ALL patients.
Design/Method: We conducted a single-centre retrospective analysis of 223 patients with ALL enrolled onto DFCI Consortium Protocol 05-001 (2006-2011). Ophthalmic exams were conducted per institutional standard at 4 timepoints (diagnosis, post-induction, off-treatment and follow-up) and exam reports were retrospectively reviewed. Event-free survival (EFS) was estimated using the Kaplan-Meier test and tested between groups with the log rank test. EFS was also modeled univariately and adjusted in multivariable models with the Cox proportional hazards model.
Results: Overall, 214 (96%) patients had at least 1 ophthalmic exam. 208 patients had an exam at or soon after diagnosis and 26 had OA, the most common of which was retinal hemorrhages (RH) (n=23). Only one patient with CNS leukemia also had a leukemic infiltrate at diagnosis (<1%). Cataracts were the most frequent OA at later timepoints occurring in 24 patients (11%), with 13 cases identified off-treatment. RH were associated with age ≥10 years (30% vs 4.5%, p<0.001), but not initial WBC or CNS status; cataracts were associated with presenting WBC ≥50,000/mm3 (22.7% vs. 8.1%, p=0.012), cranial irradiation (p=0.006) and final high or very-high risk group (p=0.047). Cataracts (p=0.003), but not RH, were predictors of visual impairment at 2 years of follow-up. Patients with RH at diagnosis had a lower 5-year EFS compared with patients without RH (69.6% vs. 88.4%; p=0.017). However, in a multivariable model adjusted for age and presenting WBC, RH was not associated with an inferior outcome [HR 1.8 (0.7-4.7);p=0.19].
Conclusion: RH was the most common OA at diagnosis and was more common in older children but was not an independent predictor of poor prognosis. The utility of routine ophthalmic evaluation at diagnosis in asymptomatic patients is of questionable benefit as findings were not associated with prognosis or subsequent visual impairment. On the other hand,

regular exams to screen for cataracts during follow-up may be useful. Continued refinement of risk stratification to reduce cumulative steroid dosage and use of cranial radiation may decrease incidence of cataracts.

Poster # 031

INCIDENCE OF BACTEREMIA IN NEWLY DIAGNOSED ACUTE LEUKEMIA PATIENTS PRESENTING WITH FEVER

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Background: A common presenting symptom of acute leukemia in pediatric patients is fever. In the setting of a patient who has a central line and is already receiving chemotherapy, fever may often be associated with bacteremia. However, recent data and our own experience indicate that patients with newly diagnosed acute leukemia and fever are rarely bacteremic.
Objectives: This study aimed to elucidate any association between a patient with newly diagnosed, febrile acute leukemia and the presence of bacteremia. A second aim was to determine how many febrile patients were exposed to broad spectrum antibiotics in this setting. We hypothesized that bacteremia would be an infrequent cause of fever at presentation of new leukemia.
Design/Method: This retrospective chart review analyzed 91 pediatric patients with newly diagnosed acute leukemia. Data collected included: temperature upon presentation, blood culture results, timing of central line placement and initiation of treatment, including whether systemic antibiotics were administered.
Results: Of the 91 patients analyzed, 25 were objectively febrile upon presentation. Blood cultures were drawn on 23 of 25 of these patients, with zero positive cultures. An additional 31 patients had fever reported by caregiver prior to presentation, but they were not febrile upon first medical evaluation. Cultures were drawn on 18 of these 31 patients; one culture was positive for a skin contaminant. Thus, we found an incidence of bacteremia of 1/56 (1.7%); however, this one result was not clinically significant. Of the 56 febrile patients (objectively or by caregiver report), 35 (62.5%) were given broad spectrum antibiotics before central line placement. Furthermore, 28 of these 56 patients (50.0%) remained febrile prior to initiation of chemotherapy, despite the observation that 22 of 28 (78.6%) of these patients were given antibiotics. Finally, it was noted that just three patients (5.4%) had a presenting illness that could have explained their fever (documented viral illness, thrombophlebitis, appendicitis).
Conclusion: These results support our hypothesis that patients with acute leukemia who present with fever are febrile more likely as a symptom of the leukemia, not due to a simultaneous serious bacterial infection. These results may support practice change that would avoid unnecessary use of broad spectrum antibiotics in patients newly diagnosed with acute leukemia and fever. Additionally, delaying systemic therapy for the purpose of blood culture results is unlikely warranted in the majority of patients.

Poster # 032

CASP10 MUTATION IN A YOUNG CHILD WITH T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA AND SEVERE INFECTIONS

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Background: Autoimmune lymphoproliferative syndrome (ALPS) is characterized by defective lymphocyte apoptosis leading to immune dysregulation. Most patients with ALPS present with lymphadenopathy (LAD), splenomegaly, and autoimmune disease, typically involving multilineage cytopenias. Ninety percent of ALPS cases are due to a defect in the FAS gene and ten percent are due to mutations in caspase-10 (CASP10). Patients with ALPS have an increased risk of lymphoma, typically of B-cell origin and described in ALPS-FAS, with a median age of diagnosis of eighteen years, though rarely is a presenting feature of ALPS.
Objectives: Describe a young child with T-cell acute lymphoblastic leukemia (ALL) and a complicated treatment course due to frequent severe infections and development of bronchiectasis who later developed progressive non-infectious lymphadenopathy without signs of ALL recurrence in the setting of a CASP10 mutation, concerning for ALPS.
Design/Method: Case report
Results: A 4-year-old previously healthy female was diagnosed with T-cell ALL after presenting with fatigue, extensive LAD, hepatosplenomegaly, a white blood cell count of 216,000 with 81% peripheral blasts and evidence of tumor lysis syndrome. She was treated with a standard chemotherapy regimen and achieved remission at the end of induction chemotherapy, as well as resolution of LAD and organomegaly. Her approximately 2.5-year leukemia treatment course was complicated by numerous life-threatening infections requiring intensive care unit admissions, including recurrent Streptococcus pneumoniae sepsis complicated by pericarditis, Klebsiella pneumoniae sepsis, numerous pneumonias and the development of severe bronchiectasis. She was managed with penicillin prophylaxis, IVIG support for hypogammaglobulinemia, and aggressive pulmonary toilet. She experienced several chemotherapy delays as well as dose reduction of chemotherapy due to infection frequency and severity. There was no known family history of immunodeficiency, lymphoid malignancy or ALPS. Nine months following chemotherapy completion, she developed persistent and progressive non-infectious cervical lymphadenopathy without signs of leukemia relapse, raising concern for ALPS. Evaluation revealed a CASP10 homozygous mutation.
Conclusion: It is rare for a patient with ALPS to present initially with malignancy, especially at a very young age. Although infections commonly complicate chemotherapy treatment, severe recurrent infections, particularly with encapsulated organisms, and the development of bronchiectasis are unusual during standard T-cell ALL therapy. This report describes a rare presentation of ALPS with a CASP10 homozygous mutation in a young child without known family history suggestive of ALPS. This report raises the index of suspicion for future patients with lymphoid malignancy experiencing significant infectious complications that otherwise cannot be explained by known underlying disease or treatment intensity.

Poster # 033

VANISHING BILE DUCT SYNDROME IN A CHILD WITH STANDARD RISK ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Liver injury due to thiopurines has been reported by the Drug Induced Liver Injury Network (DILIN) as 1-2% of all cases. Most patients recovered when the drug was removed. None of the patients was re-challenged.There are no cases reported in this registry of vanishing bile duct syndrome (VBDS) attributed to thiopurines. VBDS is a rare group of acquired disorders associated with progressive destruction and disappearance of the intrahepatic bile ducts. The pathogenesis is most likely due to immune mediated injury to the bile ducts. VBDS is most often associated with drug induced injury (e.g. phenothiazines, certain antibiotics, temozolomide, allopurinol, ibuprofen). Similar histologic findings have been seen with primary biliary cirrhosis, GvHD, sclerosing cholangitis, paraneoplastic syndromes, and sarcoidosis. The outcome of VBDS can be progressive, irreversible bile duct loss leading to extensive ductopenia and biliary cirrhosis. However, some patients experience clinical recovery with improvement in biochemical and histologic parameters.
Objectives: Discuss the case of a child with acute lymphoblastic leukemia (ALL) who developed significant hyperbilirubinemia and was subsequently diagnosed with VBDS.
Design/Method: Case Report and Literature Review
Results: A previously healthy 8yo was diagnosed with precursor B-cell ALL. The patient began treatment following the COG study AALL0932. The patient tolerated the initial cycles of chemotherapy with minimal complications. At end induction, the patient achieved an MRD negative remission. Three months after maintenance began, the patient developed a non-immune hemolytic anemia of unclear etiology. The patient continued chemotherapy at full doses. However, 4 months later, the patient presented with a total bilirubin of 25mg/dl and direct bilirubin of 22mg/dl. Chemotherapy was held and an extensive evaluation, including a liver biopsy, was undertaken. Ursodiol and oral vitamin K were started. The liver biopsy showed SEVERE CHRONIC CHOLESTASIS AND DUCTOPENIA (VBDS). Within one month, total bilirubin was <2mg/dl. The patient was restarted on chemotherapy with full dose vincristine, dexamethasone and intrathecal methotrexate (MTX). Oral MTX was started at 25% of the full dose and titrated to 100% over the next 6 months. Full dose chemotherapy was continued throughout the remainder of therapy. Mercaptopurine was never restarted. Ursodiol was continued during the entire course of chemotherapy. Labs remained near normal for the remainder of therapy.
Conclusion: This is the first report of a patient with ALL who developed VBDS, most likely attributed to thiopurine use, who remains in remission without biochemical evidence of liver injury.Bjornsson. J Clin Gastroenterol. 2017Reau. Clin Liver Dis. 2008

Poster # 034

6-MERCAPTOPURINE RELATED RECURRENT ACUTE PANCREATITIS IN PEDIATRIC ALL: IS IT JUST THE DRUG OR MORE?

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Background: Six-Mercaptopurine (6-MP) is a chemotherapeutic agent used in the treatment of Acute Lymphoblastic Leukemia (ALL), mainly during consolidation and maintenance phases. The most known side effects of 6-MP include bone marrow suppression, hepatotoxicity, anorexia, and rash. Although described in the literature, 6-MP related pancreatitis is a rare occurrence in pediatric ALL therapy.
Objectives: We report 2 pediatric patients who developed 6-MP related recurrent acute pancreatitis (RAP) while undergoing ALL treatment, one of whom was found to have a genetic predisposition to pancreatitis.
Design/Method: Case reports
Results: Patient 1: A 14-year-old Caucasian female with Pre-B ALL (high risk), received treatment as per COG AALL0232. She developed RAP: first during delayed intensification II (Day 29), while receiving 6-MP, which was initially attributed to asparaginase induced pancreatitis. The second episode occurred during maintenance cycle 2, attributed to steroid use, but she was also receiving 6-MP at that time. The third episode developed during maintenance cycle 3, when 6-MP induced pancreatitis was considered, and the drug was held. On re-challenge with 6- MP, within 10 days she developed pancreatitis again (steroids had been discontinued). Patient 2: 19-year-old African-American female with T-cell ALL was treated as per therapeutic clinical trial ALL1231 Arm B with Bortezomib. She first developed severe pancreatitis during maintenance cycle 2 while on 6-MP and steroids. Per protocol the steroids were permanently discontinued. The second episode occurred on maintenance cycle 5 and this was attributed to 6-MP which was then held and re-introduced multiple times. She continued to develop episodes of pancreatitis at 100% dosing but was able to tolerate lower doses (50-75%) without symptoms.RAP genetic testing: After all known causes of RAP were ruled out, genetic testing for hereditary pancreatitis was performed. Patient 1 had normal results and patient 2 a CFTR gene mutation.
Conclusion: 6-MP related pancreatitis though rare, should be considered as a cause of RAP in children undergoing ALL therapy if there is a strong temporal association, after ruling out other common causes and drugs. Underlying genetic mutations may predispose the patient for recurrent pancreatitis, as illustrated by our second patient. Genetic testing should be considered in the setting of drug-induced RAP in children undergoing ALL treatment.

Poster # 035

CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Musculoskeletal extremity pain in patients treated for acute lymphoblastic leukemia (ALL) is a common complaint during therapy. It is important to identify the etiology to adequately treat the cause and alleviate suffering. The differential diagnosis for extremity pain include relapse, infection, thrombosis, trauma, osteonecrosis and others. In this case, we describe

a patient with imaging and pathologic characteristics that led to a diagnosis of a rare entity chronic recurrent multifocal osteomyelitis (CRMO) and subsequent successful treatment with bisphosphonate. CRMO is an autoinflammatory non-infectious bone condition of childhood and adolescence.
Objectives: To describe the diagnosis and treatment of CRMO in a patient with B-cell ALL
Design/Method: Review of the medical record, radiographic, and pathologic studies.
Results: A 13-year-old male undergoing treatment for B-cell ALL as per AALL1131 protocol in maintenance therapy with previous complications of hepatosplenic Candida tropicalis, and pulmonary embolism developed atraumatic lower extremity pain made worse with activity. He was unable to walk long distances or jump secondary to knee and ankle pain on impact. He had mild edema of bilateral knees and right ankle. Laboratory evaluation showed elevated ESR and CRP. MRI of bilateral lower extremities revealed extensive abnormal T2 signal intensity in the proximal left tibia, fibula, and right distal tibia indicating bone edema. Given its unusual location near growth plates and dissimilar appearance from other sites of presumed osteonecrosis, we obtained a bone biopsy from the right distal tibia. The biopsy showed no evidence of leukemic disease, fungal or bacterial infection, and demonstrated histologically normal bone. Having ruled out malignant and infectious causes, this led to a diagnosis of CRMO. He received Pamidronate IV 1mg/kg/dose monthly for 12 months, which has previously been shown to be beneficial for CRMO. Throughout treatment, his pain improved remarkably and he has been able to participate in physical therapy and return to normal activities. MRI findings have normalized after a year of bisphosphonate treatment. He continues to be observed without further pharmacologic intervention.
Conclusion: We report a case of a patient undergoing treatment for B-cell ALL who developed CRMO and was treated with bisphosphonate to the resolution of symptoms and imaging findings. In this complex case with prior history of multiple complications, it was important to explore a variety of causes to the clinical findings of extremity pain with abnormal MRI findings. This led to a diagnosis of exclusion, CRMO, and successful treatment with bisphosphonate therapy.

Poster # 036

A RARE CASE OF ACUTE LYMPHOBLASTIC LEUKEMIA AND JUVENILE XANTHOGRANULOMA INVOLVING THE BONE MARROW

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Background: Juvenile xanthogranuloma (JXG) is a rare benign proliferative disorder of histiocytic cells and the most common form of non-Langerhans cell histiocytosis. JXG typically affects infants and young children and rarely can occur in adults. It is usually characterized by solitary or multiple skin nodules that resolve spontaneously over a few years. JXG rarely presents with extra-cutaneous manifestations that progress to a symptomatic systemic disorder. There are several reports of triple association between JXG, juvenile myelomonocytic leukemia (JMML) and neurofibromatosis. Cases of JXG and concurrent acute leukemia are rare.
Objectives: To describe a case of a young adult patient with JXG involving the bone marrow and B-cell Precursor Acute Lymphoblastic Leukemia (B-ALL).

Design/Method: Case report and review of literature. Pubmed was searched for concurrent JXG and acute leukemia for ages of 0 to 30 years.
Results: A 26 year-old female was diagnosed with Very High Risk B- ALL in November 2017. Her clinical course was complicated by multidrug resistant K. pneumoniae and C. dubliniensis infections with respiratory failure, multi-organ dysfunction and liver, splenic and brain lesions. She also had central pontine myelinolysis of unclear etiology. The patient received Induction chemotherapy with an individualized plan with multiple modifications due to her infections and comorbidities. She achieved morphological and immunophenotypic remission after 4 weeks of therapy and remained in remission for 4 months. Four months after her ALL diagnosis, in the setting of worsening liver and respiratory dysfunction and pancytopenia, a surveillance bone marrow biopsy revealed extensive infiltration of histiocytes and scattered multinucleated giant cells resembling Touton giant cells. Immunohistochemical analysis led to the diagnosis of JXG. Several weeks later, the patient died from progressive liver and respiratory failure. Review of the literature yields that systemic JXG, as well as bone marrow involvement are rare in both children and adults. While the association of JXG and JMML has been described more frequently, association of JXG with acute leukemia is very rare. There are 6 cases of ALL and 1 case of Acute Myelogenous Leukemia, with only 2 patients older than 5 years, reported over a 24 year period.
Conclusion: Association of JXG with hematological malignancies other than JMML is rarely described. This case of a young adult with ALL and concomitant JXG is presented to highlight the unusual association and raise level of suspicion. Further studies are needed to identify possible genetic predispositions that may contribute to the occurrence of these conditions concurrently.

Poster # 037

PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA IN A CHILD WITH RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Pityriasis lichenoides et varioliformis acuta (PLEVA) is a skin disorder that is part of the pityriasis lichenoides spectrum. Etiology is unknown; it is hypothesized to be an inflammatory condition triggered by infection, T-cell lymphoproliferative disorder, or an immune complex vasculitis. There are several reports of PLEVA associated with preceding infectious causes in otherwise healthy children, such as viral respiratory illnesses and Epstein-Barr virus, as well as recent medication administration. However, there are limited reported cases of PLEVA in immunocompromised children with leukemia.
Objectives: To highlight the importance of promptly and accurately diagnosing rashes in oncologic patients as this can lead to complications and affect management decisions, and to include PLEVA in the differential diagnosis for diffuse maculopapular rash along with more well-known etiologies like drug reactions and human herpesvirus 6 in oncologic patients.
Design/Method: An 8-year-old female with relapsed precursor B-cell acute lymphoblastic leukemia (ALL) is admitted to receive chemotherapy with Cytarabine and Erwinia Asparaginase. During this admission, she developed E. coli bacteremia and Clostridium difficile infection and

was treated with piperacillin-tazobactam and metronidazole. She also tested positive for Rhinovirus. The patient then developed a rapidly progressive diffuse, pruritic, erythematous, maculopapular, purpuric appearing rash on her scalp, arms, legs, buttocks and trunk, with no involvement of the oropharynx, palms or soles. Labs revealed neutropenia and thrombocytopenia but were otherwise unremarkable. Skin biopsy showed spongiotic change, vacuolation of the basal layer with intraepithelial lymphocytes, and superficial perivascular lymphocytic infiltrate within the dermis, consistent with PLEVA. Stains were negative for fungus and viral inclusions.
Results: Rash was treated with topical therapies (clindamycin, triamcinolone and desonide) with minimal improvement. She was then started on doxycycline 50mg twice daily for 7 weeks. One month later, the rash was healing with postinflammatory changes. She went on to receive an unrelated donor cord blood transplant and subsequently developed acute and later chronic graft vs. host disease of the skin.
Conclusion: The patient did well on doxycycline and had no recurrence of PLEVA. However, her next round of chemotherapy was delayed until the rash cleared up. The cause of eruption in this case was unclear; there was a multitude of factors that may have contributed, including infection and immunosuppression. PLEVA can be mistaken for infectious rashes and there is potential to progress to a more severe form, thus it should be kept on the differential for diffuse rashes in oncologic patients as treatment may be delayed or altered.

Poster # 038

A CASE REPORT OF USING DARATUMUMAB IN REFRACTORY T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Several immunotherapeutic approaches have been successfully developed for B-cell acute lymphoblastic leukemia (ALL), but similar therapies are not yet available for T-ALL. Daratumumab, a monoclonal antibody that binds CD38, has been approved for the treatment of relapsed/refractory multiple myeloma. Preclinical data has demonstrated efficacy in T-ALL patient-derived xenografts. Daratumumab is currently being studied in combination with chemotherapy in patients with B- and T-ALL but to date little data has been published regarding tolerance or clinical response in ALL.
Objectives: To present our experience with treating a patient with refractory early T-cell precursor (ETP) ALL with daratumumab.
Design/Method: Case Report
Results: A 19-year-old male with CD38-positive ETP ALL (PICALM-MLLT10 fusion) presented with refractory disease. At diagnosis, he was CNS 2a and started induction therapy according to CALGB 10403. On day 22 of induction, therapy was changed to high-dose methotrexate and cytarabine due to concern for parenchymal CNS disease on MRI. Follow-up MRI demonstrated sinus venous thrombus with associated hemorrhage. Disease evaluation 1 month after therapy initiation demonstrated 7% blasts and no CNS disease. Hyper-CVAD therapy was then started. Bone marrow following 5 cycles demonstrated 0.3% blasts. Single agent nelarabine was then given with subsequent bone marrow demonstrating 21% lymphoblasts. He was then enrolled on the phase 1 study of carfilzomib with

daunorubicin/dexamethasone/PEG-asparaginase/vincristine with reduction of blasts to 11%. Given demonstrated resistance to cytotoxic chemotherapy, single agent daratumumab at 16mg/kg weekly was initiated. Slow infusion rate increases as well as premedication with methylprednisolone, acetaminophen, and diphenhydramine and post-infusion oral methylprednisolone and montelukast were administered as described in early phase clinical trials of daratumumab. During the first infusion, the patient experienced mild wheezing that spontaneously resolved and elevated blood pressure that responded to isradipine and diuresis. He had no adverse events (AE) with subsequent infusions and no significant AE associated with the treatment. Bone marrow demonstrated 2.5% and 0.8% lymphoblasts following 2 and 4 doses of daratumumab, respectively. CSF remained negative. Bortezomib (1.3mg/m2 subcutaneously day 1,4,8,11 and venetoclax (800mg oral daily) were then added to weekly daratumumab in an attempt to achieve negative minimal residual disease status prior to bone marrow transplant. This treatment was tolerated with minimal toxicity, however disease evaluation on day 21 demonstrated 19% lymphoblasts. No further doses of daratumumab were given and the patient ultimately proceeded to hospice care.
Conclusion: Daratumumab was well-tolerated and produced a temporary response in a patient with ETP ALL refractory to multiple prior therapies.

Poster # 039

CANDIDA TROPICALIS THYROIDITIS AND THYROID STORM IN A PATIENT WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: We present the case of a fifteen year-old male with very high risk B-cell acute lymphoblastic leukemia (ALL) who developed anterior neck pain and swelling, odynophagia, and dizziness eight days into induction chemotherapy per Children's Oncology Group protocol AALL1131. His symptoms quickly evolved into uncompensated septic shock secondary to Candida tropicalis fungemia. He was also noted to have hand tremors, tongue fasciculation, brisk reflexes, lid lag, and palpitations. Elevated thyroxine (free T4) beyond the level of detection and suppressed thyroid stimulating hormone (TSH) in the setting of confirmed candidemia was consistent with candida thyroiditis with accompanying thyroid storm. Despite clearance of his candidemia and prompt initiation of methimazole, he developed biventricular systolic heart failure requiring support with milrinone in the cardiac intensive care unit. Treatment with propylthiouracil, steroids, and three courses of plasmapheresis led to eventual improvement in cardiac function. He ultimately required a thyroidectomy with pathology confirming budding yeasts.
Objectives: Extramedullary involvement of the thyroid gland at any point during the course of ALL treatment is a rare occurrence. Additionally, fungi are an exceedingly rare cause of thyroiditis. Amongst the limited case reports of candida thyroiditis, nearly all occurred in immunocompromised patients being treated with chemotherapy for hematologic malignancies. The symptoms of thyroiditis in a patient with ALL can be challenging to diagnose. Further understanding of this rare presentation may expedite diagnosis and lead to improved patient outcomes.

Design/Method: We describe the presenting symptoms and work-up leading to the diagnosis of candida thyroiditis with accompanying thyroid storm and heart failure in a teenage patient shortly after initiation of induction chemotherapy for ALL. The differential diagnosis, diagnostic work-up, and management options will be delineated followed by a review of the current literature on thyroid complications in acute leukemia patients.
Results: A rare case that emphasizes unique complications in immunocompromised patients undergoing treatment for acute leukemia. This case also offers a framework to discuss the range of diagnostic and management options for disseminated candidemia.
Conclusion: While pediatric thyroid infections occur infrequently, immunosuppression from chemotherapy can predispose patients to hematogenous spread of infection with end-organ complications. Our patient initially complained of pharyngitis that evolved into candida thyroiditis with accompanying disseminated candidemia, thyroid storm, and heart failure. Undiagnosed thyrotoxicosis is nearly universally fatal, while prompt and aggressive management significantly improves patient outcomes. Therefore, a high index of suspicion is needed for timely symptom recognition and treatment initiation.

Poster # 040

A CASE OF DIFFUSE LARGE B CELL LYMPHOMA DURING MAINTENANCE ALL THERAPY IN A PATIENT WITH TRISOMY 21

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Background: Trisomy 21 is associated with increased risk of malignancy, including leukemia. Acute myeloid leukemia and acute lymphoblastic leukemia (ALL) are most common; non-Hodgkin lymphoma (NHL) is less prevalent. Multiple primary malignancies in patients with trisomy 21 are rare. Also rare is the incidence of secondary malignancy during therapy for ALL in patients with trisomy 21. While these patients do have particular immunodeficiencies that could predispose them to increased risk of certain lymphoproliferative disorders and neoplasms (such as EBV-associated lymphoma), there is not a clear link between trisomy 21 and increased risk of therapy-related lymphoma during therapy for leukemia.
Objectives: We present a case of diffuse large B cell lymphoma (DLBCL) during therapy for ALL in a patient with trisomy 21. We describe rituximab alone as a possible therapy option in this setting as an alternative to the more intensive systemic chemotherapy that would generally be used for de novo DLBCL. We also review the literature to discuss possible etiologies and contributing factors to the development of lymphoma in patients with trisomy 21 undergoing treatment for leukemia.
Design/Method: Rituximab was administered at 375mg/m2/dose once weekly for four weeks. Maintenance chemotherapy for our patient's ALL was suspended during the period of rituximab administration.
Results: A 13-year-old boy with trisomy 21 was diagnosed with B cell ALL. He was treated on COG protocol AALL1131. Two years after diagnosis, while in maintenance, he was noted to have a large, painless lesion on his hard palate. Biopsy showed monomorphic B cells that were EBV+ and had a distinct phenotype from his original ALL. He was diagnosed with a new malignancy: EBV-positive DLBCL. This was thought to be a lymphoproliferative process,

related to his immunocompromised state from chemotherapy, with a possible component of immunodeficiency associated with trisomy 21. He was treated with rituximab to avoid toxicity with more aggressive chemotherapy, given his Down syndrome. The lesion clinically resolved, and CT scan showed complete resolution. ALL-directed therapy was resumed, and he is now off treatment and in remission.
Conclusion: A diagnosis of multiple primary tumors without an underlying cancer predisposition syndrome is rare. While patients with Down syndrome can have various immunodeficiencies, this patient has no evidence of specific immune defects. Further workup may be indicated to determine if he has a subtle alteration of immune function. Alternatively, he may just have had an EBV-associated neoplasm due to immunosuppression from chemotherapy.

Poster # 041

PRE-B ACUTE LYMPHOBLASTIC LEUKEMIA IN A CHILD PRESENTING WITH VAGINAL BLEEDING AND OTORRHEA

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Background: Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Initial presentations of ALL result from complications secondary to cytopenias, including bleeding and infections. Genital tract bleeding has been reported in cases of solid genitourinary tumors and extramedullary relapse of ALL and acute myelogenous leukemia. However, ALL presenting initially as vaginal bleeding, before evidence of leukemia in the peripheral blood or bone marrow, has not yet been published.
Objectives: To report a case of a child with ALL who initially presented with abnormal vaginal bleeding and concurrent otorrhea.
Design/Method: Case report
Results: A previously healthy 6-year-old female presented with nine days of left ear pain, four days of left ear drainage and fevers, and one day of vaginal bleeding. Patient was leukopenic (WBC 2.9 x 10^9/L) and anemic (hg 7.6 g/dL) on admission. Pelvic ultrasound revealed a prepubescent uterus with heterogeneous material comprising the endometrium/filling the endometrial lumen, consistent with bleeding. Abdominal ultrasound did not identify an intraperitoneal hematoma but did show bilateral nephromegaly. Abdominal/pelvic MRI was normal, ruling out solid tumor such as rhabdomyosarcoma or germ cell tumor. CT ear/temporal bone confirmed clinical suspicion for mastoiditis and the patient was treated accordingly. Physical abuse as a cause of vaginal bleeding was ruled out through evaluation by our Center for Child Protection and genitourinary examination under anesthesia by pediatric surgery. Endocrine evaluation for precocious puberty causing abnormal uterine bleeding was negative. Evaluation for an underlying bleeding diathesis was notable for only a mildly prolonged PT (15.9 sec) and prolonged platelet function assay likely secondary to anemia, with overall results not indicative of an underlying coagulopathy or platelet disorder. Abdominal/pelvic MRI was re-reviewed with radiology, highlighting bone marrow fat displacement and inhomogeneous signal, findings concerning for an infiltrative process or a developing aplastic anemia. The patient therefore underwent bone marrow aspiration (BMA). She had two undiagnostic BMAs before a third BMA showed 50% immature B cells with flow cytometry consistent with pre-B ALL without

abnormal cytogenetics. She subsequently initiated standard induction chemotherapy.
Conclusion: This case illustrates the prolonged diagnostic course of a patient who initially presented with cytopenias, abnormal vaginal bleeding, and infection. She was diagnosed with pre-B ALL after two unrevealing BMAs. This is a unique case of pre-B ALL presenting with pre-pubertal vaginal bleeding and concurrent mastoiditis. In the presence of persistent cytopenias, further or repeat diagnostic work-up must be performed with consideration for an indolent leukemia presentation.

Poster # 042

SUCCESSFUL LEUKOREDUCTION IN AN INFANT WITH PRE-B ALL PRESENTING WITH EXTREME HYPERLEUKOCYTOSIS

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Background: Patients with new-onset acute leukemia may present with hyperleukocytosis, generally defined by a white blood cell (WBC) count greater than 100,000/µl. Hyperleukocytosis is associated with tumor lysis syndrome, disseminated intravascular coagulation, and increased morbidity and mortality. Leukostasis is a life-threatening complication of hyperleukocytosis, commonly affecting the lungs and central nervous system. While some clinicians advocate for leukapheresis, its prophylactic use remains questioned. Evidence is conflicting regarding its effect on reducing early complications or improving long-term outcomes, and as a result no clinical guidelines are available describing its role as prophylactic therapy.
Objectives: To review the role of leukapheresis in the treatment of extreme hyperleukocytosis, we report a 3-month-old female presenting with pre-B-cell acute lymphoblastic leukemia (ALL) and an estimated initial white count of 1.5 million/µl. Hyperleukocytosis this extreme has not been reported in the medical literature.
Design/Method: Case report.
Results: We present a 3-month-old female who was admitted to our institution's pediatric intensive care unit acutely ill and with evidence of tumor lysis syndrome. She was found to have extreme hyperleukocytosis to 1,500,000/µl. Diagnostic studies revealed MLL gene-rearranged pre-B ALL. She was treated with hydroxyurea and three courses of leukapheresis over a period of three days. Though technically challenging with insufficient protocols for our specific case, leukapheresis was nevertheless well tolerated and resulted in a decrease in WBC to 335,000/µl. She then underwent induction therapy on the Children's Oncology Group (COG) protocol AALL15P1. At the end of induction, she was clinically well but demonstrated an M2 marrow with 8.3% blasts. She developed progressive disease during the consolidation phase with a blood lymphoblast count of 870/µl, prompting a further bone marrow study that showed 89% blasts. She underwent two cycles of blinatumomab that rendered her marrow negative for minimal residual disease at a sensitivity of less than 0.0001. Bone marrow transplantation is planned as the next step.
Conclusion: Our patient initially presented with hyperleukocytosis to a degree not previously reported. While there is no routine recommendation for prophylactic leukapheresis, published studies tend to group together cases with white counts as low as 100,000/µl. Conclusions based upon this definition of hyperleukocytosis might not extrapolate to cases of extreme

hyperleukocytosis of greater than 1 million/µl. Our patient presented with an estimated white count of 1.5 million/µl. Her successful treatment argues in favor of including leukapheresis in the management of some cases of pediatric leukemia.

Poster # 043

POLYCYTHEMIA AND NEPHROMEGALY AS PRESENTING SIGNS OF ACUTE LYMPHOBLASTIC LYMPHOMA

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Background: For the vast majority of children, the main presenting sign of acute lymphoblastic leukemia (ALL) is a decrease in one or more cell lines. The following case presentation is a rare instance where polycythemia and nephromegaly were the dominant presenting signs of acute leukemia.
Objectives: To remind clinicians of the rarer laboratory and clinical findings of acute lymphoblastic leukemia (ALL) and review the interconnectedness of kidney physiology with bone marrow function.
Design/Method: Case report
Results: A 14-month-old African American male presented to his PCP's office after 1 month of abdominal distention, fever, weight loss, palmar erythema, and migrating leg pain. Hemoglobin obtained at the 1 year well visit showed elevated hemoglobin level of 17.6 mg/dl. He was admitted for workup of a suspected malignancy. Ultrasound revealed bilaterally enlarged kidneys. CT abdomen confirmed nephromegaly without distinct masses as well as lesions in the liver, spleen, and bone. A bone marrow biopsy was performed, but there was no evidence of malignancy. Due to hypertension and nephromegaly, a renal biopsy was obtained. This showed immature cells with common precursor B cell phenotype; thus, a diagnosis of acute B cell lymphoblastic lymphoma was made. Throughout chemotherapy, hemoglobin returned to normal and kidneys decreased in size. Patient is now cancer free and developing well.
Conclusion: ALL ordinarily presents with a decrease of one or more cell lines. In this patient, though, hemoglobin was unusually elevated. Possible explanations for the polycythemia include increased erythropoietin production due to increased activity of hypoxia inducible factor pathway, decreased response of the kidney to negative feedback, or increased erythropoietin production by altered renal cells. Unfortunately, erythropoietin was not collected during the initial workup, so confirmation of this hypothesis is not possible; though hemoglobin response to chemotherapy shows that the polycythemia was likely malignancy related. This case highlights the rare occurrence of nephromegaly as a presenting finding of ALL, the unusual occurrence of evidence of lymphoma found on kidney biopsy but not bone marrow biopsy, and the even more rare occurrence of ALL presenting with polycythemia.

Poster # 044

PARANASAL SINUS CAVITY INVOLVEMENT IN CHILDHOOD B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Acute lymphoblastic leukemia (ALL) is a hemopoietic malignancy of the bone marrow with a heterogeneous manifestation, but rarely invades the sinonasal area. In this report, a 12-year-old girl patient with CNS relapse and expansive leukemia mass infiltration into the paranasal cavities.
Objectives: To describe a rare manifestation of B-cell Lymphoblastic leukemia, presentation and initial management.
Design/Method: Case report
Results: We present a case of 12-year-old girl with a history of B-LLA, negative CNS and normal cytogenetics, and combined late relapse in CNS and bone marrow 12 months after the first treatment. She received chemotherapy and radiotherapy, having bone marrow and CNS remission, but recurrent complaint of mild headache. One month at the end of treatment, there is an intensification of headache. Performed laboratory tests, including blood counts that were normal. Cerebral spinal fluid (CSF) presenting 65% lymphoid blasts, with expression of CD19, CD38 and CD10. Bone marrow without blast infiltration. MRI of the skull shows an infiltrative lesion with contrast enhancement and hipersignal in T2 weighted sequence in the ethmoid cells and apex of the nasal cavities, measuring approximately 3.8 x 2.7 x 2.4 cm. This lesion shows invasion of the frontal sinus, spheno-etmoidal sinus and medial wall of orbit. Nasofibroscopy without signs of fungal infection and negative cultures. Days after diagnosis, patient evolves with facial paralysis and mild loss of visual acuity. Initiated treatment with dexamethasone, mitoxantrone and vincristine, with rapid clinical response. Follow-up CT 2 weeks after treatment, there was a partial regression of lesion, measuring 1.5 x 2.4 cm. Unfortunately, patient progressed with disease and medullary relapse undergoing chemotherapy. She is currently in palliative care.
Conclusion: Leukemia is the most common tumor in childhood. Approximately 25% of children newly diagnosed with ALL will eventually experience leukemia relapse, and that a quarter of all cases will occur in extramedullary sites. This report describes a rare manifestation of leukemic infiltration of the paranasal sinuses, with bone destruction and orbital invasion. The symptoms was mild and progressive. The option of not performing invasive procedures for diagnosis was defined by the presence of lymphoblasts in the cerebrospinal fluid and the high risk of complication. The initial therapeutic response was satisfactory, with tumor regression e improvement of quality of life, but unsustainable due to refractoriness of the disease.

Poster # 045

SEVERE CARDIOTOXICITY AMONG PATIENTS WITH ACUTE MYELOID LEUKEMIA: A CHILDREN'S ONCOLOGY GROUP REPORT

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Background: Current AML treatment includes high cumulative anthracycline doses, which puts patients at a significantly increased risk for cardiomyopathy and consequently, congestive heart failure. Current literature has largely explored late effects of anthracycline-induced cardiotoxicity into survivorship. Recent data from AAML0531 demonstrate that early toxicity may increase non-relapse related mortality. However, clinical characteristics of patients experiencing severe cardiac dysfunction during AML chemotherapy has not been reported in granular detail.
Objectives: We sought to describe the occurrence of severe anthracycline-associated left ventricular systolic dysfunction (Common Terminology Criteria for Adverse Events grades 4 or 5 LVSD) reported Children's Oncology Group (COG) AAML0531 and AAML1031 trials, as well as the characteristics of patients who experienced the toxicity.
Design/Method: We identified all patients treated on AAML0531 or AAML1031 with documented grade 4 or 5 LVSD. We manually reviewed all Adverse Event Expedited Reports (AdEERs) filed for cardiac disorders and all patient adverse event study report forms. Patients on AAML1031 with FLT/ITD+ with high allelic ratio were excluded. We abstracted relevant clinical data for each identified case.
Results: A total of 67 patients treated on AAML0531 (n=20) or AAML1031 (n=47) had documented severe LVSD representing 2.0% and 4.3% of the respective study populations. These patients were predominantly older than two years of age (92.5%), female (67.2%), white (67.7%), not Hispanic (89.1%), and normal body weight (58.5%). The most common reporting periods of documented severe LVSD were Intensification II (25.4%) and off-protocol follow-up (34.3%). 26 patients had concurrent bloodstream infection at severe LVSD onset (38.8%). 47 patients (70.1%) had severe LVSD at first documentation, whereas 20 (29.9%) were initially documented as lower-grade LVSD that progressed to severe. 30 patients (44.8%) had documentation of receiving heart failure pharmacotherapy with 10 patients (14.9%) receiving cardiac assistance such as ventricular assist device or extracorporeal membrane oxygenation. Two (3%) received heart transplant. Overall mortality among severe LVSD was 59.7%, with 35.8% of severe LVSD patients experiencing acute mortality during the reporting period the severe LVSD was documented. 25 patients (37.3%) experienced resolution of or improvement in cardiac dysfunction.
Conclusion: This extended case series illustrates that clinical heart failure associated with anthracyclines is not only experienced in survivorship but also as an acute event that may contribute to treatment-related mortality, highlighted by the 35.8% course-specific mortality rate. Use of cardiac assistance and transplantation was uncommon. Our observations show that standardized cardiac monitoring and identification of effective strategies are needed to prevent and mitigate severe anthracycline-induced cardiotoxicity.

Poster # 046

TRANSCRIPTIONAL AND POST-TRANSCRIPTIONAL BIOMARKERS FOR MINIMAL RESIDUAL DISEASE IN PEDIATRIC AML

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Background: Current risk stratification and treatment in pediatric acute myeloid leukemia (AML) is based largely on a small panel of cytogenetic and molecular markers, combined with early response to therapy. Despite significant progress in the development of new agents to treat refractory disease, predicting poor response to induction therapy remains a challenge. Current research suggests that chemotherapy resistant clones have a more stem cell-like profile, characterized by self-renewal and quiescence.
Objectives: Using minimal residual disease (MRD) at the end of the first induction as a measure of response to therapy, we hypothesized that samples collected at time of diagnosis from pediatric AML patients who fail to respond to therapy will produce a distinct gene expression and alternative splicing signature associated with a stem cell-like phenotype.
Design/Method: We analyzed a large publicly available dataset from the TARGET initiative comprised of diagnostic bone marrow RNA-Seq samples treated according to the AAML03P1 and AAML0531 protocols. We used the software AltAnalyze to compare a group of 27 samples with available positive MRD annotation (MRD positive threshold of 0.1%) and 74 samples with negative MRD at the transcriptional and post-transcriptional level. Putative pathway and gene regulatory networks were assessed using the ToppGene informatics analysis suite.
Results: Differential gene expression analysis identified a total of 295 genes with a fold change of 1.5 and an FDR corrected $p<0.1$. Up-regulated genes, including DNMT3B, GATA2, MYCN, ERG, GFI1B, KIT, were enriched in pathways affecting primitive hematopoiesis, stem cell division, cell-cycle checkpoint and RNA-splicing, while down-regulated genes were enriched in antigen presentation and cell migration pathways. Alternative splicing analysis identified a distinct signature composed of 852 unique events with a percent-spliced-in (PSI) difference greater than 0.1 and an empirical moderated Bayes t-test $p<0.05$. Positive MRD samples demonstrated an extremely high rate of intron retained genes compared to the negative MRD (92% vs 8%, p-value <0.001). Subsequent global intron retention analysis confirmed gene-specific splicing pattern in pathways involving apoptosis, MAPK and mTOR signaling cascade.
Conclusion: Pediatric patients with AML who have a poor response to induction therapy demonstrate a distinct stem cell-like gene expression signature at time of diagnosis as well as high rate of intron retention in apoptotic and proliferation genes. As intron retention typically results in degradation of the gene product, we hypothesize such differences contribute to a global cell quiescence phenotype. Ongoing studies aim to validate these results on an independent patient cohort.

Poster # 047

HIGH INCIDENCE OF MDR GRAM-NEG. BACTEREMIA IN CHILDREN DURING AML INDUCTION AT 57357 HOSPITAL EGYPT

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Background: Children receiving intensive induction chemotherapy (IC) for Acute Myeloid Leukemia (AML) are at risk of gram-negative bloodstream infections (GNBSI) due to associated neutropenia, mucositis, translocation of gut bacteria and indwelling intravenous catheters. The increasing presence of multi-drug resistance organisms (MDR) poses a challenge in managing

GNBSI in these children.
Objectives: To describe gram-negative infectious complications during AML IC: prevalence, antibiotic resistance, morbidity and infection-related mortality (IRM).
Design/Method: Retrospective analysis of children (0-18 years) admitted for AML IC at Children's Cancer Hospital Egypt 57357, a large tertiary pediatric oncology center, between January 2015 and December 2017. Down Syndrome, M3 AML were excluded. Prophylactic Levofloxacin was initiated for all children. Prior to November 2016, empiric Amikacin and Piperacillin/Tazobactum or Carbapenem (in case of ESBL within preceding 6 weeks) were used for empiric therapy of fever/neutropenia. Given the rise in MDR organisms, empiric coverage changed to Amikacin and Carbapenem in November 2016. Antimicrobial susceptibility testing was performed using Vitek 2 system (bioMérieux). Manual susceptibility testing was done in parallel. Bacterial isolates with resistant or intermediate susceptibility to three of the five drug classes: aminoglycoside, fluoroquinolone, 3rd or 4th generation cephalosporins, anti-pseudomonal penicillin or carbapenem were considered MDR. Typhlitis was defined in children with radiological evidence of disease on abdominal Computed Topography (CT) scans. Critically ill patients were admitted to the Intensive Care Unit (ICU) for supportive care.
Results: Of the 328 children admitted for AML IC, 90 (27.4%) had at least one GNBSI and of those 72/90 (80%) children had at least one MDR GN isolate. A total of 124 GNBSI episodes were observed in the 90 children; Escherichia coli (54.8%), Klebsiella pneumoniae (16.9%), Acinetobacter baumannii (6.5%), Enterobacter cloacae (4.8%) and Pseudomonas aeruginosa (4.0%). Out of the 124 GNBSI 101(81.45%) were MDR, 21(17.7%) were non-MDR and two isolates lacked susceptibility testing. Thirty-day cumulative IRM overall was 27.8% [18.9-37.3%]: 27.9% (17.8%-38%) in the MDR group versus 28.6% (11.3%-48.7%) p value 0.86 in the non-MDR group. Observed morbidity included typhlitis in 29/90(32.2%), CLABSI necessitating central venous catheter removal in 12/17(70.5%) and ICU admission 38/90(42%).
Conclusion: We demonstrated in children receiving AML induction therapy 1) a high incidence of MDR in GNBSI with significant attendant morbidity and mortality 2) With appropriate antibiotic choice, no impact on mortality of MDR. As pediatric oncology care becomes increasingly global, knowledge of resistance patterns is essential to provide optimal care.Acknowledgement of support: Dr. Mark Kieran, Dr Liliana Goumnerova.

Poster # 048

OUTCOME OF ACUTE PROMYELOCYTIC LEUKEMIA IN PEDIATRIC PATIENTS AT NATIONAL CANCER INSTITUTE IN EGYPT

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Background: The current study reports the clinical features and treatment outcome of 36 patients with Acute Promyelocytic Leukemia (APL) treated at National Cancer Institute (NCI-Cairo), in Egypt from January 2008 to December 2015.
Objectives: To determine prognostic factors, Overall Survival (OS), Event Free Survival (EFS) and toxicity of therapy in patients with APL.
Design/Method: All evaluable patients were treated for induction with the simultaneous administration of All-Trans Retinoic Acid (ATRA) and an anthracycline. The original Children's

Oncology Group (COG) AAML0631 protocol was modified, due to resource limitations at the NCI-Cairo, by replacing of idarubicin with doxorubicin in most of the cases and omitting first consolidation as Arsenic Trioxide (ATO) was not available.
Results: Twenty boys (55.6%) and 16 girls (44.4%) were included in this study. The Median age at diagnosis was 12 years. The White Blood Cell (WBC) count at presentation was > 10 x 10(9)/L in 16 patients (44.4%). Bleeding was the most common presenting symptom (83.3%). Complete Remission (CR) was achieved in 32 patients (88.8%); the remaining four patients had Early Death (ED); two due to hemorrhage, one due to differentiation syndrome and one patient died due to sepsis. The main therapeutic complications during the induction phase were febrile neutropenia (100%), and differentiation syndrome (19.4%). chemotherapy induced left ventricular function impairment was documented in five patients (13.8%). No deaths in CR, clinical cardiomyotoxicity, or secondary malignancy occurred. Three relapses were documented; at the end of maintenance treatment, 8 and 12 months from end of treatment respectively, two patients died of disease. After Median follow-up of 37.1 months, the three-year OS for all patients was 84.7%, while the three-year EFS was 80.2%. Poor prognostic factors included age > 10 years (P=0.059), fever and significant bleeding at presentation (P=0.057) and (P=0.003) respectively, duration of initial symptoms ≤14 days (P=0.047), delay in initiating ATRA of ≥ 3 days (P=0.012) and Prothrombin concentration of > 80% (P=0.027). Other factors including; initial WBC count > 10 x 10(9)/L and molecular evidence of the t(15;17) after consolidation chemotherapy had no significant impact on survival rates.
Conclusion: Our three-year EFS and OS rates are encouraging and suggest that despite the limited resources available in developing countries patients with APL can still achieve outcomes comparable to international standards; further improvement can be achieved by reducing early mortality rate. Our results also emphasize the importance of early initiation of ATRA.

Poster # 049

OUTPATIENT SUPPORTIVE CARE FOR PEDIATRIC ACUTE MYELOID LEUKEMIA: A SINGLE INSTITUTION'S EXPERIENCE

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Background: Infections are responsible for most treatment related morbidity and mortality in pediatric acute myeloid leukemia (AML), highlighting the importance of supportive care practices. Rates of documented infection with at least one organism during AML treatment have been reported to occur in as many as 77% of children.(1) Current Children's Oncology Group (COG) recommendations include continuing hospitalization following chemotherapy until the absolute neutrophil count (ANC) reaches 200. However, prolonged hospitalizations impact quality of life and increase the risk of nosocomial infections. Amongst COG institutions, there are no standard guidelines for antibiotic prophylaxis and there is wide variation in discharge practices. There have been single institutional reviews of early discharge feasibility and safety but a recent survey showed that over 50% of COG institutions do not routinely discharge patients early.(2)
Objectives: To report our institution's experience with outpatient supportive care management, including antibiotic prophylaxis and empiric therapy for fever in children with AML and to

report our rates of infectious complications.
Design/Method: A retrospective analysis was performed of all patients at our institution treated for AML from 2010 to 2018. Data was collected on prophylactic and empiric antibiotics administered, infectious complications and duration of outpatient neutropenia.
Results: Fifteen pediatric patients with AML underwent a total of 51 chemotherapy cycles. All patients were discharged after completion of chemotherapy if clinically stable. Single agent prophylactic antibiotics were initiated in 47 cycles with a fluoroquinolone, third or fourth generation cephalosporin, carbapenem, or penicillin agent. No antibiotics were administered in 5 cycles. Patients were re-admitted for fever and neutropenia and antibiotic coverage was broadened for empiric therapy in 30 cycles. Patients were discharged home on empiric antibiotic therapy if afebrile with negative cultures. There were 5 episodes of bacteremia, 2 of bacterial sepsis, 1 of lymphadenitis, and 1 of afebrile bacteremia with cellulitis, in a total of 8 patients (53%). There were no deaths due to infection. Average neutropenia duration (ANC<200) was 23.4 days per cycle, and patients remained outpatient for an average of 15.2 neutropenia days per cycle.
Conclusion: Outpatient supportive care for children with AML is feasible and offers improved quality of life to patients and families. Rates of infectious complications at our institution did not exceed those reported in the literature for hospitalized patients. Further studies are needed to help establish guidelines for outpatient supportive care of pediatric patients with AML.1.Sung et al., Blood, 2007.2.Lehrnbecher et al., British Journal of Haematology, 2009.

Poster # 050

OUTCOME OF FLT3 GENE MUTATION IN CHILDREN WITH ACUTE MYELOID LEUKEMIA IN CCHE HOSPITAL

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Background: The presence of FLT 3 –ITD mutation in pediatric AML is associated with high rates of failure to induction, worse survival and consider as high risk group.
Objectives: The aim of the work is to evaluate pediatric AML patients with mutant FLT3 treated at Children Cancer Hospital Egypt (CCHE) during 10 years period.
Design/Method: A retrospective study to evaluate pediatric AML with mutant FLT3 from July 2007 till July 2017 at CCHE.
Results: A total of 71 patients (10.33%) had FLT3 gene mutation out of 687 patients with AML.Sixty five patients (91.6%) had FLT3 gene mutation with allelic ratio >0.4, 43 patients (66.1%) achieved CR, and 22 patients (33.8%) were refractory and died. BMT was done for 9 patients (13.8%) in 1st CR, 8 of them are alive in CR, and 1 patient (1.5%) relapsed and died. seven patients (10.7%) are alive in CR without BMT. Eight patients (12.3%) died, and 1 patient (1.5%) lost FU, 18 patients (27.6%) relapsed soon after 1stCR, 1 patient (1.5%) is in 2nd CR and alive. The rest of relapsed patients (23%) received salvage chemotherapy and died.Three years OS and EFS for the patients with FLT3 gene mutation with allelic ratio >0.4 are 26.9%-22.8% respectively. Three years OS and EFS for patient treated with BMT were 77.8%-78.8% respectively versus patients were treated and achieve CR without BMT which were 16.3%-

12.8% respectively.
Conclusion: FLT 3 –ITD mutation in pediatric AML is associated higher rates of induction failure, survival of relapsing patients is extremely poor, and BMT in first remission if possible is the best option, otherwise significantly worse OS and EFS. Trial of the FLT3 inhibitor sorafenib is mandatory to improve outcomes for this subset of patients.

Poster # 051

PREDICTORS OF MORTALITY IN NEUTROPENIC ENTEROCOLITIS AMONG CHILDREN WITH MYELOID LEUKEMIA IN EGYPT

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Background: Neutropenic enterocolitis (nec) is a life-threatening disease with substantial morbidity and mortality, especially in patients with hematologic malignancies. The frequency of nec has increased with the widespread use of chemotherapeutic agents causing severe gastrointestinal mucositis
Objectives: This study was done to detect the incidence, outcome, and predictors of mortality of nec among pediatric patient with acute myeloid leukemia at the National Cancer Institute- Cairo University.
Design/Method: This was a retrospective study at the National Cancer Institute, Cairo University. The computerized records were screened for ultrasound or computerized tomographic scan requests for abdominal pain for all acute myeloid pediatrics inpatients (2012-2016). Risk factors, clinical picture and d 30 mortality was reported.
Results: The incidence of nec among our inpatients was 24% (49/203). Forty-three children had radiologically confirmed typhlitis, and 6 had clinical features alone. Most (93%) patients were profoundly neutropenic (anc less than 100). All of the patients received conservative management. All of them needed ICU admission. Eighteen children had a variable period of bowel rest, including 12 patients who were supported with total parenteral nutrition. Three patients had laparotomy that revealed extensive colonic bowel necrosis (1), perforated bowel loop (1), and a perforated appendix (1). Two out of three cases of laparotomy were diagnosed with mucormycosis. 30-days mortality was 44.8% (22/49). Relapsing typhlitis in subsequent courses was observed in 6/27 (22%) patients. Nec related mortality was significantly higher among patients receiving high-risk protocol with more intensive chemotherapy and in patients with other co-morbidities [chest infections and/ or cardiac affection] with a p-value of 0.005 and 0.037 respectively. Also, mortality was increased among patients with more than 2 presenting clinical symptoms with a p-value of 0.01.
Conclusion: Early management and better supportive care of underlying co-morbid conditions can decrease nec related mortality. Though rare, fungal infection should be suspected especially in cases with worsening signs of typhlitis despite broad antimicrobial coverage

Poster # 052

RISK STRATIFICATION AND OUTCOMES BASED ON CYTOGENETIC PROFILE IN ACUTE MYELOID LEUKEMIAS IN PAKISTAN

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Background: Acute myeloid leukemia (AML) is a heterogeneous disease from morphologic, cytogenetic, immunophenotypic, molecular, and clinical perspectives. AML accounts for15% to 20% of all childhood leukemia. Cytogenetic and molecular data are recognised as the most valuable prognostic factors in AML. Most of the studies on cytogenetic profiling of AML are from Western countries and similar data from lower-middle-income countries is lacking. We conducted this retrospective study at a single cancer centre in Pakistan.
Objectives: To study the cytogenetic etiology in AML and its association with treatment outcomes in pediatric patients at Aga Khan University Hospital in Karachi, Pakistan.
Design/Method: Patients from birth through 18 years diagnosed from 2006 to 2017 with AML were analysed for demographics, presenting complaints, cytogenetic profiles, management plan, toxicity and treatment outcomes
Results: The cohort included 176 patients. A total of 103 patients were excluded due to incomplete data. Seventy-three patients met the inclusion criteria with median age of 13 years IQR (4-16 months). Forty-four (60%) patients were male. Fever (n = 56, 80%) was the most common presentation. From the risk stratification groups, 23 (32%) were Favorable, 36 (49%) were Intermediate, and 14 (19 %) were Adverse. Gum Hypertrophy (n=3, 4%, p = 0.58) was seen in Intermediate and Adverse whereas Chloroma (n=3, 4%, p = 0.031) was seen in Favorable, showing significant difference in risk group presentation. Forty-five (62%) were treated on Cytarabine, Daunorubicin, Etoposide protocol, 9 (12%) on Cytarabine and Daunorubicin, and 9 (12%) did not receive treatment. Chemotherapy toxicities included Cardiotoxicity (n = 14, 19%) and Neurotoxicity (n = 2, 3%). The median follow-up period was 9 months. Five-year overall survival for Favorable risk: 40% (95% CI: 5% - 76%), Intermediate risk: 38%(95% CI:19% - 57%), and Adverse risk: 49% (95% CI: 18% - 80%). The 5-year Event-Free Survival keeping relapse as an event for Favorable risk: 85% (95% CI: 66% - 104%), Intermediate risk: 57% (95% CI: 32% - 82%), and Adverse risk: 58% (95% CI: 22% - 94%).
Conclusion: Our results suggest that risk stratification based on cytogenetic etiology did not correlate with survival outcomes. This suggests that lower survival rates in our population are not due to primary disease but possibly due to higher rates of toxicity and complications.

Poster # 053

PRE-TRANSPLANT THERAPY IN TREATMENT OF JUVENILE MYELOMONOCYTIC LEUKEMIA (JMML)

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Background: Despite the intensity of hematopoietic cell transplantation (HCT), relapse remains the most common cause of death in JMML. In contrast to most other leukemias where pre-HCT

therapy is used to reduce leukemic burden to a minimal residual disease state, many patients with JMML proceed directly to HCT with active disease.
Objectives: The objective of this single-center study was to elucidate whether pre-HCT therapy has an effect on the molecular disease burden and whether this impacts outcomes post-HCT.
Design/Method: From 1990 to 2018, 21 consecutive patients with a confirmed diagnosis of JMML were transplanted at UCSF and had samples available (17 boys, 4 girls; median age at diagnosis: 12.3 months, range: 4.6mo-7.6y). All patients received therapy prior to HCT: 16 patients received moderately intense myeloid based chemotherapy, 5 patients 6-mercaptopurine and one patient azacitidine alone. The mutational burden was retrospectively analyzed at the time of diagnosis and post-therapy at the last available timepoint before HCT. DNA was extracted from patient samples and libraries were prepared using the CleanPlex technology from Paragon Genomics (Hayward, CA) with a custom amplicon approach to sequence 25 genes recurrently mutated in JMML on a MiSeq platform by Illumina (San Diego, CA) (760X mean coverage). The study was designed in accordance with the declaration of Helsinki and approved by the institutional review board of UCSF with a waiver of consent.
Results: Seven of the 21 patients achieved a significant reduction in their mutant allele frequency to <5% prior to HCT (6 with chemotherapy, one with 4 cycles of azacitidine). Event-free-survival (EFS) in the 7 responders to therapy was 100% compared to 43% for the 14 non-responders (p=0.08). There were no significant differences in baseline clinical characteristics between the two groups, including age and the number of secondary mutations.
Conclusion: In our cohort, we found that one third of patients with JMML responded to pre-HCT therapy with a significant reduction in their mutational burden. These patients had an excellent prognosis. In contrast, the outcome of patients who did not respond to therapy was poor even with high-dose conditioning as part of HCT. Importantly, molecular testing was essential to distinguish between responders and non-responders as morphology and flow cytometry failed to predict outcome. In summary, moderately intense myeloid based chemotherapy pre-HCT for patients with JMML was well tolerated, can induce molecular remissions and is a reasonable strategy to consider while evaluating patients for HCT.

Poster # 054

CHROMATIN REMODELING THERAPY AND CAPIZZI METHOTREXATE IN TREATMENT-RELATED MDS/AML

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Background: Treatment-related myelodysplastic syndrome/acute myeloid leukemia (t-MDS/t-AML) is a life-threatening complication of therapy for pediatric patients with osteosarcoma. Even with intensive chemotherapy regimens, outcome in patients with t-MDS/t-AML is very poor. These intensive regimens cause significant morbidity, poor quality of life and increased toxicity, at times precluding the ultimate goal of stem cell transplant (SCT).Chromatin remodeling therapy with decitabine and vorinostat has shown some promise in adults with relapsed/refractory AML and MDS. The synergistic combination of methotrexate and asparaginase, also referred to as ‘Capizzi methotrexate’, is not generally part of upfront treatment for AML but does have some activity in relapsed/refractory disease. We report the use of this

combination regimen in two children with t-AML where chromatin remodeling therapy with subsequent Capizzi methotrexate successfully bridged both patients to SCT.
Objectives: We sought to describe our experience using a combination of decitabine/vorinostat along with Capizzi methotrexate in two patients with t-MDS/AML who were treated at our institution between 2003 and 2018.
Design/Method: The leukemia team at Lucile Packard Children's Hospital at Stanford (LPCH) maintains a list of patients with acute leukemia or MDS who have been treated with chromatin remodeling therapy. We identified patients on that list with a diagnosis of t-MDS/t-AML and reviewed their treatment course and complications through the electronic medical record.
Results: We identified two patients with a diagnosis of t-MDS/t-AML treated with chromatin remodeling agents and Capizzi methotrexate at LPCH. Both patients were initially treated for osteosarcoma as teenagers. One patient received ifosfamide and etoposide as part of his upfront treatment due to poor necrosis at surgery. The other received ifosfamide and etoposide as treatment for recurrent osteosarcoma. Both patients were treated with multiple cycles of concurrent decitabine and vorinostat followed by Capizzi methotrexate with minimal complications. Both patients were subsequently able to receive a HSCT. One patient remained in remission from t-MDS but subsequently died of relapsed osteosarcoma two years after transplant. The other patient experienced a relapse of t-AML six months post-transplant and is currently receiving palliative chemotherapy.
Conclusion: The two cases presented here demonstrated good response to a novel combination of therapy with decitabine/vorinostat followed by Capizzi methotrexate. Given the significant toxicity associated with most regimens for t-MDS/t-AML, decitabine/vorinostat followed by Capizzi methotrexate should be considered when first line salvage chemotherapy has failed. The precise regimen as well as the optimal number of cycles prior to HSCT should be evaluated in the context of a clinical trial.

Poster # 055

MYELODYSPLASTIC SYNDROME WITH GERMLINE RRAS MUTATION; EXPANDING THE PHENOTYPE OF PEDIATRIC RASOPATHY

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Background: The RAS/mitogen-activated protein kinase (MAPK) pathway is essential for the regulation of cell proliferation, differentiation, and apoptosis. Germ line mutations resulting in activation and dysregulation of this pathway cause overlapping genetic disorders known as the RASopathies. These syndromes are characterized by a constellation of findings to include cardiac defects, facial dysmorphism, skeletal anomalies, and variable neurocognitive deficits. With enhanced and unregulated signaling through the MAPK pathway, RASopathies also exhibit an increased risk for hematologic malignancies such as juvenile myelomonocytic leukemia (JMML) and acute myelogenous leukemia.
Objectives: We report a pediatric patient with germline RRAS mutation resulting in the RASopathy clinical spectrum who developed monosomy 7 myelodysplastic syndrome (MDS). This is the first reported case of MDS in the setting of a germline RRAS mutation.
Design/Method: A retrospective chart review and review of the literature was performed.

Results: This case describes a 7-year old male who was found to have splenomegaly while undergoing scoliosis evaluation. His past medical history was notable for craniosynostosis, ventricular septal defect, and speech delay. On physical exam he had hypertelorism, small nose, crowded teeth, full lower lip, short fingers, scoliosis, and bilateral hydroceles. Ultrasound confirmed splenomegaly. Laboratory testing was significant for a platelet count of 59x10^3/µl. Given the constellation of multi-system physical exam findings, whole exome sequencing was pursued and revealed an activating RRAS mutation, heterozygous p.Gly39dup. With identification of RRAS mutation and thrombocytopenia, bone marrow testing was performed that was significant for dysplasia in both myeloid and megakaryocyte lineages, 1.4% blasts, and no absolute monocytosis. Cytogenetic testing was positive for monosomy 7 in 10/10 metaphases and 27.5% of nuclei by fluorescence in situ hybridization.
Conclusion: While sporadic MDS is commonly seen in adult patients, pediatric MDS is frequently associated with prior exposure to chemotherapy, inherited bone marrow failure syndromes, or genetic predisposition syndromes. Here we report the first case of monosomy 7 MDS in a pediatric patient with a germline RRAS mutation. RRAS mutations have been implicated in the development of juvenile myelomonocytic leukemia, but our case suggests RRAS mutations may display a broader malignant potential. Our case demonstrates the potential clinical implications of an activating germline RRAS mutation. These findings support the recommendation that RRAS be added to the list of genes tested for all patients with features of RASopathy and that, if identified, these patients undergo surveillance for the development of hematologic malignancy.

Poster # 056

CYTOKINE INDUCED MEMORY-LIKE NK CELL THERAPY IN A PEDIATRIC PATIENT WITH RELAPSED AML AFTER SCT

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Background: Acute myeloid leukemia (AML) accounts for 18% of all leukemia diagnoses in pediatric patients. Multi-agent front line chemotherapy results in remission in 80-90% of patients and is followed by consolidation therapy with additional chemotherapy (low risk) or allogeneic hematopoietic cell transplantation (HCT) (high risk). Despite a high remission rate with initial chemotherapy, about 50% of AML patients relapse. The standard of care for relapsed-refractory AML is additional chemotherapy followed by allogeneic stem cell transplantation (HCT). This therapy is successful in less than 25% of patients. Patients with relapsed disease after HCT are typically resistant to chemotherapy only approaches and donor T-cell lymphocyte infusions (DLI) are used as cellular therapy to boost graft-versus-leukemia effect. However, DLI therapies are only successful in 11% of patients with relapsed AML after HCT. Natural killer (NK) cells are an emerging cellular immunotherapy for patients with AML and have shown promise in adult patients with relapsed-refractory AML. Ex-vivo stimulation of NK cells with with IL-12,15, and 18 generates a memory-like phenotype with enhanced anti-leukemia functionality. In phase-I trials in adults with relapsed-refractory AML, treatment with cytokine-induced memory-like (CIML) NK cells was safe and induced remission in 70% of patients. This research has not yet been trialed in pediatric patients.

Objectives: To present the preliminary course of a pediatric patient with relapsed AML after HCT treated with (CIML) NK-cells in combination with DLI.
Design/Method: Case Report
Results: An 18-month-old male was first diagnosed with AML at 7 months of age. He was treated with two cycles of standard of care induction chemotherapy but had disease relapse. He then proceeded to haploidentical-HCT with persistent disease present at 0.15%. He achieved remission post-HCT. Three months later his AML recurred. Treatment with chemotherapy, including mitoxantrone and Vyxeos failed to induce remission. He was enrolled in a phase-I study using salvage chemotherapy with fludarabine, cytarabine and granulocyte colony stimulating factor followed by infusion of DLI in combination with (CIML) NK-cells from the original haploidentical donor. Preliminary bone marrow assessment at 28 days post cellular therapy demonstrated complete remission of AML and full donor engraftment. His clinical course was complicated by mild gastrointestinal graft-versus-host disease that was managed with low-dose steroids and tociluzimab.
Conclusion: DLI in combination with (CIML) NK-cells offers a treatment option for relapsed-refractory AML after SCT. Further studies and patient follow up are ongoing.

Poster # 057

MYELOID SARCOMA WITHOUT MYELOID FEATURES: DEVELOPMENT OF A LEUKEMIA

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Background: Myeloid sarcoma is a subtype of acute myeloid leukemia that presents as a solid tumor. It is the presenting feature of AML in less than 1 percent of patients and can usually occurs in soft tissues, lymph nodes, or bone. Myeloid sarcoma appears as a small round blue cell tumor on histologic examination, and diagnosis is confirmed by characterization of myeloid cells via flow cytometry or immunophenotyping.
Objectives: We describe a case of a "small round blue cell" flank mass that initially did not show myeloid features, delaying diagnosis until the patient presented with overt acute myeloid leukemia.
Design/Method: The patient presented to Oncology about two months prior to her eventual diagnosis, with a right flank mass that had been growing over the previous three months. She was asymptomatic apart from the mass. Initial biopsy revealed a small round blue cell tumor. Pathologic work-up (see below) was not able to determine a specific diagnosis; a sarcoma was suspected, but findings were not suggestive of a myeloid lineage. It was decided to perform gross resection of the flank mass, which took place about 5 weeks after presentation. About a week later, patient presented with persistent fever, and was found to have an acutely elevated WBC count, with presence of peripheral blasts.
Results: Initial CBC, electrolytes: normalInitial Surgical Pathology: Malignant small round blue cell tumor. Strong positivity for FLI1 and GATA-3. Moderate positivity of CD99 and CD56. Suspected desmoplastic small round blue cell tumor or Ewing sarcoma. Flow Cytometry: CD3-, CD4-, CD5-, CD8-, CD10-, CD13-, CD16-, CD19-, CD33+, CD34-, CD 45-, CD56 heterogeneous expression, CD57-, CD64-, CD117 dim+, kappa-, lambda-.Sarcoma Panel:

negativeBone Marrow Exam: No atypical cellsChromosome Study (Bone marrow and tumor): 50,X,i(X)(p10),+8,+10,+14,der(15)t(1;15)(q32;p11.2),+21[11]/46,XX[9]2 months later:WBC: 70.3Hg: 9.3Platelets: 52Blasts: 26%Flow Cytometry (Blood): Myeloid blasts. CD45-, CD10-, CD11B-, dim CD13+, CD14-, CD20-, CD22-, CD19-, CD33+, CD34+, CD56+, CD61+, CD64-, CD117+, HLA-DR-, CD38-, kappa-, lambda-.
Conclusion: Myeloid sarcoma can present concurrently with myeloid leukemia, or can precede bone marrow involvement entirely. This was the case in this patient; however, the lack of myeloid features in her sarcoma was unusual. The presence of the same chromosome abnormalities in both the bone marrow and the solid tumor were suggestive of a common lineage, but definitive diagnosis was not achieved until overt leukemia developed. Molecular and pathologic testing at outside institutions is ongoing to gain further insight into this challenging case.

Poster # 058

ACUTE MYELOID LEUKEMIA WITH MLL GENE REARRANGEMENT INS(10;11) AND 16P11.2 MICRODELETION SYNDROME

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Background: Overall five-year survival for pediatric patients with acute myeloid leukemia (AML) is between 60-70%; however, survival rates are dismal among certain subgroups of high-risk patients. Specific cytogenetic mutations, particularly the majority of those involving the MLL gene, are associated with a poor prognosis. Additionally, a multitude of underlying genetic syndromes have been associated with the development of AML with varying outcomes.
Objectives: To describe a pediatric patient with 16p11.2 microdeletion syndrome diagnosed with AML with an MLL gene rearrangement involving chromosome 10p.
Design/Method: The patient is a 12-year-old multi-racial female with developmental delay, short stature, and coarse facial features who presented with gingival hyperplasia, weight loss, and fatigue. Initial laboratory investigations showed leukocytosis (WBC 70,500/μL), anemia (hemoglobin 6.4 g/dL), and thrombocytopenia (platelet count 123,000/μL); PT, PTT and fibrinogen were normal. Peripheral blood flow cytometry evaluation revealed a CD45 dim myeloblast population comprising 27% of cells. Bone marrow aspiration and biopsy confirmed an increased CD34/CD117/CD14/CD33 positive myeloblast population comprising 59% of cells. Cerebrospinal fluid analysis was significant for nine nucleated cells and positive for blasts. She was diagnosed with AML with monocytic differentiation and CNS involvement. Cytogenetic analysis subsequently revealed an 11q23 gene rearrangement involving chromosome 10p. Genetics was additionally consulted due to concern for a possible underlying genetic syndrome given her constellation of presenting physical features and developmental delay. Whole genome SNP microarray revealed a 754 Kb deletion of the region 16p11.2. She was diagnosed with 16p11.2 microdeletion syndrome.
Results: The patient began treatment with cytarabine, daunorubicin, and etoposide. She was MRD (minimal residual disease) negative after first induction chemotherapy and CNS blasts cleared after her third dose of intrathecal chemotherapy. Due to her specific MLL gene

rearrangement she was risk-stratified as high-risk and received induction II therapy with mitoxantrone and high-dose cytarabine. She was treated with an additional cycle of chemotherapy (high-dose cytarabine/etoposide) and subsequently underwent a haploidentical stem cell transplantation (SCT) in first remission.
Conclusion: To our knowledge, this is the first reported case of a patient diagnosed with AML and 16p11.2 microdeletion syndrome. Interestingly, both the mitogen-activated protein kinase 3 (MAPK3) and major vault protein (MVP) genes are located within the region of her 16p11.2 deletion. The proteins encoded by these genes act in the regulation of several cellular pathways which may be important in the development of leukemia. The specific role of MAPK3 and MVP in the development of AML and its prognosis, however, is unclear.

Poster # 059

FLT3-TKD MUTATIONS ASSOCIATED WITH POOR OUTCOMES IN TWO PATIENTS WITH INFANT ACUTE MYELOID LEUKEMIA

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Background: Survival from childhood AML remains approximately 60%. Up to 25% of cases harbor FMS-like tyrosine kinase 3 (FLT3) receptor gene mutations, causing constitutive kinase activity and hematopoietic proliferation. These are commonly internal tandem duplications of the FLT3 gene (FLT3-ITD) but can also be single point (FLT3-TKD) mutations in the gene's activating loop. Literature in adult AML demonstrates that these mutations confer poorer prognoses; though they occur in 7% of pediatric patients, outcome data are limited.
Objectives: To describe two infantile AML cases with FLT3-TKD mutations.
Design/Method: Case series of two patients diagnosed in 2018 at our institution.
Results: Case 1: A four-month-old, previously healthy full-term male presented with fevers and bruising. Bone marrow evaluation demonstrated AML with 30% blasts. Next-generation sequencing detected a FLT3-TKD activating mutation at codon D835. Genomic profiling by Foundation Medicine also detected a KMT2A (MLL) rearrangement with fusion to PICALM (Phosphatidylinositol Binding Clathrin Assembly Protein). While rearrangements involving the MLL (Mixed-Lineage Leukemia) gene at 11q23 occur frequently in infantile AML, fusion with the PICALM gene has been reported in only one previous case. Post-induction marrow contained 41% leukemic blasts with persistent KMT2A rearrangement and FLT3-TKD mutation. CNS involvement persisted despite intensification of intrathecal chemotherapy. Following a second induction attempt, disease remained present in the marrow and CSF. New skin lesions developed, which were confirmed by biopsy as leukemic infiltration. His disease remains refractory to multiple re-induction attempts.Case 2: A nine-month-old, previously healthy full-term male presented with fevers, scalp lesions, and a suprarenal mass. Bone marrow examination confirmed AML with 49% blasts; scalp biopsy revealed leukemic infiltrate. Next-generation sequencing detected a FLT3-TKD activating mutation at codon N841. Chromosomal analysis also showed a KMT2A rearrangement. Post-induction marrow examination demonstrated remission by morphology, FISH, and flow-based MRD performed by Hematologics, Inc. To date, he has received three cycles of chemotherapy. Marrow and CNS remain negative, but he developed a biopsy-proven chloroma in his calcaneous that has been refractory to further

chemotherapy.
Conclusion: We describe two patients with infantile AML with FLT3 activating point mutations. It is unknown whether the FLT3-TKD mutations were responsible for the refractory nature of our patients' diseases. Given the rarity of the accompanying KMT2A-PICALM rearrangement, it is unclear whether one or both mutations drive our first patient's aggressive disease. Genetic sequencing of AML, especially among younger patients, will continue to identify potentially targetable mutations and contribute to the growing body of literature.

Poster # 060

TWIN-TO-TWIN TRANSMISSION OF TRANSIENT MYELOPROLIFERATIVE DISORDER WITHOUT CONSTITUTIONAL TRISOMY 21

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Background: Transient Myeloproliferative Disorder (TMD) is an abnormal proliferation of myeloblasts that occurs most commonly in neonates with constitutional Down Syndrome (DS). The combination of trisomy 21 and an acquired pathogenic variant in GATA1 is necessary for TMD. TMD rarely occurs in children with acquired somatic (non-constitutional) trisomy 21. We present a case of twin neonates with peripheral blood meyeloblasts at birth, development of severe thrombocytopenia, and somatic trisomy 21 with an identical pathogenic variant in exon 2 of GATA1. Given the identical GATA1 exon 2 mutations, the most likely etiology is twin-to-twin transmission of a myeloblast clone with acquired trisomy 21.
Objectives: Describe an unusual case of twin-to-twin transmission of a TMD clone in non-DS twins.
Design/Method: Case Report
Results: Monochorionic-diamniotic neonates presented with peripheral blood meyelooblasts at birth and thrombocytopenia (Twin A 52 k and Twin B 64 k/mm3). There were no phenotypic features of DS. In both patients, peripheral blood karyotype showed trisomy 21 whereas phytohemagglutinin (PHA) stimulated leukocytes showed no trisomy 21, consistent with somatic, non-constitutional trisomy 21. Identical GATA1 exon 2 variants were identified by Next Generation Sequencing (NGS) testing. Given the identical GATA1 mutations, evidence of non-constitutional 21, and lack of phenotypic features of DS, the most likely etiology was felt to be twin-to-twin transmission of a pre-leukemic clone with acquired trisomy 21. The twins required intermittent platelet transfusion support for episodes of severe thrombocytopenia until age 52 days. Blasts were not detected after age 62 days. Platelets remained normal after 90 days. The GATA1 variant was undetectable by NGS at 7 months old in both infants. Follow up clinical examination remained normal, without features of DS.
Conclusion: To our knowledge, this is the first report of twin-to-twin transmission of TMD not associated with constitutional trisomy 21, possibly through a transmissible element with potential for hematological dissemination. We acknowledge that while the exact etiology is unclear, identical GATA1 mutations in both infants, support the hypothesis of in-utero twin-to-twin transmission. TMD in non-constitutional trisomy 21 can be associated with the development of

acute myeloid leukemia later in childhood, thus, infants with this condition should be monitored with a similar schedule as children with DS-associated TMD.

Poster # 061

RESPONSE TO TARGETED THERAPY AFTER RELAPSED MIXED PHENOTYPE ACUTE LEUKEMIA: A CASE REPORT

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Background: Mixed phenotype acute leukemia (MPAL) is a rare subset of acute leukemia that is characterized by both myeloid and lymphoid lineage blast cells. For this population, treatment regimens are limited and prognosis is poor.
Objectives: To evaluate the response of sirolimus in a pediatric patient with relapsed MPAL and NRAS Q61R alteration.
Design/Method: Case Report
Results: We present a case of a previously healthy 13 year old female who presented with fatigue and weight loss, and had a white blood cell (WBC) count of 25.3, hemoglobin of 5.7, and platelets of 63 with 38% other cells on admission. Initial immunohistochemistry revealed both myeloid and lymphoid features, and additional staining confirmed mixed phenotype acute leukemia with B-myeloid lineage. Standard cytogenetics were negative. Next-Generation Sequencing revealed a t(5:11)(q35p15.5) translocation, resulting in fusion of nucleoporin 98 (NUP98) with NSD1, and an NRAS Q61R alteration. At diagnosis 90% of her blasts showed the NUP98-NSD1 fusion. Bone marrow biopsy after induction (per AAML 1031) showed NUP98-NSD1 fusion in 20.6% of her blasts. Bone marrow biopsy after Induction II showed no evidence of disease by immunohistochemistry and fluorescence in situ hybridization for NUP98-NSD1 fusion. She was bridged with FLAG-Daunoxome until bone marrow transplant (BMT). Bone marrow biopsy prior to BMT showed 1.5% early regenerating progenitor cells and 28.3% of interphase cells containing NUP98 mutation. Day +28 bone marrow biopsy showed no morphologic or flow cytometric immunophenotypic evidence of acute leukemia; however, FISH revealed NUP98 gene rearrangement in 3.7% of cells with female karyotype. She was started on systemic tacrolimus for treatment of skin graft versus host disease (GvHD). Day +60 bone marrow biopsy showed relapsed disease with 26.3% blasts by immunohistochemistry and 59.9% of cells with NUP98-NSD1 fusion. After relapse, she was started on azacitidine and skin GvHD treatment was switched to sirolimus to target her NRAS mutation, an agent that blocks the mTOR pathway. Prior to initiation, her peripheral WBC was 12.3 and peripheral blast forms were 16%. Response to sirolimus was seen at two months, with decline in both her peripheral WBC and blast forms. Unfortunately she became refractory at six months from start of therapy and died at eight months from date of relapse.
Conclusion: We demonstrate that a patient with relapsed MPAL showed initial response to targeted therapy with sirolimus. This case highlights the importance of understanding the genomic landscape of MPAL, and screening for complex cytogenetics to aide with identification of precision targeted therapies.

Poster # 062

A UNIQUE CASE OF PEDIATRIC ALL WITH FUS-ERG REARRANGEMENT UNDERGOING LINEAGE SWITCH TO AML

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Background: Lineage switch from acute lymphoblastic leukemia (ALL) to acute myeloid leukemia (AML) may occur in the setting of genetic abnormalities of early stem cells. The TLS/FUS-ERG fusion gene product results from a balanced translocation between chromosomes 16p11 and 21q22 and has been described in cases of pediatric acute myeloid leukemia (AML), often associated with poor response to chemotherapy, early relapse and overall poor prognosis. This translocation has been rarely described in acute lymphoblastic leukemia and to our knowledge there have been no reported cases of lineage switch from ALL to AML with this cytogenetic aberration.
Objectives: To describe an unusual cytogenetic abnormality with a novel natural history in a pediatric patient.
Design/Method: Case Report
Results: A 5-year old male presented at age 3 with leg pain, pallor and fever. Immunophenotyping on initial bone marrow aspirate was consistent with single lineage pre-B cell ALL (CD19+, CD20+, HLA-DR+, TdT+) without myeloid markers. Cytogenetic analysis showed an abnormal cell line with a balanced t(16;21)(p11;q22) in 30% of cells. He was started on standard risk ALL therapy. Flow cytometry for minimal residual disease was negative from bone marrow at day 29 of induction. He did well for 19 months until he was noted to have circulating blasts on a CBC during the 5th cycle of maintenance therapy. Repeat bone marrow aspirate was done due to concern for relapse and the immunophenotype showed myeloid markers (CD33+, CD13+, CD15+), diagnostic of secondary AML. Cytogenetic analysis again showed t(16;21)(p11;q22). Though the AML was initially thought to be treatment-related, the persistent cytogenetic abnormality suggests that this represented a lineage switch from lymphoblastic to myeloid leukemia without biphenotypic features. He has responded well to treatment directed towards myeloid leukemia and is awaiting hematopoietic stem cell transplant. Recent genomic sequencing revealed the somatic FUS-ERG gene fusion and germline testing was negative for pathogenic alterations.
Conclusion: This patient was initially diagnosed with ALL and responded well to standard ALL therapy. Cytogenetic evaluation at diagnosis revealed a translocation that is generally considered to be myeloid-specific. Immunophenotype on initial diagnosis was not consistent with a biphenotypic picture, further supporting lineage switch of a primordial stem cell causing clonal escape of a myeloid clone. To our knowledge, the FUS-ERG translocation has only been seen in three prior pediatric patients with ALL. This represents the first reported case of lineage switch from ALL to AML with a FUS-ERG gene rearrangement.

Poster # 063

EX VIVO FUNCTIONAL TESTING DEMONSTRATES SENSITIVITY OF RAM SUBTYPE PEDIATRIC AML TO CD56 TARGETING

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Background: With increasing genomic data and characterization of the mutational landscape of pediatric blood cancers, new subtypes are emerging that present opportunities for the development of precision treatments. The RAM subtype was identified in pediatric patients with AML harboring the CBFA2T3-GLIS2 cryptic fusion, and has been associated with both high levels of CD56 expression and low event-free survival in patients.
Objectives: To evaluate the therapeutic potential of targeting CD56 in these patients, we utilized an ex vivo functional testing platform to investigate the effectiveness of an anti-CD56 antibody-drug conjugate (ADC) developed by the NCI (m906-PBD-ADC).
Design/Method: Cell lines or primary patient samples were treated with either the anti-CD56 ADC or a non-targeted control ADC for 72 hours. Readouts were performed using high-throughput flow cytometry to quantify cell death and distinguish between populations of cancerous and healthy immune cells.
Results: In CD56-expressing cell lines, we observed a dose-response with increased killing in the presence of increasing concentrations of m906-PBD-ADC. The strength of the dose response was correlated to the original expression level of CD56 in those cell lines. We next went on to test primary patient samples harboring the CBFA2T3-GLIS2 fusion. Total white blood cells from these relapsed patients were incubated with various doses of m906-PBD-ADC, and live leukemic blasts were quantified after 72 hours of treatment. We observed a dose response with increasing concentrations of the anti-CD56 ADC, and flow cytometry analysis demonstrated CD56-specific cytotoxicity. In contrast, healthy lymphocytes present in the patient samples showed no response to the ADC.
Conclusion: 320 Hatch DriveThis specific and potent response to m906-PBD-ADC suggests CD56 may provide an immediately actionable target in this subgroup of poor prognosis patients.

Poster # 064

TARGETING CASEIN KINASE II AS AN EFFECTIVE THERAPEUTIC STRATEGY IN MYELOID LEUKEMIA

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Background: Casein Kinase II (CK2) is emerging as a valuable therapeutic target in various cancers including leukemia. Over expression of CK2 is seen is one third of Acute Myeloid Leukemia (AML) cases without detectable high risk molecular alterations. In this subset, high expression of CK2 is strongly associated with poor outcome. Treatment with specific CK2 inhibitors lead to increased apoptosis in AML. Mechanism by which CK2 inhibitors cause AML cell death is not well understood.
Objectives: It is known that CK2 promotes leukemia cell growth and proliferation via several

mechanisms including direct phosphorylation of transcription factor, Ikaros. Ikaros encoded by IKZF1 is a tumor suppressor and has a well-established role in hematopoiesis. Here we report that targeted inhibition of CK2 potentiates Ikaros mediated regulation of anti-apoptotic genes such as BcL-xL resulting in increased apoptosis.
Design/Method: Myeloid leukemia cell lines such as U937, MOLM-13 and primary AML patient samples were used for in vitro experiments. CK2 inhibitors such as CX4945 was used.
Results: Treatment of AML cell lines and primary cells with CX4945 show increased cytotoxicity, apoptosis, cell cycle arrest and decreased colony formation. Treatment of murine xenografts of AML with CX4945 showed significant anti-tumor effect. Genome-wide binding studies using chromatin immunoprecipitation coupled with next-generation sequencing (ChIP-seq) demonstrated that treatment of AML cell line, U937 with CX4945 at IC50 concentration enhances binding affinity of Ikaros at the promoter regions of several target genes. Among the significantly affected genes (more than two fold change) are anti-apoptotic genes such as BCL2A1 (B Cell Lymphoma 2 related protein A1) and Bcl-xL (B Cell Lymphoma extra-Large). These findings were confirmed qChIP where CX4945 treated AML cells showed increased binding of Ikaros to the BCL2A1 and Bcl-xL promoters. Ikaros overexpression using lentiviral transduction results in reduced expression of BCL2A1 and Bcl-xL both at mRNA and protein level. Similar results were seen with silencing of CK2 using SiRNA as well as CX4945. Increased expression of BCL2A1 and Bcl-xL was noted after Ikaros silencing using SiRNA which did not revert with CX4945 treatment.
Conclusion: In conclusion, novel CK2 inhibitors show strong anti-leukemia effect in AML both in vitro and in vivo. Inhibition of CK2 enhances Ikaros-mediated repression of BCL2A1 and Bcl-xL genes resulting in increased apoptosis. These results establish the role of Ikaros and CK2 in regulation of apoptotic pathway in AML. Targeting CK2 is a promising therapeutic strategy in myeloid malignancies and needs further validation.

Poster # 065

IDENTIFYING TARGETABLE MARKERS AND PATHWAYS FOR ACUTE MYELOID LEUKEMIA STEM CELLS

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Background: Leukemia stem cells (LSCs), defined by their functional capacities of self-renewal and ability to give rise to bulk leukemia, represent a subpopulation in acute myeloid leukemia (AML) proposed to contribute to chemotherapy resistance and relapse. LSCs exist mainly within the CD34+/CD38- compartment and have unique intracellular signaling activities, including Signal Transducer and Activator of Transcription 3 (STAT3) activity. Yet, given the marked heterogeneity of AML, no universal surface marker or signaling property encompasses all LSCs, nor reliably distinguishes them from bulk blasts or normal hematopoietic stem cells.
Objectives: By enriching for AML LSCs in vivo, we sought to identify phenotypic properties that are specific to this subpopulation, and may be targetable with small molecules.
Design/Method: We studied cryopreserved bone marrow samples from AML patients enrolled

on the Children's Oncology Group (COG) protocol AAML0531. To reduce bulk blasts and enrich for chemoresistant LSCs, we treated NSGS mouse xenografts with low dose cytarabine or saline for 3-4 days, then harvested bone marrow 5 days later. To characterize AML samples at thaw and after LSC enrichment, we performed surface immunophenotyping, and using phospho-flow cytometry, we measured STAT3 signaling in response to stimulation with G-CSF, IL-6, and HS5 stromal cell-conditioned medium.
Results: Ten AML samples were injected into cohorts of 7-15 NSGS mice, and three of these samples engrafted. Mice treated with low dose cytarabine had decreased bone marrow disease, as compared to vehicle controls. LSC enrichment resulted in a statistically significant increase in CD34 ($p=0.02$), as well as a trend toward decreased CD38, and a relative increase in CLL1 and CD44, as compared to controls. One sample, which achieved on average >40% marrow engraftment among 15 mice, showed a marked increase in the CD34+/CD38- compartment for cytarabine-exposed mice versus vehicle ($p=0.004$). Furthermore, this LSC-enriched subpopulation had an increase in CD117 and CD123, and a decrease in CD90. Phospho-flow analysis revealed higher constitutive STAT3 activity, but decreased G-CSF and conditioned media-induced STAT3 signaling, for cytarabine-treated mice compared to vehicle controls.
Conclusion: Our results show that AML LSCs can be enriched in vivo, and are consistent with adult data suggesting they exist primarily in the CD34+/CD38- compartment. CD123 positivity and CD90 negativity may also be important aspects of their surface phenotype that are distinct from bulk blasts. Interestingly, our phospho-STAT3 findings are the opposite of what has been suggested by previous work in adult AML, and will be important to explore in future experiments.

Poster # 066

POTENTIAL SYNERGY OF EPIGENETIC MODIFIERS WITH TYROSINE KINASE INHIBITORS IN FLT3-ITD AML

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Background: FLT3-ITD acute myeloid leukemia (AML) is associated with a higher likelihood of therapy resistance and relapse. Treatment of FLT3-ITD AML with tyrosine kinase inhibitors (TKIs) as single agents has shown only transient success. Multiple mechanisms of drug resistance have been implicated in patients with FLT3-ITD AML including epigenetic alterations. A variety of epigenetic modifiers are currently being studied in pre-clinical trials for AML and include DOT1L, EZH2, protein arginine methyl-transferase (PRMT) inhibitors as well as agents targeting the bromodomain protein family. However, the use of these inhibitors in combination with TKIs in the treatment of FLT3-ITD AML has not been well studied.
Objectives: To evaluate for synergistic growth inhibition of combination therapy with epigenetic modifiers and TKIs on FLT3-ITD AML cell lines.
Design/Method: Epigenetic chemical probes, synthesized to a myriad of targets including histone acetylation, protein methylation and bromodomains, were used to identify agents with activity effecting the growth of human FLT3-ITD AML cell lines, MOLM-13 and MV4-11. Non-FLT3 AML cell line (OCI-AML3) served as a control. The epigenetic probes were then studied in combination with a TKI (Quizartinib- AC220) over a 72-hour period. Cell

proliferation was assessed using the CellTiter-Glo Luminescent cell viability assay. All analysis was performed via GraphPad Prism software. $p<0.05$ was considered statistically significant.
Results: From a total of 38 probes, fewer than half resulted in greater than 10% decrease in cell proliferation (10 for MOLM13, 9 for MV4-11 cell line). Interestingly, when used in combination with the TKI (AC220), most of the investigated probes resulted in significantly increased inhibition of proliferation as analyzed by t-test, compared to each agent alone. A 35-70% decrease in cell proliferation was noted with certain bromodomain inhibitors (GSK6853, L-Moses), lysine methyl-transferase inhibitors (Bay 598, Bay6035), EZH2/H1 inhibitors (GSK343, UNC1999) and PRMT inhibitors (MSO23, SGC707) when used in combination with low dose TKI compared to no or minimal inhibitory effect when these inhibitors were used without a TKI.
Conclusion: These preliminary findings support the need to confirm epigenetic target inhibition in FLT3-ITD leukemia and further investigate cellular mechanism of effects such as apoptosis, cell cycle and differentiation. Additionally the effect of combination therapy of TKI and epigenetic agent will need to be evaluated in patient samples as well as on FLT3-ITD leukemia initiating cells in vitro and in vivo.

Poster # 067

DRUG REPURPOSING OF MEFLOQUINE AND ITS EFFECT ON ACUTE LEUKEMIA CELL LINES VIA TARGETING AUTOPHAGY

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Background: Acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) of childhood are treated with conventional cytotoxic chemotherapy agents, but there is a need for additional therapies with less toxicity profiles. Drug repurposing allows us to test already approved and well tolerated drugs used in other diseases on the treatment of leukemia. Mefloquine (MQ) is an antimalarial drug that has been identified in previous studies as a potential agent against leukemia cells, which may target the cell's process of autophagy, a pro-survival mechanism in promoting cancer proliferation. In this study, we determine the in vitro efficacy and mechanism of MQ on acute leukemia cell lines.
Objectives: The objective is to observe cell proliferation, cell viability, apoptosis, and autophagy on AML and ALL cell lines. NB4 (promyeloblast), U937 (monoblast), Thp-1 (monoblast), and Jurkat (T-lymphoblast) cell lines were treated with MQ. We hypothesized that treatment of the cell lines with MQ will decrease cell proliferation and viability via targeting autophagy and inducing apoptosis.
Design/Method: The 3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide (MTT) colorimetric assay was used to assess cell proliferation, while the trypan blue (TB) assay was used to assess cell viability. Both included MQ treatment at 48 hours to obtain the average half maximal inhibitory concentration (IC50) values. Western blotting was performed on NB4 and U937 cell lines using apoptosis markers PARP-1 and Caspase-3, autophagy markers Atg7, Atg5, P62, and LC3B, and ER stress marker CHOP.
Results: Dose response curves for the MTT assays showed a sigmoidal distribution of the concentration of cells over time, indicating a decrease in the cells' metabolic activity when treated with MQ. The average IC50 results of the MTT/TB assays for each cell line at 48 hours

of treatment were 7uM/7uM for NB4, 8 uM/10uM for U937, 7uM/7uM for Jurkat, and 10uM/13uM for Thp-1. Western blotting showed PARP-1 and Atg5 cleavage, but no Caspase-3, Atg7, or P62 cleavage.
Conclusion: With MQ treatment, the MTT assay demonstrated a decrease in cell proliferation and the TB assay a decrease in cell viability, both with similar IC50, indicating a cytotoxic effect of mefloquine on leukemia cell lines. Western blotting revealed an early induction of ER stress and autophagy response, while caspase-3 cleavage not being observed indicated a pathway to cell death other than apoptosis. Our study showed that MQ is a potential drug that can be used in the treatment of leukemia, however further investigation will be done to evaluate the mechanism by which it targets autophagy.

Poster # 068

THE ROLE OF NUP214 IN MEDIATING THE INTERACTION BETWEEN CRM1 AND THE HOXA GENE LOCUS

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Background: Chromosomal translocations resulting from fusion of CALM and AF10 genes are recurrent abnormalities in 5-10% of T-cell acute lymphoblastic leukemias. CALM-AF10 leukemias are aggressive, difficult to treat, and associated with poor cure rates. These leukemias display elevated HOXA gene expression; however, the mechanism by which CALM-AF10 targets and activates the HOXA locus is unclear. Our lab discovered that CALM contains a Nuclear Export Signal (NES) that is required for CALM-AF10-mediated leukemogenesis. The NES mediates the interaction with the nuclear export receptor protein CRM1, which typically functions to translocate NES-bearing proteins from the nucleus to the cytoplasm through the nuclear pore (NUP). We have shown CRM1 can substitute for CALM through the synthesis of a CRM1-AF10 fusion protein that is leukemogenic. In traversing the nuclear pore, CRM1 interacts with NUP components, including NUP214. Additionally, NUP214 is involved in leukemogenic chromosomal translocations that also result in increased expression of HOXA genes. Together, these observations strongly suggest that NUP214 may mediate the ability of CRM1-AF10 to activate HOXA gene expression.
Objectives: To investigate NUP214 as a candidate protein that mediates the interaction between CRM1 and HOXA genes.
Design/Method: Using a CRM1-AF10 fusion construct in which the CRM1 NUP214 binding sites have been mutated to impair binding (CRM1NUP-AF10), we have performed HOXA7-luciferase reporter methylcellulose colony assays, and transplanted the fusion into mice. To evaluate the possibility that a NUP214-AF10 fusion can induce leukemia, we have started to synthesize a NUP214-AF10 fusion protein to be tested in vivo and in vitro.
Results: Both CRM1-AF10 and CRM1NUP-AF10 were able to activate the HOXA7-Luciferase reporter assay. However, CRM1NUP-AF10 was unable to transform hematopoietic stem cell precursors in in vitro colony forming assays, and mice transplanted with CRM1NUP-AF10 in vivo did not develop leukemia. We are in the process of synthesizing a NUP214-AF10 construct for testing in vitro and in vivo.
Conclusion: Investigating the mechanism by which CRM1 interacts with the HOXA locus will

further elucidate a role for CRM1 as a transcriptional activator of leukemogenic HOXA genes. Here, we have demonstrated the importance of the interaction between CRM1 and NUP214 by showing abrogated leukemia development in mice transplanted with a mutated CRM1-AF10 fusion wherein NUP214 can no longer bind to CRM1. Our finding that mutation of NUP214 binding sites on CRM1 interferes with leukemia development warrants further exploration of NUPs as candidate proteins for HOXA gene activation, and may establish a CRM1/NUP interaction as a novel therapeutic target.

Poster # 069

A ROLE FOR THE SIX1 HOMEOBOX GENE IN CALM-AF10 LEUKEMOGENESIS

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Background: The CALM-AF10 translocation is detected in 5-10% of pediatric and adult T-cell acute lymphoblastic leukemias (T-ALLs), and in some acute myeloid leukemias (AMLs). CALM-AF10 leukemias are characterized by high expression of proleukemic HOXA genes. Since HOXA genes are difficult to target, we hypothesized that the identification of other, non-HOXA CALM-AF10 effector genes could potentially yield novel therapeutic targets. To discover novel CALM-AF10-regulated genes, we took advantage of our prior observation that the nuclear export factor CRM1/XPO1 tethers CALM-AF10 to HOXA genes by interacting with a nuclear export signal (NES) in CALM. We used RNA-sequencing and microarray to determine that, similar to HOXA genes, the expression of SIX1, a homeobox gene associated with embryogenesis, is increased in CALM-AF10 leukemias and decreased in response to the CRM1 inhibitor, Leptomycin B (LMB).
Objectives: To evaluate the role of SIX1 in CALM-AF10 leukemias.
Design/Method: RT-qPCR and Chromatin Immunoprecipitation were performed using both bone marrow progenitors and murine embryonic fibroblasts (MEFs) transduced with CALM-AF10 or an empty vector, with and without LMB. The ability of SIX1 to enhance self-renewal of hematopoietic progenitors was examined by measuring the colony-forming ability of transduced fetal liver progenitors upon serial replating in methylcellulose. SIX1 expression was silenced in Human Embryonic Kidney 293 (HEK293) cells using CRISPR-Cas9.
Results: Similar to HOXA genes, RT-qPCR confirmed overexpression of SIX1 in both CALM-AF10 transduced MEFs and CALM-AF10 leukemias, and decreased SIX1 expression was observed in the presence of LMB. Furthermore, ChIP analysis showed that CALM-AF10 binds to the SIX1 gene locus. Overexpression of SIX1 in fetal liver cells was sufficient to increase the self-renewal potential of these colony-forming progenitors. SIX1 was successfully knocked out in HEK293 cells, but this did not result in altered HEK293 proliferation.
Conclusion: The SIX1 homeobox gene is highly expressed during embryogenesis with expression normally silenced post-embryogenesis. Increased SIX1 expression has been reported in numerous solid tumors; but SIX1 involvement in leukemogenesis is uncertain. We have now determined that SIX1 is upregulated in the presence of CALM-AF10, and that SIX1 increases the self-renewal potential of hematopoietic progenitors. These observations indicate that SIX1 may play a pathogenic role in leukemogenesis, and that SIX1 could be a novel therapeutic target

in CALM-AF10 leukemias. The absence of an effect of SIX1 knockout on HEK293 proliferation suggests that SIX1 is not essential for cell survival and supports the notion that SIX1 inhibition could be effective in impairing CALM-AF10 leukemia cell proliferation.

Poster # 070

REGULATION OF CERAMIDE METABOLISM BY IKAROS IN HIGH RISK B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Ikaros, a DNA binding protein, which is inactivated in 80% of high-risk B-cell acute lymphoblastic leukemia (B-ALL), acts as a tumor suppressor via transcriptional regulation of its target genes. The mechanism through which Ikaros exerts its tumor suppressor function is largely unknown. The metabolism of ceramide is deregulated in leukemia. Deregulation of ceramide metabolism is associated with increased cellular proliferation and drug resistance. Previous results by our team suggest that Ikaros might affect ceramide metabolism via transcriptional control of genes that regulate this pathway.
Objectives: The aim of this study is to analyze the effect of Ikaros on the expression of genes that regulate the metabolism of ceramide.
Design/Method: Next-generation sequencing (ChIP-seq) and quantitative chromatin immunoprecipitation (qChIP) were performed to evaluate Ikaros binding to the promoter of genes that regulate ceramide metabolism in primary B-ALL and human B-ALL cell lines. Ikaros overexpression and knock-down was achieved by retroviral transduction and shRNA respectively. qPCR and Western blot were used to evaluate expression of Ikaros-regulated genes.
Results: Global genomic binding studies coupled with ChIP-seq shows that Ikaros binds to the promoters of several genes that are critical for ceramide metabolism in primary B-ALL. Ikaros strongly binds to the promoter of acid ceramidase ASAH1, which is overexpressed in leukemia and acts as an oncogene. Ikaros binding was validated using the qChIP assay. The effect of Ikaros on expression of ASAH1 and other genes was analyzed using gain-of-function and loss-of function experiments. Ikaros overexpression significantly suppresses the expression of ASAH1, while Ikaros knockdown with shRNA increases expression of ASAH1 in B-ALL. Inhibition of an oncogenic CK2 kinase, increases Ikaros binding in the promoter region of ASAH1, and suppresses its expression. Ikaros knockdown blocks the effect of CK2 inhibition on repression of ASAH1. Results show that CK2 inhibition represses ASAH1 by enhancing Ikaros binding to the ASAH1 promoter.
Conclusion: Ceramide metabolism in B-ALL is regulated by the CK2-Ikaros signaling axis. Ikaros directly suppresses expression of acid ceramidase ASAH1. Results reveal a novel mechanisms through which Ikaros regulates cellular proliferation and drug resistance of B-cell acute lymphoblastic leukemia.

Poster # 071

FOUR NOVEL NUDT15 HAPLOTYPES RELEVANT FOR TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

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Background: Genetic variants in TPMT and NUDT15 have been associated with thiopurine-related myelotoxicity requiring dose adjustment during treatment of acute lymphoblastic leukemia (ALL). The frequency of variants in these genes varies across different populations and comprehensive, accurate genotyping, with a short turnaround time (TAT) is critical to adjust thiopurine dosing.
Objectives: We aim to establish a novel targeted next generation sequencing (NGS) methodology to comprehensively assay TPMT and NUDT15 haplotypes with a TAT that meets thiopurine dose optimization window.
Design/Method: Eight genomic DNA samples from the 1000 Genomes Project were selected for use in assay validation. Sequencing libraries were prepared using a custom AmpliSeq assay and NGS was performed on the Illumina iSeq™ system. Sequence reads were aligned to the human reference genome (GRCh38). Haplotypes were determined based on overlapping read alignment. Known polymorphisms were further confirmed with real-time qPCR (RT-PCR).
Results: All samples were prepared and sequenced within three days and showed 100% concordance for sequence variants with both the 1000 Genomes data and the confirming RT-PCR in TPMT and NUDT15. Deep NGS allowed the assignment of variants into haplotypes. Interestingly, in addition to identifying two samples with complex heterozygous NUDT15 haplotypes (NUDT15*2/*3) we found six samples with four previously undescribed NUDT15 haplotypes. These included four heterozygous amino acid changes: p.Val93Ile, p.Pro12Leu, p.Gly13Ala, and p.Lys33Asn, two of which protein modeling has predicted to be deleterious to enzyme activity (p.Pro12Leu and p.Lys33Asn, minor allele frequency= 0.01 to 0.20, 0.003 to 0.08 respectively).
Conclusion: Genotyping of TPMT and NUDT15 is recognized as a critical test to assess the risk of thiopurine associated adverse reactions, particularly in patients with ALL. Currently, CPIC® and PharmVar have annotated 41 TPMT and 19 NUDT15 haplotypes, including many with reduced function. Our NGS assay accurately captured all regions containing variants known to affect enzyme activity and identified all known TPMT and NUDT15 haplotypes. Notably, we were able to identify four novel NUDT15 haplotypes which may affect enzyme activity. These results support the use of an NGS testing methodology for detection of known and novel TPMT and NUDT15 polymorphisms. This analysis approach is particularly important for genes in which many functional haplotypes have not yet been identified, to avoid enzyme activity misclassification. Importantly, the assay can be performed in a time frame that enables dose adjustment prior to or during treatment of ALL. Support for this research was provided by RPRD Diagnostics, LLC.

Poster # 072

DELINEATING THE ROLE OF OBESITY IN IMMUNOTHERAPY EFFICACY IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Even though there have been vast improvements in the treatment of pediatric ALL, emerging epidemiologic studies have shown that children that are obese at diagnosis have poorer overall survival and higher relapse rates. Despite these observations, the mechanisms of decreased therapeutic responses in obese individuals are not well understood. There is growing interest in understanding if altered immunity in obese patients contributes to unfavorable prognosis and if this state will adversely impact the efficacy of immunotherapies. Chronic inflammation and defective T-cell function are hallmarks of obese mice and humans; therefore, we hypothesize that T-cell based immunotherapies will be less effective at treating leukemia in patients with excess adiposity.
Objectives: 1) Determine how obesity impacts T-cell function
Design/Method: An in vitro model of obesity was developed using a protocol that allowed bone marrow-derived stromal cells to be terminally differentiated into adipocytes. This protocol results in the generation of adipocytes which secrete an array of pro-inflammatory cytokines and chemokines including tumor necrosis factor-alpha (TNF-α) and macrophage inflammatory protein-1 alpha (MIP-1α). For in vitro experiments, both human and murine isolated T-cells were stimulated for 72 hours (via PMA/Ionomycin) in the presence of conditioned media (either stromal cell-conditioned or adipocyte-conditioned media). This was followed by flow cytometric analysis to assess T-cell activation through staining of the surface-adhesion molecule CD44 and intracellular cytokines (TNF-α/IFN-γ). Ex vivo, experiments were conducted utilizing T-cells obtained from diet-induced obesity murine models. Furthermore, we assessed how obesity impacted T-cell activation in patients with and without leukemia using samples provided through the CHOA Leukemia and Lymphoma Biorepository and the Children's Clinical and Translational Discover Core, respectively.
Results: Murine and human in vitro T-cell activation studies revealed that adipocyte-secreted factors potently up-regulated CD44 surface expression on T-cells. Surprisingly, adipocyte but not stromal cell secreted factors significantly suppressed TNF-α and IFN-γ production in T-cells. Similarly, the cytokine production was compromised in T-cells isolated from obese mice, whereas, robust responses were observed if lymphocytes were activated from lean mice.
Conclusion: Our data suggests that adipocyte-secreted factors inhibit T-cell function by attenuating cytokine production. Given that T-cell based immunotherapies require robust T-cell mediated immunity to eradicate leukemia, our findings highlight a potential obstacle in using this form of immunotherapy in patients who are overweight or obese.

Poster # 073

IDENTIFYING NOVEL CRM1-INTERACTING PROTEINS IN CALM-AF10 LEUKEMOGENESIS BY PROXIMITY BASED LABELING

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Background: While substantial progress has been made in the treatment of many pediatric leukemias, certain leukemias still have a poor prognosis. CALM-AF10 leukemias, which account for ~10% of childhood T-ALL (T-cell acute lymphoblastic leukemia) and a subset of AML (acute myeloid leukemia), are particularly difficult to treat. Our laboratory discovered that the CALM protein contains a nuclear export signal (NES) that is critical for CALM-AF10-mediated leukemogenesis. The NES interacts with the Chromosomal Maintenance 1 (CRM1) nuclear export receptor. Unexpectedly, we determined that CRM1 is essential for the transcriptional activation of HOXA genes by CALM-AF10. How CRM1 interacts with HOXA gene regulatory regions is not presently understood, since CRM1 does not contain a recognized DNA binding domain. To identify proteins that mediate the interaction between CRM1 and DNA, we are using a proximity-based labeling approach with the second generation biotin ligase, BioID2, fused to CALM-AF10. Upon addition of biotin, BioID2 will biotinylate nearby proteins, and biotinylated proteins can be identified using mass spectrometry.
Objectives: To identify novel proteins that interact with CRM1.
Design/Method: We created expression plasmids in which BioID2 is cloned in-frame with HA-tagged CALM-AF10 and a CALM-AF10 mutant unable to bind CRM1, (CALM(NES*)-AF10). To ensure that BioID2 does not sterically interfere with CALM-AF10 activity, we used luciferase reporter and colony forming assays, and confocal microscopy. Human Embryonic Kidney 293 (HEK293) cells were transiently transfected with expression plasmids, followed by incubation with biotin. Purified biotinylated proteins will be analyzed using mass spectrometry using the Fusion Orbitrap/Peptide Spectrum Masses (PSM) method.
Results: CALM-AF10 and CALM(NES*)-AF10 fusion plasmids containing BioID2 were synthesized and confirmed via Sanger sequencing. Western blot demonstrated expression of fusion proteins containing BioID2. Similar to CALM-AF10, BioID2-CALM-AF10 activates the HOXA7 luciferase reporter 6-7-fold compared to the empty vector, transforms hematopoietic progenitor cells (HPCs) upon serial replating, and localizes primarily to the cytoplasm. The expression of biotinylated proteins in transfected HEK293 cells following biotin exposure was confirmed by Western Blot. Purified biotinylated protein samples have been submitted to mass spectrometry for analysis.
Conclusion: The presence of the BioID2 moiety does not interfere with CALM-AF10 activity, as evidenced by similar: 1) enhancement of HOXA7 promoter activity; 2) immortalization of HPCs; and 3) subcellular localization. Furthermore, the BioID2 ligase is active when fused to CALM-AF10. Based on these findings, biotinylated samples have been submitted to the Mass Spectrometry Core and further results will be presented at the conference.

Poster # 074

VINCRISTINE INDUCES APOPTOSIS BY INHIBITING CELLULAR AND EXOSOMAL MIR181-a IN PEDIATRIC ACUTE LYMPHOCYTIC LEUKEMIA

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Background: Vincristine is a standard chemotherapeutic agent for the treatment of pediatric acute lymphocytic leukemia (P-ALL). Mechanistically, the drug induces apoptosis by blocking

tubulin dimers from polymerizing to form microtubules. The role of vincristine on exosomal micro-RNA expression and functional regulation is not yet investigated. Elevated levels of miR-181a in circulating exosomes (nanoparticles) has been shown to lead to cancer progression including ALL. We have previously shown that leukemic exosomes induce leukemia cell proliferation via upregulated miR-181a and silencing of exosomal miR-181a reverses this effect.
Objectives: To investigate the functional role of vincristine on cellular and exosomal miR-181a in ALL.
Design/Method: JM1 and SUP-B15 leukemic cell lines were treated in vitro with vincristine (0.1 to 4.0 μM) in exo-free medium and apoptosis was measured by MTS assay. Total cellular RNA was isolated and cDNA prepared for miR-181a analysis. Expression of miR-181a was analyzed by q-PCR. Exosomes were isolated by ultracentrifugation from conditioned medium as well as from patient serum at time of ALL new diagnosis. Total exosomal RNA was isolated from exosomes (Exo-RNA) by Trizol method. cDNA was prepared with the miScript II RT kit.
Results: Vincristine promotes apoptosis in JM1 SUP-B15 cells in a dose-dependent manner in leukemia cell lines (JM1, SUP-B15). Both cellular and exosomal miR-181a in ALL was down-regulated by vincristine (leukemic cell lines and patient serum exosomes). These findings demonstrate that cellular miR-181a down regulation is stable and carried forward to exosomes, confirming the concept that exosomes are the fingerprint of the parent cells.
Conclusion: Our data suggest the novel finding that vincristine treatment may induce apoptosis by suppressing miR-181a at a cellular and exosomal level in pediatric ALL.

Poster # 101

HODGKIN LYMPHOMA IN CHILDREN UNDER FIVE YEARS OF AGE IN CENTRAL CALIFORNIA

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Background: Hodgkin lymphoma (HL) has a very distinct bimodal age-incidence curve of presentation. The first peak of the curve is in the adolescent and young adult period and the second around 60 years of age. HL accounts for approximately 7 percent of childhood and adolescent cancers in the United States. The prognosis for most patients with Hodgkin Lymphoma is good, with 5 year event free survival > 80%. Hodgkin Lymphoma in children less than 5 years of age is rare. In the US, its incidence has been reported as 1.7% for the intermediate/high risk and higher for patient with low risk (26% in patients < 10 years of age). In the developing country, the incidence appears to be as high as 22%.
Objectives: To study the clinical characteristics and outcomes of children less than 5 years of age with HL at a single institution in central California.
Design/Method: Retrospective Review after IRB approval, a retrospective review of HL patients diagnosed and treated at Valley Children's Hospital from 1999 to 2018 was performed. We reviewed the stage at diagnosis, histopathology, treatment and outcomes.
Results: Over the study period, 140 patients were diagnosed with HL at Valley Children's Hospital. This corresponded to an average of 10% of the total cancer diagnoses during that timeframe. We found 7 cases of HL in children less than 5 years of age. This was ~ 5% of all HL

patients. Patients' age ranged from 2 to 4 years. The male to female ratio was 6:1. One patient was Caucasian and 6 were Hispanic. The most common histology was nodular sclerosis (n=4) and mixed cellularity (n=3). Four patients had low (1A and 2A) risk and 3 patients had high risk disease (3A with bulky disease, 4A and 4B). All patients received treatment with ABVE or ABVE-PC regimen for low or high risk respectively. All 7 patients were rapid responders. The 3 children with high risk HL received radiation therapy. All 7 patients are alive and without evidence of disease.
Conclusion: At our institution the incidence of HL in children less than 5 years of age is ~ 2% for patients with high risk disease and ~ 8% for patients with low risk disease. Even though the numbers are low, it appears that they are more likely to have low stage disease without bulky disease or B symptoms. In general, the outcome of HL in children less than 5 years is excellent.

Poster # 102

PRE-THERAPY INFLAMMATORY PLASMA PROTEINS AND CLINICAL OUTCOMES IN PEDIATRIC HODGKIN LYMPHOMA

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Background: The immune microenvironment that characterizes Hodgkin lymphoma (HL) is known to play a significant role in disease pathogenesis. Hodgkin Reed-Sternberg (RS) cells distinguish HL from other types of cancer and induce an inflammatory infiltration, which in turn promote survival of RS cells, fibrosis, and suppression of cell-mediated immunity. The immune infiltrate contributes to pathogenesis and prognosis of adult HL. However, the roles of immune cell interactions in pediatric HL is largely undefined.
Objectives: Our objective was to investigate whether inflammatory mediators detectable in plasma of children with HL could identify biomarkers associated with disease (risk) and outcomes (therapy response and relapse).
Design/Method: Plasma samples were obtained from subjects with pediatric HL prior to initiation of therapy and from healthy pediatric controls. Plasma concentrations of 144 cytokines and chemokines were measured with the Luminex platform (Milliplex MAP kits, EMD Millipore). Associations between plasma protein concentration and disease characteristics (risk, response to therapy, relapse) were determined by class comparison analysis using a multivariate permutation test with a confidence level of false discovery rate assessment at 80 percent and maximum allowed proportion of false-positive proteins at 0.1.
Results: Fifty-six patients with HL (mean age: 13 years, range 3-18) and 56 age-matched controls were included in the analysis. The cytokine profile of subjects with HL (n=56) was quite distinct from controls (n=56): subjects with HL had a significantly higher concentration of 35 cytokines, including TARC (18.7-fold, p<1e-07), MDC (5.3-fold, p<1e-07), IL-6 (3.7-fold, p<1e-07), IL-10 (3.7-fold, p=7e-06), and IL-9 (2.5-fold, p=2e-04). Compared to subjects with low/intermediate-risk HL (n=43), subjects with high-risk HL (n=13) had a significantly higher concentration of 12 cytokines, including sTNFR1 (1.8-fold, p=1e-06), IL-10 (7.9-fold, p=2e-05), and TNF-α (2-fold, p=3e-04). Evaluating differences in pre-therapy plasma and response to

therapy, slow early responders (SER) (n=10) had a significantly higher concentration of IL-28a (5.9-fold, p=5e-04) and IL-1RA (6.0-fold, p=8e-04) than rapid early responders (RER) (n=46). Relapsed patients (n=7) had a significantly higher concentration of IL-6 than non-relapsed patients (n=49) (7.3-fold, p=2e-04).
Conclusion: This pilot series demonstrates that pre-therapy plasma proteome of pediatric patients with HL is distinct compared to healthy controls and may correlate with disease characteristics and outcomes. Once validated in a larger cohort, these biological predictors could be incorporated into biologically based risk stratification and individualized treatment strategies, ultimately optimizing outcomes and minimizing toxicities for children with HL.

Poster # 103

PROGNOSTIC IMPACT OF PATHOLOGICAL SUBTYPES IN CLASSIC HODGKIN'S LYMPHOMA; A COMPREHENSIVE ANALYSIS

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Background: Histologic subtypes of classical Hodgkin lymphoma (cHL) (e.g., nodular sclerosis (NS), mixed cellularity (MC), lymphocyte rich, lymphocyte depleted, and not otherwise specified (NOS)) are epidemiologically and prognostically distinctive. Lymphocyte-Depleted Classical Hodgkin Lymphoma (LDHL) is the rarest and most aggressive subtype of classical Hodgkin lymphoma that is generally seen in young adults. Lymphocyte-Depleted Classical Hodgkin Lymphoma is a vanishing category of classical Hodgkin lymphoma (CHL); many cases previously placed in this category are now recognized as diffuse large B-cell lymphoma (DLBCL), anaplastic large-cell lymphoma (ALCL), or nodular sclerosis CHL with lymphocyte depletion. In addition, the recent recognition of high grade B-cell lymphomas intermediate between DLBCL and CHL (grey-zone lymphomas) raises the question of whether LDHL exists at all as a category of CHL.
Objectives: to report survival of different pathological subtypes of hodgkin's lymphoma
Design/Method: We analyzed histology-specific classic HL patients charts at CCHE, all diagnosed by lymph node biopsy, and their outcome (Overall survival, Disease free survival) .They were all given the same protocol with a backbone of ABVD (Adriamycin- Bleomycin – Vinblastin - Dacarbazine) and involved field radiation therapy. Multivariate analysis to emphasize pathological subtypes of classic HL and their impact on outcome was performed.
Results: Classic HL cases in CCHE were 1197 patients enrolled in the study from August 2007 till end of 2017. Children with mixed cellularity (37.2%) had an overall survival of 95.68% while children with nodular sclerosis (52.7%) had an overall survival of 96.43%, lymphocyte rich children were (2.1%) had 96.15% overall survival, for children with pathology NOS (1.2%) overall survival was 87.5%, , while Lymphocyte Depleted pathology was the least in number (0.8%) had the worst overall survival 68.57%, and also the least Event free survival 48%. While the other subtypes had an event free survival ranged between 84-87%.
Conclusion: The pathological subtype lymphocytic depleted cHL although is difficult to diagnose, it had the least OS and EFS and must be treated differently than the rest of cHL subtypes with a more intensive therapy to increase its survival.

Poster # 104

PREDICTION OF OUTCOME USING PRETREATMENT RISK FACTORS AND PET SCAN IN PEDIATRIC HODGKIN LYMPHOMA

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Background: During the last decades, the prognosis of Hodgkin lymphoma (HL) has been improved significantly with the introduction of effective chemotherapy and the implementation of risk-adapted treatment approaches. Identification of reliable risk factors is crucial to guide treatment throughout the disease.
Objectives: We aimed to identify independent predictors of event-free survival (EFS) in pediatric/ adolescent HL using clinical data known at diagnosis and treated with the ABVD regimen at our hospital.
Design/Method: This is a retrospective study done at Children's cancer hospital Egypt from July 2007 to December 2017. ALL Patients with Classical HL were enrolled in the analysis. The chemotherapy backbone was ABVD +/- RTH. Data analysis included all pretreatment Demographics, clinicopathological characteristics, and Laboratory findings. PET scan was performed at baseline and after two cycles of chemotherapy. Treatment was not changed according to the results of the interim scan.
Results: A total of 737 patients were eligible for analysis.The Five-years OS 94.9% and the EFS 87.8% in these patients. Pretreatment Significant univariate predictive factors for the EFS were: Age<9.5 (HR 0.421; p = 0.002),, ESR (HR 0.421; p = 0.002), Hemoglobin <10.5 (HR 1.373; p = 0.014), TLC >11,000 (HR 0.368; p = 0.000), Stage IV(p = 0.000) and treatment groups (HR 0.180; p = 0.000). Although the pathological subtypes has a diverse EFS;NS: 86.6% MS: 92.9% Lymphocyte rich: 87.5% and Lymphocyte depleted: 41.7%, Histology has shown to be a powerful independent predictor of outcome (p = 0.000).In the multiple regression model, NS Histology and stage remained strong predictive factors with a p-value of 0.011and 0.026 respectively, In addition to the significance of the Albumin level (HR 0.047, p= 0.011). The interim PET, as well as RTH, were highly significant on both univariate (p= 0.000 and 0.0002 respectively) as well as multivariate analysis (p= 0.001and 0.000 respectively).
Conclusion: Age; stage IV disease; white blood cell count, and hemoglobin level are independent predictors of survival that can significantly impact survival. Optimizing initial therapy may improve overall EFS for these patients. Although CHL pathology is a significant independent predictor of EFS, its subtypes have different EFS and OS, which should be translated into changes in the treatment approach.

Poster # 105

CAN CHILDHOOD HODGKIN INTERNATIONAL PROGNOSTIC SCORE MITIGATE PET USE IN PEDIATRIC HODGKIN LYMPHOMA?

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Background: Although 'interim' positron emission tomography (I-PET) may inform therapeutic decisions, Risk stratification at diagnosis allows earlier and potentially better modification during treatment of HL.
Objectives: In this study, we aimed to validate Childhood Hodgkin International Prognostic Score (CHIPS) proposed by the COG in predicting the prognosis of HL at our hospital and its prognostic correlation with I-PET.
Design/Method: This is a retrospective, single-center study where a total of 1140 patients with newly diagnosed Classical Hodgkin lymphoma were enrolled. PET scan was performed at baseline and after two cycles of chemotherapy (ABVD). Treatment was not changed according to the results of the interim scan. Stage 4 disease, large mediastinal mass, albumin (<3.5), and fever were each assigned one point in the CHIPS. Log-rank testing was used to compare EFS for each CHIPS (0–4). A secondary analysis to detect EFS in relation to IPET was done.
Results: Only 737 patients were eligible for analysis of both IPET and CHIPS scoring. The 5-year EFS was 95% for patients with CHIPS=0, 94% for patients with CHIPS=1, 84.3% for patients with CHIPS=2, 82.4% for patients with CHIPS=3 and 70% for CHIPS=4 (P-value 0.001).The 5-year OS was 97.4% for patients with CHIPS=0, 97.9% for patients with CHIPS=1, 93.1% for patients with CHIPS=2, 94.7% for patients with CHIPS=3 and 85.6% for CHIPS=4 (P-value 0.039).Slow early responders as detected by PET have 5-years EFS 73.8%, in comparison, those with evidence of rapid early response by PET had 5-year EFS of 91.3 %. Among this better risk patients, CHIPS further classified patients; EFS 96.4% of patients with CHIPS 0 or 1 versus 85.8% for those with CHIPS 2, 3 or 4 who had an adverse outcome, even in the setting of response by PET (P<0.001).
Conclusion: CHIPS is a useful tool for predicting risk in patients with HL that may help to tailor therapy to risk factors known early at diagnosis. The benefit of using CHIPS versus early response PET scan suggests the feasibility of eliminating the costly PET scans, especially in developing nations.

Poster # 106

PHASE 1/2 STUDY: FRONTLINE BRENTUXIMAB VEDOTIN + AVD IN PEDIATRIC PTS WITH ADVANCED HODGKIN LYMPHOMA

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Background: Pediatric patients (pts) with classical Hodgkin Lymphoma (cHL) have better responses to therapy than adults; however, combination regimens and radiotherapy can result in significant morbidity.
Objectives: Phase 1 primary endpoints of the ongoing phase 1/2 study (NCT02979522) in pediatric pts with advanced-stage, newly-diagnosed cHL were to determine the recommended phase 2 dose (RP2D) of brentuximab vedotin combined with doxorubicin, vinblastine, and dacarbazine (A+AVD), and to assess dose-limiting toxicities (DLTs), adverse events (AEs), and

serious AEs (SAEs). Pharmacokinetics (PK) was a secondary endpoint.
Design/Method: Eligible pts were aged 5 to <18 years, with treatment-naïve stage III/IV cHL, Lansky Play/Karnofsky Performance Status ≥50, and bidimensional measurable disease by radiography. Pts received ≤6 28-day cycles of 48mg/m2 brentuximab vedotin with AVD on days 1 and 15 of each cycle. RP2D was confirmed by a modified 3+3 design; ≥3 pts were monitored for DLTs during the evaluation period (cycle 1+28 days; from the first dose through study day 56), if 0/1 DLTs were observed, ≥3 additional pts were enrolled and monitored for DLTs. Reduced dose brentuximab vedotin (36mg/m2) was available if >1 DLT was observed. Toxicity was evaluated per NCI CTCAE, v4.03. Granulocyte-colony stimulating factor (G-CSF) use was not permitted during DLT-evaluation.
Results: Eight pts were enrolled (phase 1): male, 50%; aged 6–17 years; stage III/IV, n=5/3; two/no extranodal sites, n=4/4. Two pts were DLT-unevaluable due to G-CSF administration. Six DLT-evaluable pts completed the 56-day DLT evaluation period with no DLTs reported. The brentuximab vedotin RP2D was 48mg/m2. During DLT-evaluation all six pts reported ≥1 treatment-emergent, treatment-related AE. Six pts experienced treatment-related Grade (G) 4 AEs (neutropenia or neutrophil count decreased [6 pts; n=8 events], and white blood cell count [WBC] decreased [3 pts, n=3 events]); one SAE was reported (treatment-related G3 febrile neutropenia, duration 2 days). G≥3 treatment-related AEs in two DLT-unevaluable pts were: G4 neutropenia (n=3), G3 neutrophil count decreased (n=4), and G3 WBC decreased (n=1). Dose delays during DLT-evaluation were due to neutrophil count decreased or neutropenia (5 pts, n=8 events leading to delay), stomatitis (n=1), and WBC decreased (n=1). All phase 1 pts receiving the RP2D completed 6 cycles of A+AVD. PK concentrations were within target range and consistent with prior brentuximab vedotin studies (NCT01712490, NCT01492088).
Conclusion: Safety, tolerability, and PK profiles of brentuximab vedotin were as expected, and the R2PD was confirmed as 48mg/m2 in combination with AVD. Phase 2 will enroll 55 patients at the RP2D.

Poster # 107

PHASE 1/2 STUDY DESIGN: FRONTLINE BRENTUXIMAB VEDOTIN + AVD IN PEDIATRIC ADVANCED HODGKIN LYMPHOMA

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Background: Pediatric patients with classical Hodgkin lymphoma (cHL) have improved outcomes compared with adult patients. However, many chemotherapy regimens used in treatment result in significant morbidity, including secondary malignancies, cardiovascular disease, and infections. Furthermore, serious sequelae of radiation and alkylating chemotherapy are pronounced in younger patients, in whom growth and development are particularly active when therapy is administered. Brentuximab vedotin has been assessed in pediatric patients with relapsed/refractory cHL [1], but has not yet been studied in newly diagnosed pediatric patients. The current study (Clinicaltrials.gov NCT02979522) is the first to assess brentuximab vedotin combined with multi-agent chemotherapy in frontline treatment of cHL in a pediatric population.
Objectives: This phase 1/2, open-label, multicenter study assesses the feasibility of brentuximab

vedotin combined with doxorubicin, vinblastine and dacarbazine (A+AVD) in pediatric patients with advanced-stage, newly-diagnosed, CD30+ cHL. Phase 1 primary objectives were to assess safety and tolerability, and determine the recommended phase 2 dose (RP2D). Phase 2 primary objectives include overall, complete, and partial response rates, the proportion of patients who are positron emission tomography (PET)-negative after 2 cycles, and the proportion of patients who complete 6 cycles of therapy at the RP2D. Secondary phase 2 objectives include evaluation of progression-free, event-free, and overall survival (PFS, EFS, OS), duration of response, immunogenicity, pharmacokinetics, safety, and immune reconstitution.
Design/Method: Eligible patients are 5 to <18 years of age, with stage III or IV cHL, Lansky Play/Karnofsky Performance Status ≥50, and bidimensional measurable disease by radiography.Following determination of the RP2D (phase 1), additional patients will be enrolled for a total of 55 patients at the RP2D, with A+AVD administered on days 1 and 15 of each 28-day cycle for up to 6 cycles.Response to treatment includes assessment by computed tomography, magnetic resonance imaging, and PET after cycle 2 day 25 and between 3–7 weeks after last dose (end of treatment). Follow-up for PFS and OS will be performed every 12 weeks for 12 months, then every 24 weeks thereafter for a maximum of 2 years from date of last patient enrolled.
Results: The RP2D of brentuximab vedotin in combination with AVD was confirmed as 48 mg/m2 [2].
Conclusion: Phase 2 is currently open for enrollment in the USA, Italy, Singapore, Taiwan, Hong Kong, Japan, and Brazil. A total of 55 patients will be enrolled, of which 21 patients were enrolled as of 02Jan2019.1. Locatelli, Lancet Haematol, 20182. Franklin, ASH, 2018

Poster # 108

GEMCITABINE AND VINORELBINE 3RD LINE CHEMOTHERAPY FOR PRIMARY REFRACTORY/RELAPSING HODGKIN LYMPHOMA

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Background: Hodgkin lymphoma (HL) is one of the most curable forms of childhood cancer,with estimated 5year survival rates exceeding 98%, yet long-term overall survival continues to decline, from both delayed deaths and late effects of therapy.For patients with relapsed or primary refractory disease,the potential for cure remains approximately 50% with current therapies including high-dose chemotherapy and (AHSCT).Clinical risk factors including first remission <12 months, poor performance status, chemoresistance, extranodal disease at relapse and receipt of regimens other than ABVD/ABVD-like for first line therapy predict reduced survival post AHSCT. Almost every class of chemotherapy drug has been shown to have some efficacy in HL, with the possible exception of the antimetabolite drugs such as 5-fluorouracil.
Objectives: to report the response rate and toxicity profile of the 3rd line chemotherapy Gemcitabine/Vinorelbine in primary refractory/relapsing HL.
Design/Method: A retrospective analysis including all patients who received Gemcitabine/Vinorelbine as 3rd line salvage chemotherapy following ABVD +/- radiotherapy as

1st line, and ICE as 2nd lines chemotherapy diagnosed and treated at the Children Cancer Hospital Egypt during 10 years period.
Results: Between July 2007 and end of December 2017 116 patients relapsed or had a progressive disease.Ninety-eight patients received ICE as second line chemotherapy. Thirty patients out of 116 failed second line and received third line.,4 patients were excluded from analysis as they received other type of chemotherapy (Navelbine/Ifosfamide), while 32 patients received Gemcitabine/Vinorelbine and were included in our study. The most common pathologic subtype was nodular sclerosis (62.5%), followed by mixed cellularity (21.9%).According to Ann Arbor staging, 1 patient (3.1%) was stage I, while 6 (18.7%) were stage II, 10 stage III (31.3%), and 15 (46.9%) stage IV.Chemotherapy cycles varied from 1 to 6 with a mean of 3 cycles. Thirteen patients (40.6%) were responders to Gemzar/Navelbine and underwent hematopoietic stem cell transplantation, while (59.4%) progressed and continued treatment on palliative basis.High risk patients were 21(65.6%), intermediate risk 5(15.6%), and low risk 6 (18.8%).Sixteen patients (50%) had late relapse (>1 yr), 8 (25%) early relapse(3 months-1 year), and 8 (25%) were progressive/refractory (less than 3 months). 8(42.1%) died, 5 of them(62.5%) due to disease progression, and 3(37.5%) out of chemotherapy toxicity. The 2 years overall survival for responding patients was 87.5%, for non-responders was 72%. Multivariate analysis included sex, risk stratification, type of relapse, stage and showed no significant association.
Conclusion: Gemzar/Navelbine is safe to be given as 3rd line chemotherapy for relapsing or primary refractory HL.

Poster # 109

DIFFERING REFLECTIONS OF HODGKIN LYMPHOMA ON LOCAL AND DISTANT IMMUNOLOGICAL MICROENVIRONMENTS

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Background: The Hodgkin lymphoma (HL) tumor microenvironment is central to its biological behavior and response to treatment. We recently showed that the proportion of CD38/HLA-DR co-positive lymphocytes in affected lymph node (LN) tissue was an independent predictor of event-free survival (Pediatr Blood Cancer; 2018 Nov 15;65(11):e27307). A previously described favorable association between treatment outcome and lower peripheral blood (PB) absolute monocyte count (AMC), as well as higher absolute lymphocyte count (ALC) to AMC ratio, in nodular sclerosis (NS) HL indicate peripheral lymphoid tissue characteristics as potential biomarkers.
Objectives: In this study, we evaluated the flow cytometric characteristics of the bone marrow (BM) cells and their association with LN and PB cells in patients with HL.
Design/Method: Flow cytometric analysis of diagnostic BM aspirate samples performed for 22 cases were reviewed in this retrospective study. Flow cytometry data were also available on the involved LN tissue in 8 and on PB cells in another 8 cases. List mode re-analysis was performed using gating on lymphocyte, monocyte and myeloid populations. Flow cytometric data were analyzed against patient clinical and laboratory parameters.
Results: Median age was 15 years (10-18); 12 were female, 15 NS subtype, 1 with BM

involvement, 13 stage 4 disease, and 12 with B symptoms. Significant differences were observed for lymphocyte characteristics in LN versus BM by flow cytometry: CD4 positive T cells constituted 53.9% of the lymphocyte composition in LN and 25.3% in BM tissue (p=0.001); CD8 positive cells 14.8% and 36.8% (p=0.001), CD4/CD8 ratio 5.3 and 0.85 (p=0.002), and CD38/HLA-DR co-positive lymphocytes 57.3% and 37.6% (p=0.005), respectively. Additionally, CD3+/CD5-dim reactive T-large granular lymphocytes was higher in BM in comparison with LN tissue (10.5% vs. 4.5%; p=0.036). BM CD38/HLA-DR co-positive lymphocyte proportion inversely correlated with proportion of CD4 positive lymphocytes, as well as CD4/CD8 ratio in the BM; there was also an inverse correlation with peripheral blood ALC ($p<0.03$). There were no significant differences between PB and BM flow cytometric profiles of lymphocyte, monocyte and myeloid cells.
Conclusion: Our results indicate differences in lymphocyte make-up between affected LN tissue and BM, likely due to tumor cell activity, either through secretion of certain cytokines/chemokines and/or direct cell-to-cell interactions. Lack of difference between BM and PB cells may suggest presence of the same lymphoid tissue alterations affecting many sites outside the disease locations. Studies investigating the mechanisms and role of lymphocyte profile differences in LN and BM tissues are warranted.

Poster # 110

PRODUCTIVITY OF 18F-FDG-PET/CT DIAGNOSTIC TOOL IN THE MANAGEMENT OF PEDIATRIC LYMPHOBLASTIC LYMPHOMA

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Background: Lymphoblastic lymphoma (LL) comprises approximately 20% of childhood non-Hodgkin lymphoma (NHL). T-lymphoblastic (T-LL) subtype constitutes 75% of LL cases, with the remainder being B-cell LL (B-LL).18F-FDG-positron emission tomography/computed tomography (18F-FDG-PET/CT) is emerging as a potential non-invasive diagnostic modality for lymphoma including NHL. However, few studies had investigated the role of 18F-FDG-PET/CT in pediatric LL patients.
Objectives: We aim in this study to assess the role of 18F-FDG-PET/CT in the initial staging of newly diagnosed pediatric patients with LL as well as in the assessment of response after induction chemotherapy.
Design/Method: A pioneer prospective study enrolled on biopsy proven newly diagnosed pediatric LL patients presenting in Children Cancer Hospital Egypt (CCHE) during the period from October 2014 to October 2016. 18F-FDG-PET/CT was done initially before therapy and after induction of chemotherapy in all patients. The patients were followed until end of April 2018 (mean 23.5 months).
Results: Eighteen patients were included (14 males and 4 females; median age, 13 years), 11 had T-cell (61.1%) while 7 had B-cell Lymphoblastic Lymphoma (38.9%). All lymphoma involvement lesions (n=43) were FDG avid and the intensity of nodal FDG uptake was variable. Two patients (11%) had bone marrow (BM) involvement by < 25% blast cells with corresponding positive BM focal uptake in 18F-FDG-PET/CT (SUVmax= 4 and 4.5). There was non-significant correlation between SUVmax of involved lesions and both tumor Size (r= 0.356,

p= 0.161) and LDH level (r= 0.347, p= 0.172). Evaluation post induction phase, CT detected 8 residual lesions in 8 patients (44.4%), while 18F-FDG-PET/CT detected only 3 Deauville-positive residual lesions in 3 patients (16.6%). No intensification of therapy was done in all post-induction positive patients. Repeated 18F-FDG-PET/CT at week 18 for post-induction patients, revealed cleared all Deauville-positive residual lesions. On the other hand, repeated CT at week 18 detected regression but still residual in 4/8 (50%) post-induction CT lesions with clearance of the rest (50%). We found the specificity of post-induction 18F-FDG-PET/CT was 81% while the negative predictive value was 87% compared to 50% and 80% for post-induction CT respectively.
Conclusion: In initial staging; 18F-FDG-PET/CT is a useful tool for disease extent evaluation of pediatric LL. Moreover, it could provide a diagnostic hint for BM involvement. 18F-FDG-PET/CT done after induction therapy has a good negative predictive value with higher specificity than CT alone but it not an indication for treatment intensification due to false positive results. However larger sample size is required for better conclusion.

Poster # 111

REDUCTION OF IT BURDEN BY UTILIZING L-ARA-C AND DETECTION OF CSF MRD BY PCR IN CHILDREN WITH B-NHL

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Background: The liposomal formulation of cytarabine (L-ARA-C/Depocyte®) was shown to result in a 40-fold increase in the terminal half-life of free cytarabine in the CNS compared to ARA-C resulting in therapeutic cytarabine concentrations for 9 ± 2 days (Chamberlain et al, JCO, 1993). To maintain excellent outcomes and safely reduce the number of intrathecal injections, a clinical trial (REBOOT) was designed to investigate the addition of L-ARA-C/Depocyte® to FAB chemotherapy. Furthermore, prior studies have demonstrated that more sensitive techniques (flow cytometry and PCR) can detect CSF B-NHL with higher sensitivity than cytomorphology in adults with aggressive B-NHL (Wilson, Haematologica, 2014).
Objectives: To determine the safety and efficacy of L-ARA-C administration with ANHL01P1 chemoimmunotherapy (Goldman/Cairo, Leukemia, 2013; Goldman/Cairo, BJH, 2014) and changes in CSF minimal residual disease (MRD) by PCR in children with CD20+ CNS+/- mature B-NHL.
Design/Method: The prior FAB chemotherapy backbone utilized 9, 10, and 13 therapeutic intrathecal injections in patients classified as Group B, Group C CNS-, and Group C CNS+, respectively (Cairo et al, JCO, 2012). With the addition of L-ARA-C, the number of therapeutic IT injections were decreased to 5, 7, and 9, respectively. CNS- patients receive 2 doses of L-ARA-C and CNS+ patients receive 4 doses of L-ARA-C; the dose of L-ARA-C was 35 mg in patients <16 years and 50 mg in patients ≥16 years (Bomgaars, JCO, 2004). The MRD of CSF was assayed by PCR using primers to the FR1 region of the variable IgH regions (Shiramizu et al, BJH, 2011).
Results: Forty-two patients are enrolled in the study and received L-Ara-C with dexamethasone prophylaxis without noted toxicity. Forty-one/42 patients are alive and NED (98% EFS/OS).

Among 8 Group C patients, 6 were CSF+ by cytology. Serial CSF PCR were available for 5 CSF+ Group C patients which were all positive at pretreatment. PCRs remained + through second induction cycle (despite negative CSF cytology) in 4 patients but eventually cleared. One CSF+ patient was positive prior to induction 1 and negative prior to induction 2 but later suffered from combined systemic and CNS relapse.
Conclusion: This strategy of incorporating L-Ara-C and reducing the total number of IT treatments appears safe for both prophylaxis and treatment of B-NHL patients. In order to better understand if L-Ara-C is an effective IT substitute and the sensitivity of detecting CSF MRD by PCR requires further study with a larger cohort and longer follow-up.

Poster # 112

LOW CARDIAC TOXICITY AFTER CHEMOIMMUNOTHERAPY WITH REDUCED ANTHRACYCLINE DOSES IN MATURE B-CELL NHL

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Background: Anthracyclines are implicated in dose-dependent long-term cardiotoxicity (Oeffinger et al., NEJM 2006). There was no significant improvement of 10-year EFS in children with advanced non-lymphoblastic lymphoma when doxorubicin was added to the COMP regimen (Sposto et al., Med Pediatr Oncol 2001). We developed a clinical trial (REBOOT) investigating modifying the FAB chemotherapy backbone (Patte/Cairo et al., Blood 2007; Cairo/Patte et al., Blood 2007) with the addition of immunotherapy (rituximab) and a 60% reduction in anthracycline dose from the Group B COG ANHL01P1 regimen (Goldman/Cairo, Leukemia 2013) to maintain excellent outcomes and reduce long-term cardiotoxicity in pediatric patients with B-NHL,
Objectives: To investigate cardiotoxicity by monitoring echocardiograms and serum cardiac biomarkers during treatment and follow-up.
Design/Method: Group B (COG ANHL01P1) patients received chemoimmunotherapy (FAB Group B and 6 doses of rituximab at 375 mg/m2/dose) with total doxorubicin of 50mg/m2; Group C patients received chemoimmunotherapy (FAB Group C and 6 doses of rituximab at 375 mg/m2/dose) with total doxorubicin of 240mg/m2 (Goldman/Cairo et al., BJH 2014). Echocardiograms and cardiac biomarkers were tested: pre-therapy, during therapy, end of therapy, 1 and 2 years post-therapy. Cardiac biomarkers cTnT and NT-proBNP were measured using chemiluminescence and ELISA assays, respectively (LifeSpan BioSciences).
Results: Among 42 patients enrolled, 28 were available for cardiac analysis with median follow-up 48 months (range 12-60). The estimated 2-year EFS and OS for the Group B patients was 100%. Echocardiograms revealed stable left ventricular function with mean ±SD shortening fraction of 37.6 ±4.5 at baseline, 36.7 ±8.9 during therapy, 37.4 ±5.4 4-weeks-post therapy, 35.8 ±4.1 at 1 year and 36.1 ±6.6 at 2 years. There were no significantly elevated values of cTnT with a mean of 27.4 ±29.5 at baseline, 28.9 ±31.1 during therapy, 30.0 ±32.5 4-weeks-post therapy, 34.9 ±30.8 at 1 year. The cTnT increased over time, but the levels were not significantly elevated. There were no significantly elevated values of NT-proBNP with a mean of 51.6 ±72.1

at baseline, 42.4 ±63.0 during therapy, 39.9 ±54.9 4-weeks-post therapy, 19.2 ±35.1 at 1 year.
Conclusion: Reducing the dose of doxorubicin from 120 mg/m2 to 50 mg/m2 was associated with 100% EFS and OS. Furthermore, there has been no significant change in cardiotoxicity. Patients followed for 2 years showed stable ventricular function and no significant increase in cardiac biomarkers. Further follow up and investigation for a longer time period with a larger cohort is warranted.

Poster # 113

PILOT FEASIBILITY STUDY: DA-EPOCH-R IN THE TREATMENT OF CHILDHOOD MATURE B-CELL MALIGNANCIES

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Background: Cure rates for mature B-cell lymphomas such as Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) are now >90% in the pediatric population. However, high-risk patients have an overall survival (OS) closer to 80%, and patients with relapsed or progressive disease have an OS <20%. Current upfront therapies have considerable toxicity, with over 70% pediatric patients experiencing grade 3 or higher toxicity every cycle. Improved therapeutic approaches are needed for high-risk patients to maximize cure and minimize side effects. Adult BL/DLBCL studies have shown excellent outcomes and lower treatment toxicity with dose adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone and rituximab(DA-EPOCH-R) therapy
Objectives: Evaluate the safety and feasibility of DA-EPOCH-R in the treatment of children and young adults with mature B-cell lymphomas in a prospective institutional pilot trial(NCT01760226).
Design/Method: Patients between 0-30 years of age with newly diagnosed Group B/C BL,DLBCL or Primary mediastinal B-cell lymphoma (PMBL) were eligible.The efficacy and toxicity data of the first four patients treated on the protocol is presented.
Results: Four patients (1 female, 3 males) with a median age of 14 years (range, 6-17 years) were enrolled between December 2012 - February 2014. Two patients had stage IV BL, 1 patient had stage III PMBL and 1 patient had stage IV DLBCL. Patients received a median of 6 cycles (range, 4-8 cycles) and only 1 patient reached maximum dose level. The mean cumulative doses of doxorubicin, cyclophosphamide and etoposide were 236.4mg/m2, 5214mg/m2, and 1400.4mg/m2 respectively. Febrile neutropenia was the most common grade 3 serious adverse event (3 patients), and 1 patient had grade 2 cardiac toxicity. All patients achieved a partial response after 2 cycles. Two patients are in durable remission, and 2 patients had progression on therapy. Of those with progression, 1 patient (stage IV DLBCL) is in remission after salvage chemotherapy and allogeneic stem cell transplant and the other (Burkitt leukemia) failed salvage therapy and died of disease. Based on these outcomes, excellent survival and minimal toxicity reported on COG ANHL1131, the latter was adopted as the institutional standard and DA-EPOCH-R trial was closed.
Conclusion: DA-EPOCH-R therapy was tolerable in children with no toxicity related deaths. The mean cumulative doses of cyclophosphamide and etoposide were less than

thoseadministered on the ANHL1131 Group C arm.Except in PMBL,where data from frontline DA-EPOCH-R therapy in the COGANHL1131 study are pending, further evaluation of DA-EPOCH-R in pediatric BL/DLBCL is no longer warranted in the frontline setting.

Poster # 114

PEDIATRIC AND ADOLESCENT PERIPHERAL T-CELL LYMPHOMA CASE SERIES: A SINGLE INSTITUTION EXPERIENCE

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Background: Peripheral T-cell lymphomas are very rare in pediatric and adolescent patients, representing only about 1-2% of all non-Hodgkin lymphoma cases. Both in adults and pediatric patients, survival rates are poor and treatment advancements have been relatively slow.
Objectives: To review clinical presentation, treatment and outcomes of Peripheral T-Cell Lymphomas in pediatric and adolescent patients treated at Children's Hospital of Orange County.
Design/Method: The design is a retrospective review of institutional lymphoma database.
Results: A total of five patients with Peripheral T-cell Lymphoma (PTCL) were identified over a period of 16 years: four patients with PTCL not otherwise specified (PTCL-NOS) and one patient with Gamma-Delta Hepatosplenic T-Cell Lymphoma (HSTCL). The patients ranged in age from 2 to 19 years old at the time of diagnosis. All but one presented with advance stage disease. Of the PTLC-NOS patients, the 2-year-old patient's therapy was based on COG lymphoblastic lymphoma protocol and 16 years after diagnosis she is still alive. Two other PTLC patients were treated with CHOEP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone and Etoposide) followed by autologous stem cell transplantation and have been in remission 2 and 3 years respectively. Finally, the fourth patient represents an extremely rare case of Primary Central Nervous System PTCL-NOS. He is still undergoing therapy with a regimen that includes HD MTX and HD Cytarabine, and is clinically responding well thus far. The HSTCL patient was initially treated with CHOP, followed by IVAC therapy, and underwent a matched sibling hematopoietic stem cell transplantation (HSCT). Approximately two years after HSCT, the patient was diagnosed with diffuse pulmonary fibrosis, and expired 28 months after the HSCT without evidence of recurrent HSTCL.
Conclusion: Due to the rarity of Peripheral T-cell Lymphomas, they are not well characterized in the literature, respond poorly to treatment and have been difficult to study. There are no cases Primary Central Nervous System PTCL-NOS in the pediatric literature. This case series documents rare childhood lymphomas at a single institution and all are currently alive, with the exception of the HSTCL patient, who expired in remission due to complications from stem cell transplantation.

Poster # 115

EBV-DIRECTED VST THERAPY FOR TREATMENT OF EBV DRIVEN LYMPHOPROLIFERATION IN TWO PATIENTS WITH PID

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Background: Viral specific T-lymphocytes (VSTs) are a form of manufactured cellular therapy primarily used for the treatment of viral reactivation following bone marrow transplant. They have also been used as a treatment for Epstein Barr virus (EBV)-associated post-transplant lymphoproliferative disorders (PTLD) and Hodgkin lymphoma. Ataxia-telangectasia (AT) is an autosomal recessive disorder characterized by an impaired DNA damage response resulting in progressive ataxia, immune deficiency, and increased risk for developing hematologic malignancies (particularly lymphomas). These lymphomas are frequently driven in part by EBV infection. Management of malignancies with conventional chemotherapy in patients with AT is complicated due to profound chemosensitivity which can lead to significant toxicity and infectious complications.
Objectives: To describe the use of EBV-directed VSTs in the treatment of EBV-associated lymphoma in two patients with AT
Design/Method: VSTs with activity against multiple viruses, including EBV, were manufactured as previously described using peripheral blood mononuclear cells pulsed with viral peptide pools. Peptides from the EBV protein EBNA1, BZLF1, and LMP2a were used to generate activity against EBV. Patients were enrolled in our ongoing institutional phase I/II study using third party healthy donors as a source for VST.
Results: Patient 1 was a 3 year old female with biopsy proven EBV-associated large B-cell lymphoma, primarily of the liver and mediastinum. Her lesions did not respond to anti-CD20 therapy and she did not tolerate two cycles of conventional chemotherapy. The patient achieved a durable remission following infusion of VSTs from a third party donor matched at 6/10 HLA loci. Patient 2 is a 10 year old male with EBV-associated classic Hodgkin lymphoma, primarily of the liver, who developed progressive disease after therapy with brentuximab-vedotin and subsequently failed to respond to nivolumab. The patient has received 4 VST infusions from two separate donors, both matched at 3/10 HLA loci. To date, the patient has had an ongoing partial response with decreased number and size of lesions and a greater than 20-fold decrease in EBV viral load in blood. Neither patient had any acute infusional toxicities or de novo graft-vs-host symptoms attributable to VSTs.
Conclusion: Treatment with VSTs appears to be both safe and efficacious in our two patients with AT and virus-associated lymphoproliferation. This approach should be considered as an alternative to conventional chemotherapy for virus-associated lymphomas in patients with AT or other conditions associated with high risk of complications from chemotherapy.

Poster # 116

BOWEL OBSTRUCTION AND PERFORATION IN PEDIATRIC INTESTINAL MATURE B CELL LYMPHOMA

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Background: Perforation and obstruction are serious life-threatening complications of lymphoma involving the gastrointestinal tract.
Objectives: Our aim was to define incidence, clinical features, and outcome associated with perforation or obstruction in pediatric intestinal mature B cell lymphoma.
Design/Method: A retrospective, non-Randomized study was done. All newly diagnosed intestinal mature B cell lymphoma patients less than18 years old who were complicated with intestinal obstruction or perforation were included from July 2007 till end of July 2017 in Children Cancer Hospital Egypt (CCHE).
Results: Intestinal obstruction with or without perforation developed in 34 patients (7.9%) out of 429 patients with intestinal mature B cell lymphoma, with median age 4.85 years (2-15.8) years. All of them were treated accordingly to LMB protocol. The 5 years OS among patients were operated out of intestinal obstruction, and who were operated out of perforation were 87.7%, 78.6% respectively, and the 5 years EFS among the 2 groups were 75.1% , 78.6% respectively with no significant statistical differences. The 5 years OS among the patients who were operated before and after time of evaluation was 81.3%, 88.9% respectively. The 5 years EFS among these 2 groups was 81.6%, 65.2% respectively with no significant statistical differences. The EFS among patients with viable malignant cell by pathology versus no malignant cell was 56.3%, 94.4% respectively with significant statistical differences. Five years OS for patients didn't have surgery, and who had surgery was 85.5%, 87.8%, respectively, and the 5 years EFS for the 2 groups were 81.2%, 69%, respectively with no significant statistical differences.
Conclusion: Intestinal complication in the form of obstruction with or without intussusception, or obstruction perforation followed by exploration is not adverse prognostic factor for survival in pediatric patients with intestinal mature B cell lymphoma. Operation with viable malignant cell was associated with significant lower outcome.

Poster # 117

PROGNOSTIC FACTORS AND TREATMENT OUTCOME OF RELAPSING/REFRACTORY MATURE B CELL NHL, CCHE EXPERIENCE

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Background: The treatment of non-Hodgkin lymphoma (NHL) is an example of the successful therapy of cancer in children with cure rate approximately 80%. Unfortunately, relapsed NHL has a dismal prognosis, and customary treatment is by highly toxic chemotherapy followed by hematopoietic stem cell transplantation (HSCT).
Objectives: To analyze prognostic factors and to report treatment outcome of relapsing/refractory mature B cell NHL.
Design/Method: A retrospective study including all patients less than 18 years initially diagnosed as mature B cell NHL who were primary refractory to chemotherapy or relapsed during the period between July 2012 till end of 2017 at Children Cancer Hospital Of

Egypt(CCHE).
Results: Thirty four patients (7%) out of 494 patients were included in our study. Twenty three (67.6%) had Burrkitt lymphoma, while five(14.7%)had diffuse large B cell lymphoma. The majority were males,(79.4%) with a median age 6.2 years. According to Modified Murphy Staging,6 patients (17.6%)were stage II, twenty four(70.6%) stage III, and four(11.8%) stage IV. At presentation, bone marrow (BM) involvement was detected in 2 patient(5.9%)(1 of them had BM relapse, and the other had CNS relapse),and 3(8.8%) had CNS involvement (1 had CNS relapse and 2 had bone marrow relapse).30 patients (88.2%)received LMB protocol, and 4(11.8%) received R-CHOP as primary chemotherapy. One patient (2.9%) was treated as group A, twenty eight(82.4%) as group B, and five(14.7%)as group C. Median delay in 1st line treatment was 22 days (range 0 to 162). Twenty two patients(64.7%)relapsed, while 12(35.3%)had tumor progression.Early relapse was documented in 15 (68.2%),and late relapse was in 7 patients(31.8%). Relapse was documented by tissue biopsy in 30 patients (88.2%),bone marrow aspirate in 3(8.8%). Patients relapsed at sites other than primary site in 6 out of 34(17.6%),CNS relapse was in 8 out of 34(23.5%),BM relapse was in 8(20.5%)BM and CNS relapse was in 2 (5.9%),BM only in 6(17.6%),CNS only in 6 (17.6%). R-ICE(Rituximab-Ifosfamide,Carboplatin and Etoposide) was the 2nd line of treatment in 29 patients(85.3%) and complete 2nd remission was achieved in 7 patients (20.6%). Allogeneic hematopoietic stem cell transplantation (HSCT) was done for 2 patients (5.9%), and autologous HSCT for 3 patients (8.8%). The 3 years Overall survival (OS)was 35.3%, with no statistical difference between relapsing and progression.The 3 year OS for patients who underwent HSCT was 80% compared 20% for no HSCT (p value 0.034).
Conclusion: Relapse rate is similar to or higher than the literature because of delay of chemotherapy. HSCT in patients with second remission improve the outcome.

Poster # 118

LYMPHOMA RISK AND GENETICS OF IMMUNE-DYSREGULATION AND LYMPHOPROLIFERATION: SCALING BEYOND ALPS

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Background: First modern description of lymphoid neoplasm dates back to the advent of microscopy. The term Hodgkin's disease like Virchow's subsequent term lymphoma was initially used by Thomas Hodgkin in 1832 to designate swollen lymph nodes of unknown cause ("neoplasm"). Lymphoma is a malignant neoplasm of the immune system. It protects through innate and adaptive immune response, dependent on lymphocyte ontogeny and location based proteins triggered by many genes including receptors and regulators. Epidemiology of lymphoid neoplasia as understood today includes auto-inflammation, chronic infections and antigen stimulation, oncogenic viruses, proliferation/apoptosis and immune check point imbalance, chemical and environmental exposure as well as genetic background. Recent advances in the diagnostic genomics have ushered in the identification of many new germline genetic syndromes of immune dysregulation orchestrating the interplay between nonmalignant lymphoproliferation and lymphoma.
Objectives: As with almost all cancers, hereditary predispositions are increasingly coming to

light. Identifying genes that confer lymphoma risk in families has potential to help better understand the biology of lymphomagenesis, and guide the individual patients to adapt to medical, psychosocial and reproductive implications of their disease.
Design/Method: Diligent long term follow up and collection of personal and family history to guide risk assessment has allowed us to accumulate patient clinical profiles at NIH-CC. The cancer and lymphoma susceptibility lessons learnt from ALPS-FAS (Autoimmune Lymphoproliferative Syndrome due to Fas defect) and RALD (RAS Associated Leukoproliferative Syndrome) over many years can be used as a paradigm for assessing lymphoma risk in many recently described genetic disorders of immune system including CTLA4 haploinsufficiency, PIK3CD, and MagT1defects (XMEN).
Results: Risk of predisposition to lymphoma and other malignant neoplasms is considerable (10-25%) in all of them. Integration and collaboration of specialists in hematology, oncology, genetics and immunology can bridge the gaps in critical thinking needed for risk assessment, diagnosis and management of complications including lymphomas as we become aware of these immune-mediated lymphoma predisposition syndromes. Thus these rare genetic disorders helped us elucidate the critical immune surveillance pathways to malignant neoplasia and treat them better with targeted therapeutics.
Conclusion: Studying patients with germline genetic mutations leading to cancer and lymphoma susceptibility should guide us to better and early anticipation, diagnosis, management and prevention of malignant neoplasms in general population. Clinical translation of this knowledge can be aided by collection and sharing of clinical history, archived biological material to guide counseling, risk assessment and by profiling both germline and tumor DNA in all newly diagnosed children with cancers.

Poster # 119

GENOMIC CHARACTERIZATION OF A PEDIATRIC COHORT WITH NON-MALIGNANT LYMPHOPROLIFERATIVE DISORDERS

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Background: Pediatric non-malignant lymphoproliferative disorders (LPDs) are a clinically and genetically heterogeneous group of disorders. Misdiagnosis or delayed diagnosis often contribute to substantial morbidity or mortality. Thus, identification of the molecular causes and underlying disease mechanisms may facilitate timely interventions and potentially guide targeted or curative therapies
Objectives: To define the genomic spectrum and clinical characteristics, including Epstein-Barr Virus (EBV) status and presence of hemophagocytic lymphohistiocytosis (HLH), associated with outcomes in a diverse cohort of children with non-malignant LPDs.
Design/Method: Patients at Texas Children's Hospital or collaborating referral centers who met criteria for non-malignant LPDs (lymphadenopathy lasting >3 months, splenomegaly, with or without recurrent or chronic Epstein-Barr virus infection (CAEBV)) were offered participation in this research study, approved by the Baylor College of Medicine Institutional Review Board. All

subjects and/or family members provided written informed consent to have their clinical and genetic information published in scientific journals and presented at national conferences. Genetic testing was performed clinically or through research-based whole-exome sequencing (WES).
Results: Fifty-six subjects (from 52 different families) with non-malignant LPDs were identified. Research-based WES was performed in 91% (51/56) of patients; the remaining 5 patients had clinical WES performed. An approximately equal proportion of boys (n=29) and girls (n=27) were recruited into this study, and 53% (30/56) of patients were Hispanic. Thirteen subjects (23%) met HLH-2004 diagnostic criteria. Twenty-six patients (46%) had EBV-associated lymphoproliferative disorders (EBV-LPD). Only 6 of the 56 (~10%) developed malignancy, and 4 of these 6 patients experienced a history of persistent EBV viremia. Of the families who received research WES, potential disease causing genetic defects were identified in approximately 50%. Overall, 18% of patients enrolled in this study had diagnoses that resulted in a clinical decision: 9% received targeted therapy and 9% received a bone marrow transplant. The overall survival (OS) for the entire cohort was 82%. For patients with EBV-LPD/CAEBV, OS was 69%, and for patients with HLH, OS was also 69%.
Conclusion: Pediatric LPDs represent a high-risk population with relatively poor overall survival despite designation as "non-malignant." This study supports complete evaluation and close follow-up for these patients. WES identified a clinically-significant variant in approximately half of the pediatric LPD patients tested. Early identification of these mutations can help us understand the pathogenesis of both non-EBV and EBV-LPDs and help choose novel therapeutic strategies to decrease the high burden of morbidity and perhaps mortality associated with these disorders.

Poster # 120

CASTLEMAN DISEASE PREVELANCE, PRACTICE ESSENTILAS AND OUTCOME AMONG CCHE PATIENTS

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Background: Castleman disease (CD) describes a group of rare lymphoproliferative disorder with characteristic histopathology. It presents with heterogeneous clinical features whether unicentric (UC) or multicentric disease (MCD). Our aim is to present the outcome of CD in a pediatric single center
Objectives: to describe clinicopathlogical characteristics, management and outcome of different types of castleman disease
Design/Method: All children with Castleman disease treated from 7/2007 till 12/2017 were retrospectively analyzed as regard diagnosis, management and outcome.
Results: Twelve patients with a median age of 11.5 years (ranging from 4 - to 17 yeras) were enrolled. Of them 8 were males, 4 were females. Histopathology was either hyaline vascular in 8 patients or plasma cell variant in 4 patients. Nine patients were UC with lymphadenopathy. While 3 were MCD with 1) immune bicytopenia, small intestinal thickening and splenomegaly 2) extensive pulmonary involvement and respiratory distress, 3) pleural effusion & ascites

respectively. HIV Ab was negative for all patients. For the 3 MCD, IL6 was normal, extremely high, and not done in patients respectively. All UC underwent exclusive surgical excision and are alive and well till now. All MCD patients received systemic steroids then R CHOP as salvage therapy (rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone) or singla agent Rituximab and Anti IL6 for the second patient only. Of them 2 showed partial response and the one with pulmonary involvement is still with uncontrolled systemic manifestation.
Conclusion: Unicentric castleman is a localized surgically cured disease. MCD treatment remains challenging, and the outcome is controversial. Uniform treatment guidelines are mandatory.

Poster # 121

COMPARISON OF HEMATOPOIETIC STEM CELL TRANSPLANTATION CONDITIONING REGIMENS FOR PEDIATRIC HLH

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare hyper-inflammatory immune-regulatory disorder. Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only curative treatment. The choice of intensity of the conditioning regimen remains challenging as previously utilized myeloablative regimens are associated with significant toxicity and reduced intensity regimens (RIC) are associated with mixed chimerism, risk of relapse and graft failure (GF).
Objectives: To compare overall survival (OS) and event free survival (EFS) of children with HLH treated with a treosulfan-based regimen to patients treated with a busulfan-based and a RIC regimen.
Design/Method: In a retrospective study, we compared a treosulfan-based conditioning regimen (treosulfan: days -6 to -4, 14,000 mg/m2/dose, 12,000 mg/m2/dose for patients < 1 year; fludarabine days -6 to -3, 40 mg/m2/dose, 1.3 mg/kg/dose for patients < 10kg; cyclophosphamide days -3, -2, 60 mg/kg/day; thymoglobulin day -3 to -1, 2.5mg/kg/dose) to a busulfan-based regimen (busulfan, cyclophosphamide, etoposide +/- thymoglobulin), and a RIC regimen (fludarabine, melphalan and alemtuzumab). Data points evaluated included patient characteristics, engraftment, donor lymphocyte infusions (DLI), GF, chimerism, relapse, OS and compound EFS (relapse, GF, second transplant or DLI).
Results: Thirty-five patients with HLH were analyzed. Eight patients received treosulfan-based regimen, 15 received busulfan-based regimen, and 12 received RIC regimen. The median follow up times were 13.7 months (range: 1-20), 97 months (range: 2- 211), and 36 months (range: 10-62) respectively. In the treosulfan cohort, all patients engrafted with no secondary GF. In the busulfan cohort, 1 patient (7%) developed primary GF and no secondary GF was observed. In the RIC cohort, no primary GF was observed, but a significantly higher incidence of mixed chimerism occurred and five patients (42%) developed secondary GF (P=0.004). No HLH relapses were observed in the busulfan cohort, whereas in the treosulfan group, 1 (13%) patient and in the RIC group 6 patients (50%) relapsed (P=0.006). Acute post-transplant complications including ICU admissions and veno-occlusive disease were significantly higher in the busulfan

cohort.Estimated 4-year OS and compound EFS were 87.5%, 73.3%, 66.7% (p=0.94) and 87.5%, 73.3%, 33.3% (p=0.052) respectively in patients who received a treosulfan-based, busulfan-based or RIC regimen.
Conclusion: The described treosulfan-based conditioning regimen is a promising regimen to treat children with HLH. The regimen is less toxic than a busulfan-based regimen and patients experienced less GF than patients treated with a RIC regimen. Further studies are warranted to prospectively test this regimen in a larger cohort of patients with HLH.

Poster # 122

PROTECTIVE EFFECTS OF KIR-2DS1, KIR-2DS5 AND KIR-2DL5 ON EBV-HLH TREATED WITH HLH-94 AND RITUXIMAB

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Background: Killer immunoglobulin-like receptors (KIRs) are known to affect susceptibility to various viral and virus-related benign or malignant disorders. Some papers show that the combined of rituximab with conventional HLH-directed therapy improves symptoms and diminishes inflammation, especially in EBV-HLH. However, the influence of KIR genotype profile on the effectiveness of treatment in EBV-HLH with HLH-94 and rituximab has not been studied
Objectives: We evaluated association between KIR gene polymorphisms and the response to treatment with HLH-94.
Design/Method: EBV-HLH patients were diagnosed according to the guidelines HLH-1994 from the Histo-cytology Society. EBV copies was determined by realtime PCR method. Using polymerase chain reaction (PCR) with specific primers, the KIR genotypes of 20 patients treated with rituximab and 20 patients treated without rituximab were determined.
Results: In 11 patients EBV-HLH who partial or no responded with combined treatment, the frequencies of KIR2DS1, 2DS5 and 2DL5 were significantly lower than in conventional treatment individuals (18.2% vs 60% for each three, $P<0.05$) and 9 EBV-HLH who completely responded with combined treatment (18.2% vs 55.6% for each three, $P<0.05$). Three KIRs were significant protective factors for the completely response of EBV-HLH treated with rituximab than in those patients had partial or no response. 60% patients with EBV copies >10,000 copies/ml possessed at least one of KIR2DS1, 2DS5, and 2DL5. The 1-year overall survival rates of the patients with and without KIR2DS1, KIR2DS5 and KIR2DL5 were 53% and 32%.
Conclusion: KIR2DS1, KIR2D5 and KIR2DL5 could have good effects on the treatment with rituximab of the HLH-EBV patients and may also be associated with good prognosis of patients. These data support the role of KIR genotypes in the combined treatment with rituximab in future for patients with EBV-HLH.

Poster # 123

TRIAL OF ANAKINRA IN HEMOPHAGOCYTIC LYMPHOHYSTIOCYTOSIS

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Background: Hemophagocytic lymphohystiocytosis (HLH) is is an uncommon yet potentially devastating systemic disease, arising from uncontrolled activation of the immune system. Secondary HLH can be triggered by malignancy, metabolic disease and immune mediated diseases. Use of the IL-1 receptor antagonist, Anakinra, has shown some promise in the treatment of this disorder.
Objectives: Interleukin-1 receptor antagonists such as Anakinra have been used effectively in the treatment of pediatric systemic onset juvenile idiopathic arthritis and other autoinflammatory disorders. We hypothesize that this immunomodulator can also successfully treat patients with secondary HLH. This case series describes the diagnosis, progression, and therapy of three patients at Cook Children's Medical Center with secondary HLH.
Design/Method: This case series employed the use of review of electronic medical records for three patients at Cook Children's Medical Center.
Results: Three patients within the Cook Children's network were diagnosed with HLH between 2014 and 2016 and treated per HLH-2004 protocol. The 1st patient, diagnosed with HLH at age 10, sustained relapse after five weeks of therapy with etoposide and dexamethasone, requiring reintensification. Thereafter, she developed fever, body aches and cytopenias with eventual diagnosis of systemic onset juvenile idiopathic arthritis, treated with prednisone and Anakinra, leading to remission. Thereafter, she was treated with tociluzumab, progressively weaned and now discontinued for several months, given continued remission.The 2nd patient, 16-year-old male, completed treatment for HLH followed by rising levels of ferritin, generalized erythematous rash, and hypotension. After completing treatment, he flared and developed a swollen right elbow with erythema and pain. At that time, he was diagnosed with systemic juvenile idiopathic arthritis and treated with Anakinra daily. He is currently in remission while continuing Anakinra for 10 months.The 3rd patient, 12-year-old female with past medical history of type 1 diabetes and polyarticular juvenile idiopathic arthritis, was diagnosed with EBV driven HLH, treated with dexamethasone, etoposide, and rituximab. As part of workup, she was found to have depressed NK cell activity. She presented a year later with symptoms concerning for recurrence of HLH. Given her history of juvenile idiopathic arthritis, she was treated with Anakinra with resolution of her symptoms. She remains in remission for over two years.
Conclusion: The diagnosis of HLH can be elusive and is often accompanied with multiple systemic manifestations. For those patients with a concurrent diagnosis of systemic onset juvenile idiopathic arthritis, the introduction of Anakinra has shown significant improvement in both arthritic symptoms and HLH markers.

Poster # 124

DIAGNOSTIC TESTING IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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Background: Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) represent a spectrum of rare but life-threatening hyperinflammatory syndromes in which early diagnosis remains a challenge. The addition of serum ferritin, soluble IL-2r (sIL-2r), and natural killer (NK) cell activity diagnostic criteria enables more rapid diagnosis however the benefit of these tests can be limited by inefficiencies in the clinical laboratory setting.
Objectives: To identify the factors which negatively impact the timely diagnosis of HLH-MAS.
Design/Method: Retrospective chart review was conducted for pediatric patients diagnosed with a hemophagocytic syndrome based on ICD code query at Kaiser Permanente Southern California facilities during 2005-2017. Records were reviewed for patient demographics, outcomes, and laboratory results.
Results: Thirty-two pediatric patients accounted for 43 episodes of HLH-MAS during the study period. Four of five deceased patients died from complications related to HLH-MAS. Seven patients were diagnosed with sJIA concurrently or within one year of their episode of HLH-MAS. Acute infectious triggers were identified in ten patients. The initial ferritin sample was elevated and diagnostic in all participants during their first occurrence of HLH-MAS (mean 9,082 ng/mL, range=568-43,332). Ferritin testing was performed internally with an average turnaround time of 17.5 hours (range=5.2-32.5) which included transportation of specimens to a regional laboratory. Specimens for NK cell activity and sIL-2r testing were submitted to a contracted local private diagnostic laboratory or a specialized academic testing center. A significant proportion of NK cell samples were rejected at both laboratories (private 28%, academic 25%). The most common reason for sample invalidation was sample age (>24 hours) (54.5%), specimen receipt on days when testing was not performed (18.2%), insufficient volume (18.2%), or inappropriate type (9.1%). NK cell activity turnaround time was comparable between the private (mean 3.8 days; range 1.4-6.6) and academic (mean 4.9 days; range 2.0-8.0) facilities. A variation in turnaround time for sIL-2r was identified for testing performed at the local private laboratory (mean 7.5 days; range 1.4-21.0) compared to specimens tested at the academic center (mean 1.5 days; range 0.9-3.9).
Conclusion: Earlier diagnosis of HLH-MAS is achievable with the addition of higher specificity serum tests but providers must account for more restrictive specimen handling requirements, sample transportation and logistics, and laboratory throughput. Process optimization can address the factors which prolong the time until life-saving interventions can be initiated. We developed a structured diagnostic workflow to address the sources of error and inefficiency identified in our study and will evaluate its clinical impact prospectively.

Poster # 125

OUTCOME OF LIVER INVOLVEMENT IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS

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Background: Liver involvement in pediatric Langerhans' cell histiocytosis (LCH) usually presents as a part of a disseminated disease, its frequency is known to be high and is associated

with adverse outcomes
Objectives: To assess the frequency and outcome of liver involvement in pediatric LCH.
Design/Method: A Retrospective study included 52 pediatric LCH patients with liver involvement. All patients treated at the Children's Cancer Hospital-Egypt during the 10 years period 2007 - 2017. Patients from 2007 to 2011 were received therapy according to LCH-III protocol, while patients from 2012 to 2017 were treated according to LCH-IV protocol. Liver involvement was determined by the following: unexplained liver enlargement more than 3 cm below the costal margin and/or dysfunction (Hypoalbuminemia, hyperbilirubinemia, hypoprothrombinemia and/or increased liver enzymes).
Results: Of 117 children with multisystem LCH, 52(44.4%) had liver involvement. The median follow-up of patients with liver involvement was 44 months (range, 2 to 131). Of 52 studied patients, 30(57.6%) patients had hepatomegaly without disturbed liver function, 21(40.4%) patients had hepatomegaly with liver dysfunction, and one patient (2%) `had average-sized liver with disturbed function. The 5-year overall survival (OS) and event free survival (EFS) of all patients with liver involvement was 65% and 38.5% respectively.For patients with liver dysfunction (n=22), the 1-year OS and EFS was 63.3% and 35.8% respectively compared to 96.7% and 86.7% respectively for those with hepatomegaly (n=30). (P<.001, and P=.001 respectively).At end of induction, disease progression was seen in 13/22 patients (59%) with liver dysfunction, of them 10/13 patients (77%) died, and in 4/30 patients (13%) with hepatomegaly, of them only one patient (25%) died.
Conclusion: Though Liver is considered as a high risk organ in management of LCH, patients with disturbed liver functions tend to have a refractory disease and dismal outcome compared to those with hepatomegaly alone. Further studies are recommended to confirm this poor outcome and hence, this group of patients might benefit from upfront different therapeutic planning.

Poster # 126

LIMBIC ENCEPHALITIS AS PRESENTATION OF HODGKIN LYMPHOMA IN A PEDIATRIC PATIENT: THE OPHELIA SYNDROME

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Background: The Ophelia syndrome is the association of Hodgkin Lymphoma with limbic encephalitis as a paraneoplastic neurological syndrome. Its pathophysiological mechanism is unknown, but it is believed to be an autoimmune response to Hodgkin Lymphoma. Antibodies to the metabotropic glutamate receptor 5 (mGluR5), which is found mainly in the hippocampus and is responsible for behavioral learning and behavior, have been associated with Ophelia syndrome.
Objectives: There is very little literature available about this syndrome, with only 11 case reports in the existing literature around the world in adult and pediatric patients combined. We present this case in order to aid in the knowledge about this rare condition.
Design/Method: A 15-year old female presented with intermittent fevers and alteration in sensorium, quickly progressing and leading to intubation and placement on mechanical ventilation. She was diagnosed with a viral aseptic meningitis after CSF analysis. Brain

computer tomography and magnetic resonance imaging (MRI) were unremarkable. She was treated empirically with intravenous antivirals, making a full recovery within three days. She returned three days later due to recurrent altered mental status. Brain MRI then showed a pattern consistent with limbic encephalitis in the left temporal lobe. Workup for an autoimmune encephalitis, including markers for a paraneoplastic syndrome, yielded no answers. Despite trying multiple treatment modalities for encephalitis, including high dose steroids and IVIG, the patient continued to deteriorate neurologically. Plasmapheresis was the next step in treatment. A central line for plasma exchange was placed, and a post-operative chest x-ray revealed a mediastinal mass. Thoracoscopic resection of the mass later confirmed it to be classical nodular sclerosing Hodgkin Lymphoma.
Results: After completing the first two cycles of chemotherapy, she was found to be a rapid early responder, and by then she had made a near-complete neurological recovery, with only some remnants of memory loss. In our patient, a paraneoplastic panel was mildly positive for neuronal voltage gated potassium channel antibodies and striational antibody. Antibodies to metabotropic glutamate receptor 5 (mGluR5) were negative.
Conclusion: Literature through published case reports suggest these patients can have a good prognosis if treated promptly, with resolution or near-resolution of neurological symptoms and signs. It is important to recognize the possibility of a paraneoplastic syndrome in a patient with limbic encephalitis, and its association with Hodgkin Lymphoma, a very treatable disease.

Poster # 127

A CASE REPORT OF INTRACARDIAC HODGKIN LYMPHOMA IN AN ADOLESCENT FEMALE

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Background: Primary cardiac tumors in the pediatric population are rare, even more so are primary lymphomas of the heart, constituting 1.3% of primary cardiac tumors. Here we present a case of Hodgkin lymphoma presenting as an intra-cardiac mass in an adolescent female. There is no established standard of care in the management of this entity.
Objectives: Review the presentation of intracardiac Hodgkin lymphoma and its subsequent management.
Design/Method: Case Report
Results: A 14-year-old female of mixed ethnicity presented with shortness of breath, lightheadedness, and sensation of heart pounding on exertion. She was referred to cardiology and echocardiogram revealed a mass in her right atrium, which was confirmed by cardiac magnetic resonance imaging (MRI). The mass measured 4.7 x 4.7 x 5 cm and extended into the superior vena cava (SVC) and innominate vein. It caused mild-moderate tricuspid regurgitation and mechanical obstruction. The lobular configuration of the mass in the superior mediastinum and surrounding nodularity was suggestive of tumor infiltration and mediastinal lymphadenopathy. Computed tomography (CT) of the neck, thorax, abdomen and pelvis did not show adenopathy or organ involvement other than that seen on MRI. Biopsy was performed by interventional radiology of the right atrial mass, as well as a mediastinal lymph node, and revealed classical

Hodgkin lymphoma. Bilateral bone marrow biopsies were negative. Positron emission tomography (PET) was avid within the right atrial mass and in the anterior mediastinum bilaterally. She received chemotherapy consisting of 4 cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide (ABVE-PC). Her symptoms resolved after 1 cycle of chemotherapy, and findings of obstruction and tricuspid regurgitation were significantly improved as well. Reimaging after 2 cycles of chemotherapy with PET and CT, revealed resolution of FDG uptake in the right atrial mass (Deauville 3), as well as the component extending into the SVC, proximal brachiocephalic and azygous veins, and the mediastinal lymphadenopathy (Deauville 1). She tolerated chemotherapy well. End of therapy imaging with PET was negative (Deauville 1); CT showed continued decrease in the size of the mass and resolution of mediastinal adenopathy. She continues to follow with cardiology and is asymptomatic from that standpoint.
Conclusion: Primary intracardiac Hodgkin lymphoma is exceedingly rare, with few published case reports. This case highlights the presenting symptoms of right atrial tumors and indicates that the standard chemotherapy regimen of ABVE-PC can result in remission in these patients.

Poster # 128

AN ATYPICAL PRESENTATION OF HODGKIN LYMPHOMA INVADING THE LEFT AND RIGHT ATRIAL WALLS

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Background: Pericardial involvement by Hodgkin lymphoma (HL) has been found in up to 20% of children. Despite the relatively high frequency of pericardial involvement by HL, disease of the myocardium itself appears to be a rare occurrence. Myocardial disease may be particularly problematic because of the potential risk of structural compromise of the heart wall with chemotherapy-induced tumor necrosis.
Objectives: We describe an 18-year-old male diagnosed with HL who presented with a mediastinal mass, large pericardial effusion, invasion of the left and right atrial walls, and intra-atrial tumor extension. We review the reported frequency of pericardial and myocardial involvement by HL.
Design/Method: We describe a clinical case and review the medical literature. An 18-year-old male with a past medical history significant for idiopathic thrombocytopenia three years earlier presented with recurrent back pain anterior to his left scapula. Vital signs were notable for a heart rate of 105 bpm and a pulsus paradoxus of 18 mm Hg. He did not have peripheral lymphadenopathy or organomegaly. CT angiogram showed mediastinal and left hilar adenopathy as well as a large pericardial effusion. Cardiac MRI demonstrated that the mediastinal mass invaded the left and right atrial walls and extended into both the left atrium and left pulmonary veins. Mediastinal lymph node biopsy and subsequent evaluation showed nodular sclerosing HL, stage IIAE. In the absence of eligibility for a clinical trial, therapy was initiated according to National Comprehensive Cancer Network guidelines. Following two cycles of ABVD chemotherapy, cardiac MRI showed near complete resolution of disease and no evidence of atrial wall defects. A PubMed search of publications between 1989 and 2019 was conducted using the

terms Hodgkin, heart, cardiac, myocardium.
Results: Analysis of 273 children with HL treated at St. Jude Children's Research Hospital found 13 (5%) with pericardial involvement. In the most comprehensive examination of 1423 children participating in the COG trial AHOD0031, 288 (20.2%) had pericardial effusions. Neither study noted myocardial disease. While pericardial disease in HL is described in numerous case series some of which are large, published case reports of myocardial involvement of HL include only four individual patients, two of whom had an isolated intra-atrial thrombus. A recent review of 616 cardiac hematologic malignancies found none to have HL.
Conclusion: HL frequently presents as a mediastinal mass and extension to the pericardium is common. In contrast, disease of the heart wall or cardiac chambers is exceedingly unusual.

Poster # 129

HODGKIN LYMPHOMA COMPLICATED BY CNS GRANULOMATOUS ANGIITIS REQUIRING FURTHER THERAPY: A UNIQUE CASE

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Background: Granulomatous angiitis of the CNS (GACNS) is a rare phenomenon described in the literature only through case reports in association with Hodgkin lymphoma (HL). It is thought to be a paraneoplastic process, though the etiology remains poorly understood. GACNS typically presents with severe neurologic complications including seizure, hemiparesis, and coma. Diagnosis of GACNS often precedes the diagnosis of HL, although cases have been diagnosed post-mortem as well. It has been suggested that therapy for the GACNS should focus on treatment of the HL; however, more recent cases are highlighting the need for additional therapy to appropriately treat the vasculitis and improve overall survival.
Objectives: To review a unique presentation of GACNS associated with HL and highlight the need for additional therapy to treat the vasculitis.
Design/Method: We report a clinical case and review the relevant literature.
Results: Here we report the case of a 19-year-old male who presented to our clinic with 6 months of progressive neck swelling and non-specific fatigue. He was subsequently diagnosed with stage Ia nodular lymphocyte-predominant HL. Treatment with 3 cycles of doxorubicin, vincristine, prednisone, and cyclophosphamide (AV-PC) was initiated. Over the course of his second cycle, he developed significant polyuria and polydipsia. Workup revealed new diabetes insipidus along with other pituitary-related endocrinopathies. His neurologic exam remained normal. Brain MRI was obtained and revealed two enhancing lesions in the CNS, one extending from the hypothalamus and pituitary stalk and the other around the pineal gland. Due to location, initial concern was for a second malignancy, mainly germinoma. However, serum and cerebrospinal fluid (CSF) tumor markers were negative, as was CSF cytology. Subsequent biopsy of one of the lesions revealed GACNS. HL chemotherapy was continued to complete 3 cycles with end of therapy PET scan negative for HL; however, repeat brain MRI revealed expansion of the vasculitic lesions with invasion into the optic chiasm. Therefore, the patient began additional therapy for the GACNS with a 5-day high-dose methylprednisolone burst followed by prolonged prednisone taper and 3 cycles of monthly cyclophosphamide. Brain MRI

at one month showed decreased size of the CNS lesions with resolution of the optic chiasm enhancement.
Conclusion: Our case demonstrates a unique presentation of GACNS associated with HL not previously described in the literature. It also suggests that additional therapy for the underlying GACNS is needed, along with HL therapy, to appropriately treat this rare complication.

Poster # 130

HODGKIN LYMPHOMA AND PULMONARY SCHISTOSOMIASIS

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Background: Schistosomiasis is an endemic disease in Egypt caused by the trematode schistosoma which has different species. Hepatic and intestinal schistosomiasis represent the known forms of chronic disease. The occurrence of malignancy with disseminated pulmonary schistosomiasis is rare. Our main concern is to know is it safe to continue chemotherapy in such patients.
Objectives: We report a case of acute pulmonary schistosomiasis in a patient with Hodgkin lymphoma after two cycles of chemotherapy in which lung biopsy was done and it identified the presence of schistosomal ovum surrounded by granuloma. Reporting such rare case is important to assess the impact of chemotherapy on the dissemination of schistosomiasis and the importance of biopsy from progressive lesions during the course of treatment
Design/Method: Male patient 10 years old, initially presented to children cancer hospital Egypt with history of hematuria for 9 month duration, images for abdomen showed multiple urinary bladder intra vesical soft tissue lesions and irregular wall thickening. Cystoscopic biopsy showed bilharzial cystitis with ulceration. The patient gave history of Nile water contact. By examination the patient had clinically right cervical and supraclavicular lymph node enlargement, biopsy was taken and it showed classical Hodgkin lymphoma, interfollicular type. Positron Emission Tomography-Computed Tomography(PET-CT) showed right cervical lymphomatous nodal lesions uptake, otherwise was free, he received antibilharzial treatment with praziquental and started chemotherapy, hematuria improved, after 2 cycles, interim PET-CT showed complete regression of right cervical lymphomatous lesions but there were newly developed variable sized discrete pulmonary nodules measured 1.1 cm without uptake, It was very astonished to us. We tried to confirm the nature of this lesion and to exclude fungal or disease progression, open surgical biopsy was done, the result was granulomatous inflammation of bilharzial etiology, and few multinucleated giant cells were seen engulfing viable and calcified bilharzial eggs. Praziquental dose repeated after consultation of tropical department. He received total of four cycles of chemotherapy and radiotherapy.
Results: The patient achieved complete remission. Chest images at the end of treatment showed regressive course in the size of multiple bilateral scattered pulmonary nodules, with hyperdense calcification. He is under follow up with no more hematuria or chest symptoms.
Conclusion: Continuation of chemotherapy for Hodgkin lymphoma in infected patient with pulmonary schistosomiasis is safe. The pathophysiology of acute pulmonary disease is not well-understood but is related to immune response. PET-CT is good negative test in Hodgkin lymphoma, biopsy is crucial from progressive lesions during the course of treatment.

Poster # 131

CAN FDG-PET REPLACE BIOPSY FOR EVALUATION OF RESIDUAL TUMOR IN MATURE B CELL NHL?

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Background: The presence of residual mass by CT scan at time of evaluation during the course of chemotherapy in pediatric mature B cell NHL poses many difficulties. Surgical or radiological documentation of viable residual malignant cells is sometimes difficult, invasive, and may pose unnecessary risks.
Objectives: to evaluate the role FDG-PET in detection of viable tumor cells through comparing its results with the pathology of surgically or radiologically biopsied residual tumor. Also to detect the negative predictive value (NPV), positive predictive value (PPV), sensitivity and specificity of PET referred to the pathology in mature B cell NHL.
Design/Method: A retrospective, cross sectional study including all mature B cell NHL; who had a residual tumor at time of evaluation detected by CT, and underwent PET followed by pathologic documentation, either by elective surgical biopsy or radiologically taken.
Results: : Thirty four patients (7%) out of 481 patients with mature B cell NHL enrolled between July 2007 and July 2017 at Children Cancer Hospital Egypt (CCHE) were included in our study. Thirty two patients (94.1%) had BL, and 2 had DLBCL. The majority were males (82.4%), mean age was 7.2 years, range 2.7 to 15.6. Median follow up period was 60 months. Site of biopsy was from abdominal mass in 28 patients (82.3%). PET and biopsy were positive for viable malignant tissue in 10 patients (29.4%) (true positive), negative for viable malignant tissue in 12 patients (35.2%) (true negative), while 10 patients (29.4%) had low FDG uptake, 3 of them (8.8%) had a positive residual malignant cells by pathology, with a median FDG uptake of SUV 3.5. Seven patients (20.5%) had low FDG uptake with median SUV 2.1, and their biopsy was negative. Two patients (5.8%) with negative FDG uptake by PET had viable malignant tissue by biopsy (false negative). NPV and sensitivity were 85%, while PPV and specificity were 65%. (PET and biopsy were true positive in 38.2%, true negative in 35.2%, false positive in 20.5%, and false negative in 5.8%).
Conclusion: FDG PET is highly sensitive for the detection of viable malignant residual tumor mass in comparison to conventional CT. changing therapy on the basis of a positive FDG-PET/CT finding alone at time of evaluation is not recommended in children with NHL, and biopsy confirmation is required. False negative is accounted then biopsy confirmation is required but FDG PET-CT can replace biopsy if the latter is inaccessible or carries an unnecessary risk.

Poster # 132

AN 8-YEAR OLD BOY WITH LOCALIZED ANAPLASTIC LARGE CELL LYMPHOMA

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Background: Anaplastic Large Cell Lymphoma (ALCL) accounts for 10-15% of pediatric non-Hodgkin lymphoma. Overexpression of Anaplastic Lymphoma Kinase (ALK) gene is shown to be the molecular trigger for oncogenesis. ALCL cells are CD30+ and in contrast to adult ALCL, ALK is almost always positive in children. The majority of pediatric ALCL cases present with advanced stage disease, so data regarding stage I disease are scarce.
Objectives: We describe an 8-year old boy diagnosed with ALCL in the subcutaneous tissue of his back and discuss his treatment.
Design/Method: Case report/literature review
Results: An 8-year-old healthy boy presented to his pediatrician with a painless, progressively-enlarging soft tissue mass in his mid-back. He had no systemic symptoms. Ultrasound demonstrated a subcutaneous complex fluid collection. A pediatric surgeon performed a gross total resection of a 4.5 x 3 x 1.5 cm mass. Gross pathology review reported a palpable, red, well-circumscribed nodule (0.8 x 0.7 x 0.7 cm) on the skin surface. Microscopy was consistent with lymphohistiocytic variant of ALCL CD30+, ALK1 positive. FISH testing was positive for ALK gene rearrangement. There was diffuse infiltration of the dermis and subcutaneous tissue, involving the resection margin. Staging evaluation, including CT neck/chest/abdomen/pelvis, PET/CT scan, CSF analysis and bilateral bone marrow biopsies did not show evidence of ALCL. We considered him to have stage I, primary cutaneous ALK-positive ALCL with microscopic residual disease. We treated him with standard chemotherapy for advanced-stage ALCL per ALCL99. He remains in remission, 14 months after therapy completion.
Conclusion: Primary cutaneous CD30-positive lymphoproliferative disorders occur in adults but are very rare in children. Pediatric ALCL is characterized by advanced disease at presentation in 75% of cases; over 90% have nodal involvement and about 75% have associated B symptoms. Our patient presented with the extremely rare finding of ALK-positive, localized disease that appears to have originated in the skin. Although data are limited, it has been suggested that stage I ALCL that is incompletely resected has a relapse rate similar to advanced-stage ALCL [1]. We therefore felt that intensive multi-agent chemotherapy was justified to prevent local or systemic recurrence; this strategy has been effective with more than one year of follow-up.[1].
Attarbaschi, A, Blood, 2011.

Poster # 133

NK/T-CELL LYMPHOMA, NASAL TYPE SUCCESSFULLY TREATED WITH PBRT AND CONCURRENT SMILE CHEMOTHERAPY

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Background: NK/T-cell lymphoma is a rare subtype of Non-Hodgkin Lymphoma that typically affects adults and extremely infrequently children. Most patients present with localized disease involving the nasal cavity causing obstructive symptoms. Aggressive disease presents with B symptoms of night sweats, fevers and weight loss along with involvement of non-nasal sites. These cytotoxic cells cause angioinvasion and necrosis which explains its aggressive course and

prognosis. The cell of origin may be NK or T-cell with considerable immunophenotypic overlap. They express CD56, CD2, cytoplasmic CD3 epsilon and variable degree of CD30. Infection with Epstein-Barr Virus (EBV) is almost universal. Chromosome 6 changes are common, along with activation of JAK/STAT pathway, BCOR mutation (30%) and PD-L1 expression (80%). PET-CT is useful in initial stating but there's no data in assessing response to therapy. The 5-year OS and EFS for all patients is 59% and 34%, respectively. Extranodal NK/T-cell lymphoma (ENKTL), nasal type is resistant to anthracyclines. There's no standard of care based on randomized controlled trials in pediatrics, some regimens use chemotherapy before or concurrent with radiation. SMILE regimen is considered the best regimen for adults but there's limited data in children.
Objectives: To report a pediatric case of ENKTL, nasal type successfully treated with proton beam radiation therapy (PBRT) and concurrent SMILE chemotherapy.
Design/Method: Case report
Results: 8-year old female who presented with a five year history of intermittent fevers, fatigue, periorbital swelling and erythema. Initially they occurred 2-3 times per year with symptoms lasting for 5-10 days. In between flares she was completely asymptomatic. With time episodes became more frequent and she struggled with sinus infections. She underwent evaluation for recurrent fever syndrome and empirically received high-dose steroids, colchicine and canakinumab with no improvement. Two months prior to diagnosis she developed diplopia, blurry vision, epiphora and headaches, which lead to evaluation by ophthalmology. MRI showed an infiltrative soft tissue mass involving the left inferior and medial rectus muscle, left maxillary antrum, sphenoid & ethmoid sinus and bilateral nasal cavity. Biopsy confirmed EBV-positive ENKTL, nasal type. PET CT revealed no evidence of extracranial lymphoma. Bone marrow and CSF were normal. Patient received a total of 5040 cGy of PBRT concurrent with 6 cycles of SMILE chemotherapy (Dexamethasone, Methotrexate, Ifosfamide, L-asparaginase & Etoposide) with few uncomplicated episodes of febrile neutropenia. She achieved complete remission and has remained disease free for a year now.
Conclusion: PBRT with concurrent SMILE chemotherapy is effective in pediatric ENKTL, nasal type.

Poster # 134

TREATMENT OF HEPATOSPLENIC T CELL LYMPHOMA

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Background: Hepatosplenic T cell lymphoma (HSTL) is a rare and aggressive systemic neoplasm that arises from cytotoxic T cells, usually of gamma delta T cell receptor type. Induction treatment with CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) has shown beneficial response but standard treatment options are nonexistent. Long-term outcome remains poor with 5-year overall survival of 7%. Thus, there exists a critical need to identify new therapies for this fatal disease.
Objectives: To outline treatment of a child with HSTL leading to disease remission
Design/Method: Electronic medical records review
Results: A 16-year-old female presented with three weeks of fatigue, easy bruising, weight loss

and petechial rash. CBC revealed anemia, thrombocytopenia, and 9% blasts. Initial bone marrow aspirate showed no evidence of leukemia or lymphoma. A test for Mycoplasma returned positive for current infection. The patient met criteria for hemophagocytic lymphohistiocytosis (HLH) and was diagnosed with acquired HLH and treated per HLH 2004 protocol. Upon completion of HLH therapy her cytopenias and fevers returned. A repeat bone marrow aspirate and biopsy then revealed an abnormal T cell population and clonal T cell receptor consistent with hepatosplenic gamma delta T cell lymphoma. The patient was initially treated with two cycles of CHOP-E (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, Etoposide) but developed severe heart failure (ejection fraction 17%) thought to be anthracycline induced. She then received one cycle of Alemtuzumab and Cladribine with the intention of targeting CD52 lymphoma cells and limiting cardiotoxicity. This regimen was discontinued after 1 cycle due to worsening disease. She was subsequently treated with a combination of low dose steroids, Lenalidomide and Gemcitabine, which she tolerated well. Her heart function improved (ejection fraction 56%) with the addition of an inotrope and beta-blocker. She completed a bone marrow transplant workup and was deemed stable to proceed with transplant. Unfortunately, the patient died of septic shock and subsequent multiorgan failure 2 days prior to her planned transplant admission. At the time of her autopsy it was revealed that she had no evidence of malignancy in her bone marrow, liver or spleen suggesting that she achieved disease remission.
Conclusion: HSTL is a rapidly progressive disease refractory to widely-used treatments. This patient was able to achieve disease remission with low dose steroids, Lenalidomide and Gemcitabine though her demise was related to infection. Further research investigating potential therapies for treatment of this fatal disease are warranted.

Poster # 135

SUCCESSFUL TREATMENT OF PEDIATRIC SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA WITH CYCLOSPORINE A

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Background: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare malignancy characterized by infiltration of subcutaneous tissue by neoplastic T-cells. This uncommon lymphoma has a widely variable clinical course and often responds poorly to traditional anthracycline-based chemotherapy; therefore novel therapy approaches are necessary. Recently, there have been reports of adult patients receiving cyclosporine A (CSA) as a therapeutic intervention. Given the rarity, no consensus exists for treatment of pediatric patients with refractory disease.
Objectives: We present our experience with CSA in a pediatric patient with SPTCL.
Design/Method: We report the case of a 14 year-old boy who was diagnosed with SPTCL that was refractory to multiple chemotherapy regimens and ultimately achieved remission after treatment with CSA.
Results: The patient was healthy until age 14 years + 11 months when he presented with fevers, fatigue, poor appetite, and subcutaneous nodules scattered throughout his extremities. Biopsies of the subcutaneous nodules revealed an atypical lymphohistiocytic infiltrate surrounding adipose tissue characterized by cytotoxic T-cells with alpha-beta T-cell receptor (TCR),

consistent with SPTCL. Positron emission tomography/computerized tomography (PET/CT) scan revealed extensive PET avid subcutaneous lesions extending from the mid-chest to bilateral feet.Therapy was initiated with vinblastine and pulsed dexamethasone, however the subcutaneous nodules progressed and the patient experienced mild manifestations of hemophagocytic syndrome (HPS), including return of fevers. Therapy was intensified to a regimen including fludarabine, mitoxantrone, and pulsed dexamethasone, yet the nodules were refractory and fevers again recurred after cessation of steroids. Dexamethasone was resumed and CSA was initiated at a dose of 4 mg/kg/day divided BID with a goal trough level of 200-250 ug/L. Within 2 weeks there was dramatic improvement of the subcutaneous nodules and resolution of fevers, which continued after dexamethasone was stopped. PET/CT scans showed near resolution and complete resolution of PET avid disease at 4 months and 1 year post-initiation of CSA, respectively. CSA was discontinued after 24 months and the patient remains clinically well with no evidence of disease 5 months after completing therapy. This patient experienced hypertension that was controlled with amlodipine and carvedilol while on CSA. No other adverse events were noted.
Conclusion: CSA has been effectively used to treat SPTCL in adults and we are enthusiastic to share a unique case of successful applicability to a pediatric patient. This suggests that CSA is a potentially safe, tolerable, and effective therapy for SPTCL in children. It is important to investigate this further to improve outcomes of pediatric patients with SPTCL.

Poster # 136

CD30-(+), EBV-(+) T-CELL LYMPHOMA ASSOCIATED WITH CHRONIC ACTIVE EBV: TREATMENT WITH BRENTUXIMAB

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Background: Chronic active Epstein-Barr virus (CAEBV) is a rare disease where infection with the EBV-virus is inadequately controlled by the host immune system leading to circulating EBV DNA and infiltration of organs by EBV-positive lymphocytes. Disease manifestations include fever, lymphadenopathy, splenomegaly, hepatitis and pancytopenia. In the absence of effective therapy, progressive disease results in opportunistic infections, hemophagocytosis, multiorgan failure or EBV-positive lymphomas. Allogeneic hematopoietic cell transplantation (HCT) is recognized as the only curative therapy.
Objectives: To illustrate a rare case of CD30+ T-cell lymphoma in a patient with CAEBV following allogenic HCT
Design/Method: Case Report
Results: A previously healthy 9 year old female initially presented with daily fevers, sore throat, fatigue, and weight loss. She was subsequently diagnosed with CAEBV based on the presence of circulating EBV DNA and evidence of EBV positive lymphoproliferation seen on biopsies of the appendix and an inguinal lymph node. She received treatment with a matched sibling donor allogeneic HSCT. Despite having undetectable circulating EBV DNA at the time of transplant, circulating EBV DNA reappeared only 10 days after transplant and she received two infusions of donor derived EBV directed cytotoxic T-lymphocytes on days 40 and 54 post-HSCT. Five months after HCT, she developed a 2 cm exophytic lesion inside the right upper lip. Biopsy of

the lesion demonstrated a CD30+, EBV+ T-cell lymphoma. Immunohistochemistry was negative for ALK. A PET scan demonstrated uptake in the right upper lip with no other areas of increased FDG uptake. Local treatment was not considered to be a reasonable option due to its location as well as concern that this could represent systemic disease in the setting of significant immunosuppression. Treatment with brentuximab vedotin was started at a dose of 1.8 mg/m2/dose administered every 3 weeks. She had rapid resolution of the lesion after the first dose. She received a total of eight doses of brentuximab vedotin, requiring a dose reduction to 1.2 mg/m2/dose after the fifth dose due to peripheral neuropathy. She is currently 18 months from the completion of brentuximab with no recurrence of CD30+ lymphoproliferation.
Conclusion: EBV-positive lymphoma is a known complication of CAEBV infection. In this rare case of CAEBV complicated by CD30+ T-cell lymphoma, brentuximab vedotin led to a rapid and sustained response with manageable toxicity.

Poster # 137

CHRONIC ACTIVE EPSTEIN-BARR VIRUS AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: TREATMENTS AND OUTCOME

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Background: Chronic active Epstein-Barr Virus (CAEBV) is a rare diagnosis defined by prolonged history of symptomatic illness with EBViremia and organ involvement, without underlying known primary immune disorder. Although commonly found within the B cell population, EBV may be harbored within T or NK cells. Reported cases of CAEBV have mainly involved the latter cell lines, with only rare cases reported involving B cells. Sequelae include immunodeficiency, hemophagocytic lymphohistiocytosis (HLH), and lymphoma, with the only effective treatment being allogeneic hematopoietic stem cell transplant (HSCT).
Objectives: Report clinical sequelae of CAEBV, outlining the case pathology, genetics, and outcome.
Design/Method: Retrospective electronic medical record review of a single patient case.
Results: A 6 year-old, previously healthy female, presented with rash, fevers, hepatosplenomegaly, and anemia for several months duration. She was found to have EBV infection with high titers and subsequently demonstrated persisting and increasing EBV PCR viral loads, unresponsive to therapeutic trials of valganciclovir, IVIg, prednisone, or hydroxyurea. The patient developed criteria for HLH and received dexamethasone and etoposide therapy per HLH-94. EBV PCRs normalized with chemotherapy and fevers resolved. Extensive genetic and immunogenic testing obtained revealed decreased cytotoxic T cell function with decreased number of naïve CD4+ and CD8+ T cells; decreased CD25 and increased CD95 expression on CD4+ T cells; normal CD107a and T cell mitogen/antigen stimulation and degranulation studies; increased perforin expression in NK cells, with normal quantitative and qualitative function. HLH and SCID comprehensive genetic panels and whole exome sequencing were negative in regions of interest. She then had asymptomatic EBV reactivation (by PCR) ten weeks after completion of HLH-94 therapy. Patient received Rituximab with depletion of CD19+ B cells, but no appreciable response with persistent/increasing EBV PCR viral load. This suggested that the CAEBV was likely of T or NK cell origin and she was referred for allogeneic

HSCT. She received reduced intensity conditioning with alemtuzumab, fludarabine, thiotepa, and melphalan followed by a 10/10 matched unrelated, EBV seropositive, donor bone marrow transplant.
Conclusion: CAEBV infection is a rare, progressive disease that does not respond to available therapies outside of the treatment of associated HLH. Without tissue confirmed diagnosis, it is difficult to determine if the CAEBV infection is of B, T, or NK cell origin, which could drive a more targeted therapeutic plan. At this time, allogeneic HSCT likely offers the best chance for cure, but is limited by recurrent EBV viremia and disease, which is associated with a poor prognosis.

Poster # 138

TREATMENT OF PHENOTYPIC STAT1 GAIN-OF-FUNCTION PRESENTING AS IPEX-LIKE SYNDROME AND CAEBV

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Background: STAT1 gain of function (STAT1 GOF) mutations impair nuclear dephosphorylation and/or increase phosphorylation leading to GOF for STAT1-dependent responses and inhibiting STAT3-mediated Th17 cell differentiation. The clinical phenotype of STAT1 GOF mutations range from infections to autoimmunity, aneurysms and/or malignancy. Patients may have immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX)-like features; however, the frequency and function of Treg cells are normal. Management includes infection prophylaxis, IVIG, JAK inhibitors, and in certain cases, hematopoietic stem cell transplant (HSCT). Aberrant STAT activation in various malignancies may predispose patients to pathogenic Epstein-Barr virus (EBV) infection. Chronic active EBV (CAEBV) is a rare persistence of EBV in T and/or B-cells that infiltrate tissues causing fevers, lymphadenopathy, hepatitis and pancytopenia. While typically refractory to most treatments, successful responses to immunosuppressives, autologous EBV-specific cytotoxic T-cells and/or HSCT have been reported. We present a patient with a STAT1 GOF phenotype who developed CAEBV successfully treated with HSCT.
Objectives: To broaden the current understanding of STAT1 GOF and CAEBV and offer support for timely treatment.
Design/Method: Case report.
Results: Our patient presented at 6 months of age with refractory diarrhea and failure to thrive. He developed lymphadenopathy, autoimmune hemolytic anemia, eczema, chronic ear infections, and hypergammaglobulinemia. The number of FOXP3+ CD4+ cells and FOXP3 protein expression were initially decreased but normalized. He was started on tacrolimus for IPEX-like syndrome. By 2-3 years, he developed lymphoid interstitial pneumonia treated with steroids and recurrent EBV lymphoprolipherative disorder controlled with rituximab, but complicated by neutropenia/mucositis requiring GCSF. He developed B-cell dominant CAEBV requiring aggressive treatment with bortezomib combined with ganciclovir followed by rituximab. Whole genome sequencing was unrevealing. T-cell function testing demonstrated increased STAT1 phosphorylation in response to cytokines consistent with STAT1 GOF phenotype. He is 45 days after an 11/12 HLA MUD bone marrow HSCT using a reduced intensity preparative regimen

using distal alemtuzumab, fludarabine and melphalan with tacrolimus/MMF for GVHD prophylaxis. He engrafted on day 19 with 90% donor chimerism. His EBV remains negative and his donor participated in a study to generate EBV specific T-cells.
Conclusion: IPEX-like STAT1 GOF can be a life-threatening condition with a variety of infectious and autoimmune sequelae. In our case, the development of CAEBV refractory to rituximab prompted use of bortezomib, ganciclovir, and rituximab as a bridge to a reduced intensity MUD BM HSCT with successful engraftment.

Poster # 139

SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN AN INFANT WITH DISSEMINATED HISTOPLASMOSIS

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Background: Hemophagocytic lymphohistiocytosis (HLH) is an overwhelming inflammatory response, associated with an outpouring of cytokines and inappropriate activation of the macrophage system, which can cause severe morbidity and possible death. It can be a familial condition or secondary to a variety of other conditions including; but not limited to, oncologic, infectious, or rheumatologic conditions. Histoplasmosis-associated-HLH is a relatively rare disorder for which data are limited regarding optimal treatment and clinical outcomes in children. Here we describe a rare case of a 3-month-old child with disseminated Histoplasmosis infection and secondary HLH.
Objectives: Our aim is to broaden physician awareness and prompt further discussion and investigation of the optimal treatment strategy for secondary HLH in the pediatric population.
Design/Method: We report a unique case of an infant with a disseminated Histoplasma capsulatum infection and secondary HLH. A 3-month-old male presented with a history of fever for 11 days. On initial hospital evaluation, he had fever, lethargy, and hepatosplenomegaly. Laboratory testing showed pancytopenia. Abdominal computer tomography confirmed the hepatosplenomegaly. Additional laboratory testing revealed elevated ferritin (830 ng/mL; reference 50–200 ng/mL), low fibrinogen level (132 mg/dL; reference 200–400 mg/dL), elevated triglycerides (213 mg/dL; reference < 75 mg/dL) and elevated soluble interleukin-2 receptor (9,560 unit/mL; reference 334-3026 unit/mL). An HIV serologic test result was negative. Histologic examination of bone marrow showed many activated macrophages and evidence of hemophagocytosis. Further evaluation of the bone marrow sample demonstrated fungal elements characteristic of Histoplasma capsulatum. Serum and urine antigen assays were positive for Histoplasma capsulatum. Cerebrospinal fluid was negative for Histoplasma antigen. On the basis of clinical and laboratory findings, the patient received a diagnosis of disseminated Histoplasma capsulatum with secondary HLH. Treatment was started with intravenous Amphotericin B for 14 days followed by a 3-month course of oral itraconazole.
Results: Shortly after starting antifungal therapy, the patient's clinical condition stabilized, and he remains afebrile. Previously noted cytopenias rapidly improved. Soluble IL-2 and IL-18 as well as other laboratory findings consistent with HLH continue to trend toward normal, despite no treatment specific to HLH being started.

Conclusion: This case demonstrates an infant who had disseminated histoplasmosis, a rare infection that caused secondary HLH. Treating the infection with Amphotericin B and itraconazole initiated resolution of the secondary HLH. The infant was spared exposure to etoposide and dexamethasone as well as the long-term complications of these agents by only treating the infection.

Poster # 140

UNUSUAL PRESENTATION OF CMV INDUCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN TWO PEDIATRIC ALL PATIENTS

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by hyperinflammatory state due to aberrant activation of immune cells. Most HLH cases are triggered by infection and can be either familial or secondary to malignancy or autoimmunity. Histiocyte society suggested HLH-2004 protocol for diagnosis and treatment modalities including immunochemotherapy to stem cell transplant. However, there is no consensus on how to treat patients with HLH in the setting of underlying acquired immunosuppression.
Objectives: To report two pediatric cases of Cytomegalovirus (CMV) induced HLH during maintenance therapy of acute lymphoblastic leukemia (ALL).
Design/Method: Case series
Results: Our first case was a 3-year-old girl with high risk pre B-ALL admitted for evaluation of febrile neutropenia. She had hepatosplenomegaly on exam and was pancytopenic. Empiric antibiotic therapy was started but the fever persisted more than 7 days. Bone marrow biopsy was done that showed occasional hemophagocytosis without any blasts. Further testing revealed CMV viremia, quantitative polymerase chain reaction (PCR) being >2 million IU/ml. Complete work-up completed for HLH and she fulfilled 6 criteria. No genetic mutation was detected for HLH. The second case was a 4-year-old girl with high risk pre B-ALL, admitted for recurrent fevers, cough and non-bloody diarrhea. She only had faint macular rash on exam and was pancytopenic. Although she had been initially treated with empiric antibiotics, the fever persisted. Bone marrow biopsy was done that showed hemophagocytosis. She was found to have a quantitative CMV PCR of 1.3 million IU/ml. She was diagnosed with HLH with 6 criteria, started on dexamethasone and ganciclovir. The genetic analysis for HLH showed heterozygote mutation at UNC13D gene.Both patients initially had fever, cytopenia, hyperferritinemia, hypertriglyceridemia, hemophagocytosis, elevated soluble interleukin 2 receptor (sIL-2r) in serum. The fever resolved two days after starting steroid and antiviral therapies. Total therapy was completed to 4 weeks in total, until serum CMV PCR was undetectable and ferritin trended down. On follow-up, they successfully continued maintenance chemotherapy at full dose.
Conclusion: CMV-induced HLH is a rare phenomenon in non-transplant ALL patients. Delayed recovery of T-cells in leukemia patients during maintenance therapy can predispose them to develop HLH. There are five smiliar cases in the literature. They were also treated with antivirals, steroids and some also with IVIG. We suggest that the aggressive cytotoxic therapy

may be avoided in the treatment of HLH, especially in the face of active CMV infection and underlying chemotherapy induced immunosuppression.

Poster # 141

A RARE FHL INHERITANCE SCENARIO IN HALF-BROTHERS

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Background: Hemophagocytic lymphohistiocytosis (HLH) is characterized by massive infiltration of several organs by activated macrophages/ T-lymphocytes resulting in clinical symptoms of fever, hepatosplenomegaly, cytopenia and less frequently neurological abnormalities. HLH can be sporadic (secondary to infections, tumors, autoimmune diseases or acquired immune deficiencies) or genetic (known as familial hemophagocytic lymphohistiocytosis or FHL). FHL can result from pathogenic variants in several genes and its incidence is 1:50,000 live births. The age of onset for FHL is typically infancy or childhood and is fatal unless treated with hematopoietic stem cell transplantation. Both secondary and familial forms of HLH can be triggered by infections and are clinically indistinguishable.
Objectives: To describe a rare FHL inheritance in two half-brothers with a novel deletion and different missense variants in STXBP2
Design/Method: Case report
Results: A 3-month-old African American male patient presented with fevers, pancytopenia, hepatosplenomegaly, respiratory distress, elevated triglycerides and decreased fibrinogen. He had a maternal half-brother who was also diagnosed with HLH at 5 months and passed away at 14 months. The half-brother had genetic testing in 2010 and sequencing of PRF1, UNC13D, XIAP and SH2D1A did not identify any pathogenic variants. With the availability of more comprehensive genetic testing, our current patient was evaluated using a 16 gene HLH sequencing panel and was found to be heterozygous for a likely pathogenic variant (c.389T>C(p.Leu130Ser)) in exon 6 of STXBP2 (NM_006949.3). Follow up deletion/ duplication analysis of STXBP2 identified a heterozygous partial deletion involving intron 13 to exon 19, which confirmed his diagnosis of FHL. Interestingly, when this new expanded HLH sequencing panel was performed posthumously on his deceased half-brother using leftover sample, he appeared to be homozygous for a separate missense pathogenic variant (c.1621G>A (p.Gly541Ser)) in exon 18 of STXBP2. Deletion/ duplication analysis of STXBP2 in his half-brother identified the same partial deletion seen in our patient, which showed that the p.Gly541Ser missense variant was truly heterozygous and only appeared homozygous because of its overlap with the deleted region. Our patient also has a full sister who was found to be a carrier of the partial deletion in STXBP2 but not the missense variants identified in her brothers.
Conclusion: We describe a rare FHL inheritance scenario in half-brothers. Molecular diagnosis is critical in FHL patients to confirm diagnosis, establish recurrence risk and allow pre-symptomatic testing of at-risk siblings.

Poster # 142

DIAGNOSTIC COMPLEXITY IN PEDIATRIC PATIENTS WITH LYMPHOMA-ASSOCIATED HLH

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Background: Hemophagocytic Lymphohistiocytosis (HLH) is a life-threatening disorder characterized by severe immune dysregulation. The diagnosis of HLH is complicated by variable presenting symptoms that often overlap with a wide range of illnesses. Further, differentiating familial from acquired HLH in association with malignancy is challenging due to similar presentations and rarity in pediatrics. While cases of malignancy-associated HLH (M-HLH) exist, there are few reports of pediatric lymphoma subtypes. These unique cases illustrate the obstacle in prompt recognition of M-HLH and describe an association with non-Hodgkin lymphoma.
Objectives: To present two atypical pediatric cases of lymphoma-associated HLH.
Design/Method: Case Series.
Results: Case 1: A 16-year-old boy with a preceding diagnosis of viral myopericarditis was readmitted for month-long fever, dyspnea, acute hypotension, and tachycardia. Laboratory evaluation revealed anemia, thrombocytopenia, and elevated inflammatory markers. Further testing showed hyperferritinemia, hypertriglyceridemia, and elevated soluble IL-2 receptors (sIL-2R). Bone marrow aspiration demonstrated hemophagocytosis, helping to confirm a diagnosis of HLH. CSF was negative. CT chest/abdomen/pelvis revealed hepatosplenomegaly and a soft tissue mass in the pelvis with bony metastases (rib). Biopsy revealed anaplastic large T-cell lymphoma. The patient was treated with steroids for his HLH (post-biopsy) and received chemotherapy to treat his lymphoma. Organomegaly resolved following steroids; the soft tissue mass and metastatic disease responded to standard therapy.Case 2: A 9-year-old boy presented with a 2-month history of recurrent fevers, neutropenia, thrombocytopenia, and an enlarging right thigh nodule. Initial imaging of the nodule showed a nonossifying fibroma vs fat necrosis. Physical exam revealed additional subcutaneous nodules, petechiae, and splenomegaly. Labs showed hyperferritinemia, decreased NK cell function, and elevated sIL-2R meeting criteria for HLH. Perforin gene mutation confirmed familial-HLH. Biopsy of the thigh nodule was diagnostic for a subcutaneous panniculitis-like T-Cell lymphoma (SPTCL). Patient underwent chemotherapy and achieved remission; however, he relapsed four months later with recurrence of both the lymphoma and HLH. Following stem cell transplantation, he is currently in second complete remission (CR2).
Conclusion: Conclusion: These cases illustrate the diagnostic challenge of lymphoma-associated HLH in pediatrics, specifically, the variability in presentation and genetic findings. Due to the aggressive nature of both HLH and different lymphomas, it is vital to maintain a high suspicion for M-HLH as initiation of appropriate treatment can be lifesaving. Similar to the second patient, M-HLH can be associated with genetic findings that become important in treatment decisions and the choice to pursue transplant. Additional guidelines would be helpful to effectively diagnose and treat M-HLH in children.

Poster # 143

IMMUNE RELATED ROSAI–DORFAMAN–DESTOMBES DISEASE: A CASE OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Rosai–Dorfman–Destombes (RDD) is a rare non Langerhans cell histiocytosis caused by activated histiocytes accumulated in body tissues. The most common presentation of RDD is massive cervical lymphadenopathy, and less common the presence of extranodal disease in the skin, sinuses or central nervous system. RDD can coexist with immunological disorders. The association of RDD and systemic lupus erythematosus (SLE) is rare with one case reported in the literature.
Objectives: To describe a case of an adolescent female with biopsy-proven RDD associated with LES with severe renal involvement.
Design/Method: Case Report
Results: A 15-year-old female presented with one month history of left-sided neck swelling. At initial evaluation she had a small (1.5 – 2 cm), soft, mobile lymph nodes in the anterior cervical chain and the pre-auricular area. The lymph nodes were reportedly decreased in size from the initial presentation (2 times smaller). Her complete blood cell count, liver and renal functions, electrolytes, erythrocyte sedimentation rate, lactate dehydrogenase, and uric acid were within normal limits as was a chest XR. Three days later the swelling of her neck increased up to 14 cm in diameter and she developed fever and pain. A fine needle aspiration showed a benign lymph node with reactive sinus histiocytes. A repeat incisional biopsy showed sinus histiocytosis, emperipolesis, and prominent eosinophilic infiltrate compatible with RDD. In between biopsies her massive cervical lymphadenopathy spontaneously regressed but she developed generalized edema, hypertension, and elevated creatinine. Additional evaluation included ANA screen and SS-A and B antibody which were all negative. C3 and C4 were low. Fungal and viral testing was negative. An abdominal CT showed extensive lymphadenopathy below the diaphragm and splenomegaly. Since hypertension and acute renal failure persisted a kidney biopsy was performed showing diffuse proliferative glomerulonephritis consistent with active lupus nephritis INS/RPS class IV. The patient received treatment with Rituximab.
Conclusion: RDD is a rare disease that can occur in association with autoimmune diseases. In the presence of other associated symptoms, in this case (hypertension, edema, and renal failure) RDD should be seen more as a manifestation of an underlying diagnosis either autoimmune or malignant unless a specific genetic predisposition is found to explain RDD.

Poster # 201

DIAGNOSIS AND OUTCOMES OF PEDIATRIC INCIDENTALOMAS: A STUDY OF 55 CASES FROM A SINGLE CENTER

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Background: An incidentaloma is a lesion discovered during an imaging study, which is unrelated to the original reason for ordering the test. Their significance is often unclear, and little is described regarding the outcome of pediatric incidentalomas.
Objectives: The goal of this review is to describe the clinical course of pediatric incidentalomas discovered at a single center.
Design/Method: Charts of patients with newly diagnosed solid tumors seen by oncology at Texas Children's Hospital in Houston, Texas between January 2015 to May 2018 were manually reviewed. Patients were considered to have an incidentaloma if their lesion was found incidentally on imaging obtained for unrelated reasons. In those cases, clinical data including size of lesion, additional imaging studies, whether biopsy and or surgical resection was pursued, diagnosis, and outcome were extracted from the electronic medical record.
Results: Incidental lesions were identified in 55/786 (7%) of the patients reviewed. The lesions had a mean size of 4.7 cm (range 0.6-17.5 cm). 48/55 patients had follow-up imaging with a mean of 1.9 subsequent imaging studies per patient (range 0-6). Ultrasound was the most common follow-up imaging modality (29%), followed by MRI (26%), CT (23%), MIBG (14%), x-ray (6%), PET (1%), and echocardiogram (1%). 22/55 patients had surgical or IR-guided biopsy of the lesion, and 32/55 patients had surgical resection of the lesion. The 14 patients in whom biopsy or surgical resection was not pursued had lesions with a mean size of 3.1 cm and in the following locations: adrenal (4), bone (3), liver (2), and other (5). These diagnoses were made based on characteristic radiological findings. 37/55 lesions were benign with the most common diagnosis being benign bone lesions (7/37), followed by ganglioneuroma (4/37), and mature teratoma (4/37). 18/55 lesions were malignant with the most common diagnosis being neuroblastic tumors (7/18), followed by papillary thyroid carcinoma (4/18), and malignant renal tumors (3/18). Follow-up information was available in 53 patients. Two patients died of reasons unrelated to their incidentaloma. All other patients are alive and asymptomatic from their incidentaloma at the time of last follow-up.
Conclusion: Pediatric incidentalomas are an uncommon finding with an incidence of 7% in this series of oncology referrals. However close follow-up is warranted in this population as malignant lesions occurred in 33% of these patients.

Poster # 202

SUPRA-RENAL MASS IN PEDIATRIC GROUP: CASE SERIES FROM THE PERIOD 2009–2018 IN SOUTHERN TAIWAN

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Background: Supra-renal mass is a commonly encountered problem in clinical setting. Among pediatric populations, it is discovered in symptomatic patients or incidentally in asymptomatic patients who undergoing abdominal image studies. The diagnosis encompassed variety of possible etiologies from congenital to acquired, benign to malignant, and varies differently across all ages. To discriminate malignancy from benign etiology remains challenging.
Objectives: We want to assess etiologies, image findings and characteristics and clinical presentations of supra-renal mass among children and young infants. at a medical center in southern Taiwan.

Design/Method: Patients under 18-year-old who had been hospitalized and visited outpatient clinic from Jan. 2009 to June. 2018 at National Cheng Kung University Hospital were enrolled. Clinical characteristics, image findings, pathological reports and final diagnosis were reviewed retrospectively from medical records.
Results: Totally fourty-five patients aged 0 to 18 years are enrolled. Thirty-tow patients are diagnosed with adrenal hemorrhage, ten patients are the case of malignancy, and three patients turn out to be adrenal hyperplasia. The primary diagnosed image tool is ultrasound. Among thirty-two patients with adrenal hemorrhage, they are almost term infants, delivered by normal spontaneous delivery with mainly neonatal jaundice as the clinical presentation. Sonographic features are usually unilateral (right > left), heterogeneous, hypoechoic without blood flow, ranging from 1.0 × 0.66cm to 5.05 × 3.75cm in size. For those with malignancy, they came with mainly gastrointestinal symptoms (vomiting, abdominal pain, fullness, or abdominal mass). The image features come into diverse appearance-from homogeneous to heterogeneous, cystic to multiple calcifications, with negative to positive blood flow signs. Notably, calcification and positive blood flow signs are present in malignancy while those are absent in benign mass.
Conclusion: The current study provides information concerning etiologies, image findings, characteristics and clinical presentations of supra-renal mass among the pediatric group. Some risk factors, clinical presentations and images features are well-recognized and of clinically important values, especially for malignancy. Large, well-designed study is warranted in the future to establish well-organized approaching method aiding physician in clinical practice.

Poster # 203

CLINICAL UTILITY OF HEMATURIA ON URINALYSIS IN THE DIFFERENTIATION OF RENAL AND ADRENAL TUMORS

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Background: Abdominal masses in pediatric patients can grow quite large and often obscure normal anatomy, which makes determining the organ of origin quite difficult. In the United States, treatment for most renal tumors involves upfront nephrectomy. Children with adrenal masses like neuroblastoma that obscure normal anatomy may be subjected to unnecessary surgical procedures, which may impair the ability to give nephrotoxic therapies. As microscopic hematuria presents itself in 25% of cases of Wilms' tumor, we sought to determine whether patients with renal tumors had a higher incidence of hematuria than patients with adrenal tumors. This study aimed to provide data on a simple biomarker that can help avoid unnecessary surgical procedures in patients with abdominal tumors.
Objectives: The purpose of this study was to investigate the utility of hematuria on urinalysis at diagnosis in differentiating renal from adrenal neoplasms.
Design/Method: This is a single center, retrospective analysis of patients between ages 0 and 18 from January 1, 2000 and June 19, 2018 who had one the following ICD-O site codes: C64.9-Kidney NOS, C74.9-Adrenal gland NOS, C74.0- Adrenal gland cortex, C74.1-Adrenal gland medulla. Patients were included in analysis if urinalysis data was available and the date of urinalysis preceded the date of initial/diagnostic surgery. Hematuria from the urinalysis was categorized as absent, 1+, 2+, 3+ or 4+. Data were analyzed using logistic regression and Wald

based 95% confidence intervals (CI) were generated for all associations. Analyses were performed between the absence and presence of hematuria as well as between the hematuria category.
Results: 281 patient records were reviewed, and urinalysis data was available on 146 (52.0%) patients. 99 patients had a renal neoplasm and 47 patients had an adrenal neoplasm. Hematuria was present in 38 (38.4%) and 10 (21%) patients with renal and adrenal neoplasms respectively. 4+ hematuria was present in 21 and 1 patients with renal and adrenal neoplasm respectively. Patients with any hematuria were more likely to have a renal tumor than adrenal (OR 2.31, CI 1.02-5.23 p=0.046) as were patients with 4+ hematuria (OR 12.74, CI 1.56-104.1, p=0.018).
Conclusion: The presence of any hematuria as well as 4+ hematuria compared to the absence of hematuria is associated with an increased odds of a renal neoplasm than with adrenal neoplasm and may aid in the diagnostic workup of and abdominal tumors in children and adolescents.

Poster # 204

OUTCOME AND PROGNOSTIC FACTORS OF HIGH RISK NEUROBLASTOMA IN LOW INCOME COUNTRIES

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Background: Children with high-risk neuroblastoma have poor outcome.There was progress in treatment using myeloablative chemotherapy and radiotherapy plus purged ABMT with significant difference in 3-year event free survival (EFS) compared with conventional chemotherapy (CC), although overall survival (OS) was not significantly different.
Objectives: This work aims To ASSES IMPACT OF DIFFERENT PROGNOSTIC FACTORS ON (OS) and (EFS) of high risk neuroblastoma patients
Design/Method: Retrospective study at the National Cancer Institute, Egypt including 133 high risk Neuroblastoma patients recruited from 1/01/2008 to 31/12/2015 .
Results: All patients received induction chemotherapy (VP16/CARBO,alternating with CADO) (6 to 8 cycles) ,post induction two patients died from septic shock ., Two were in CR, 15 patients were in VGPR, 82 were in PR, 23 had NR& 9 had PD.,There was no statistically significant impact of different metastatic sites on the overall survival except for liver metastasis that showed inferior 3 years overall survival (12.5%) compared to those without (41.4%) with P =0.003.3 years OS for (CR,VGPR& PR) group was (51.7%) compared with (19%) (NR& PD) group in correlation to induction therapy with (P<0.001). 71 patients needs salvage (ICE), 9 died from septic shock as complication of salvage treatment and 13 showed CR , VGPR in 11 , PR in 5 , 33 patients had progressive disease Patients with MYCN amplification showed inferior 3 years overall survival (35.9%) compared with non-amplified MYCN (40.4%) with P=0.900,high serum ferritin , stage 4 vs 3, unfavorable pathology were associated with significantly inferior OS.,EFS . Single HSCT was done in 49 patients(no tandem transplant is done in our center). Patients who received HSCT showed better 3 years overall survival (66.5%) than those who did not (24.4%) (P<0.001). surgical resection regardless extent of resection, consolidation by HSCT and radiotherapy , maintenance by CisRetinoic has significant positive impact on outcome .At end of treatment, 16 were dead as treatment complication, 26 were in CR, 10 were in VGPR, 6 were in PR and 75 patients had PD.The median follow-up period was 22 months . At the end of

the study, 91 patients died. The cumulative OS,EFS at 24, 36 months was (48.8%,29.3%) and (39.7% , 22.7%) respectively .
Conclusion: High risk Neuroblastoma still having poor outcome especially in low income countries with lack of facilities and financial support , more insights should be directed to tandem transplant and immune therapy to improve outcome.

Poster # 205

INTERMEDIATE-RISK NEUROBLASTOMA: EXPERIENCE FROM NATIONAL CANCER INSTITUTE, EGYPT (2008-2015)

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Background: The survival rate among patients with intermediate-risk neuroblastoma who received reduced-dose chemotherapy is excellent.
Objectives: We performed a retrospective review of patients treated for intermediate-risk neuroblastoma to estimate eventfree survival (EFS) and overall survival (OS) and to evaluate the impact of response to chemotherapy and degree of resection on the outcome of these patients.
Design/Method: Medical records of patients with intermediate-risk neuroblastoma, who were treated at National Cancer Institute in Egypt from 2008 to 2015, were reviewed. First line chemotherapy was OJEC & OPEC or Vp16/CARBO & CADO. The patients were evaluated after 4 cycles for possibility of surgical excision and if not possible; they continued on the same chemotherapy till being operable if there was response. Both OS & EFS were computed and analyzed in relation to different prognostic variables.
Results: Fifty patients were candidate, 25 males and 25 females, 84% abdominal primary tumors, 66% stage III. We reported a complete response (CR) or a very good partial response (VGPR) to induction chemotherapy, with or without surgery in 26% of patients that has increased to 60% after 8 cycles. The 5-year OS and EFS were 83% and 73% respectively. There was statistically significant difference in 5-years OS and EFS between patients with stage III vs IV {93% and 52%; p=0.002 versus 81% and 46%; p=0.01 respectively}. Moreover, 5-years OS and EFS for patients who underwent ≥90% versus <90% resection of primary tumour were not statistically significant {92% and 77%; p=0.3 versus 84% and 63%; p=0.14 respectively}. The 5-years EFS rate among those who achieved CR or VGPR post induction therapy was slightly higher than those achieved PR only {84% and 69% respectively; p=0.28} but the 5-years OS was the same {84% and 83%respectively; p=0.86}.
Conclusion: Acceptable rate of survival among patients with intermediate-risk neuroblastoma (especially stage III) was achieved with chemotherapy ± surgery. The extent of surgical resection of the primary tumor didn't influence the outcomes. Adopting biological-based treatment is required for better risk stratification.

Poster # 206

NEUROBLASTOMA IN CHILDREN OLDER THAN 10 YEARS: UNUSUAL CLINICOPATHOLOGIC AND BIOLOGIC FEATURES

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Background: Neuroblastoma is one of the most common malignancies in children and accounts for 15% of pediatric cancer deaths. It is most common in young children where the median age at diagnosis is 2 years. The survival of patients depends on the presence of numerous prognostic factors including age. The occurrence of neuroblastoma in children over 10 years of age is rare and few clinical studies are published in this age group emphasizing their poor outcome.
Objectives: Describe 4 cases of neuroblastoma in children older than 10 years and highlight their unusual clinicopathologic and biologic features, including results of deep targeted exome sequencing, single nucleotide polymorphism DNA microarray, and ATRX immunohistochemistry results.
Design/Method: This is a case series. We reviewed our archives for patients with neuroblastoma aged 10-18 years and summarized their clinicopathologic and genetic records. Of 96 patients with neuroblastoma, four patients with five tumors were identified in this age group.
Results: Four tumors were abdominal and one presacral. Tumor sizes ranged from 3-20cm. All tumors were high risk at clinical stages 3 and 4, with metastasis to bone marrow and other areas. Four tumors were poorly differentiated with unfavorable histology and one patient with bilateral adrenal disease had an intermixed ganglioneuroblastoma on one side. Another tumor exhibited pheochromocytoma-like morphology. MYCN amplification was present in bone marrow metastasis in only one case. The same case had partial loss of ATRX immunohistochemistry in the primary tumor. Complex chromosomal gains and 19p deletions were common. Exome sequencing revealed ALK variants in two cases and previously unreported MAGI2, RUNX1 and MLL mutations. All patients initially received standard therapy per Children's Oncology Group protocols (including ANBL0532 and ANBL1232), and two patients eventually received ALK-targeted trial therapy. Three patients died of disease, ranging 18-23 months after diagnosis. One patient has active disease and is receiving trial therapy.
Conclusion: Neuroblastoma in children older than 10 years may exhibit unusual clinicopathologic and genetic features with large tumors, bilateral adrenal disease, rare morphologic features, complex DNA microarray findings and novel mutations. Patients have grim prognoses despite genomic profiling-guided targeted therapy.

Poster # 207

BILATERAL SUPRARENAL NEUROBLASTOMA

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Background: Bilateral suprarenal Neuroblastoma (BSN) is a rare presentation; it could occur on both sides simultaneously or less commonly metachronously. Few previously published literature showed patients with BSN to have more favorable biological features and prognosis.
Objectives: To evaluate clinical and biological features and outcome of patients with BSN

treated at the Children Cancer Hospital-Egypt (CCHE/57357).
Design/Method: This retrospective study included patients with BSN presented to CCHE from 2007 to 2017. A pre-treatment biopsy of the primary tumor, PET-CT/MIBG as well as other imaging studies and bone marrow evaluation were done at time of presentation. Clinical variables; age, gender, stage, MYCN gene status, histological classification and risk group were determined and analyzed in relation to overall (OS) and event free survival (EFS).
Results: Study included 33 patients with BSN; representing 2% of CCHE patients with neuroblastoma during study period, 17 were males and 16 females. Twenty four patients were infants less than 1 year old versus 9 above 1 year of age (range: 1 month to 3 years). Metachronous disease was present in only one patient. Ten patients had amplified MYCN, 18 were not amplified and 5 were not done. At diagnosis, most patients had metastatic disease (20/25 stage 4, 5/25 stage 4s), 6 were stage 3 and 2 patients had stage 2 disease. Fifteen were treated as high risk (HR), 15 as intermediate (IR), 2 as low risk (LR) and 1 was undetermined due to inadequate tissue biopsy. Total number of deaths were 13 (39%).The 3-year OS for HR and IR patients were 37.8% and 78.3% versus 21.7% and 52.9% EFS; respectively.
Conclusion: Patients with BSN have carry poorer biological features and more advanced disease compared to patients with unilateral adrenal disease of similar stage and risk category as well as poorer outcome than previously reported in literature.

Poster # 208

PLASMA CELL-FREE DNA FOR NONINVASIVE MOLECULAR DIAGNOSTICS IN WILMS TUMOR PATIENTS

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Background: Renal tumors are generally managed in North America with up-front nephrectomy followed by chemotherapy. Biopsy of these tumors is often avoided due to concerns of local upstaging. In contrast, patients in Europe and elsewhere with renal tumors are treated with neoadjuvant chemotherapy prior to surgery. The former approach favors prompt accurate diagnosis whereas the latter favors reduced surgical morbidity. If one could noninvasively identify clinically relevant diagnostic tumor biomarkers, then the paradigm could be shifted to favor both diagnostic accuracy and reduced surgical morbidity.
Objectives: Circulating cell-free DNA (cfDNA) has been shown to be a noninvasive platform to determine molecular profiles of solid tumors. This study aims to determine if it is feasible to detect cfDNA at diagnosis in children with Wilms tumor.
Design/Method: Plasma cfDNA and matched buffy coat were collected from patients with Wilms tumor prior to their surgical resections, at or near diagnosis. Once extracted, cfDNA was analyzed by targeted and shallow whole genome sequencing (sWGS) to determine somatic mutations and copy number alterations. The matched buffy coat was also analyzed to filter out germline mutations. Molecular profiles of the primary tumors were determined after resection by MSK-IMPACT, an FDA approved clinical sequencing assay, to determine whether somatic mutations identified in the tumor matched those identified in cfDNA.
Results: Eight patients, 7 favorable and 1 diffusely anaplastic, with 3 localized and 5 metastatic

Wilms tumors were analyzed. Somatic mutations and copy number alterations were noted in the plasma cfDNA of 7/8 (87.5%) patients, including alterations in AMER1, DICER1, CTNNB1, MAPK1, TP53, and DROSHA. In 2 patients, neoadjuvant chemotherapy rendered tumors completely necrotic thus limiting both histologic and genomic evaluation, however mutations in AMER1 and DICER1 were detected in cfDNA samples collected at diagnosis. In another 2 patients, gain of 1q was also noted by sWGS of the cfDNA samples.
Conclusion: This study demonstrates that it is feasible to use plasma cfDNA to noninvasively determine the driver mutations and molecular features of Wilms tumors at diagnosis, notably including the detection of prognostically relevant mutations (e.g. TP53) and copy number alterations (e.g. 1q gain). In patients with necrotic tumors following neoadjuvant chemotherapy, this platform provided molecular confirmation of the diagnosis. Future studies are warranted to determine if plasma cfDNA can help direct the use of novel targeted therapies, detect clonal evolution, and identify minimal residual disease.

Poster # 209

INTRACAVAL EXTENSION OF NON-WILMS PEDIATRIC SOLID TUMORS AT THE TIME OF INITIAL DIAGNOSIS

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Background: Non-Wilms pediatric abdominal tumors with direct intravascular extension are rare and there are no standard treatment guidelines.
Objectives: To review the occurrence, treatment and outcomes of children with non-Wilms abdominal tumors with intracaval extension present at diagnosis over a 10-year period at a single institution.
Design/Method: A retrospective chart review was performed for June 2008-June 2018 at Texas Children’s Cancer Center. Charts of all known patients diagnosed with neuroblastoma and clear cell carcinoma were examined. Diagnostic radiology reports were evaluated for the presence of intracaval tumor extension. In the case of unclear involvement radiology then reviewed the diagnostic scans to confirm intracaval extension. Inclusion criteria required extension into at least the vena cava present at diagnosis and treatment initiated and completed at our institution.
Results: Three patients met inclusion criteria. 2 had stage IV neuroblastoma and 1 had stage IV clear cell sarcoma of the kidney. The incidence of patients presenting with intracaval tumor extension into major vessels was 1.4% for neuroblastoma (2 of 142 patients), and 17% for clear cell sarcoma of the kidney (1 of 6 patients). All 3 patients had extension of tumor into the inferior vena cava extending into the right atrium. All patients underwent neoadjuvant chemotherapy with subsequent intravascular tumor shrinkage at the end of induction in the 2 patients with neuroblastoma leading to regression of the tumor thrombus from the right atrium. The patient with clear cell sarcoma showed stable disease but no regression. Surgical resection was completed in all 3 patients with cardiopulmonary bypass only required in the patient with clear cell sarcoma. Both neuroblastoma patients achieved complete remission with subsequent recurrence and death. The patient with clear cell sarcoma is currently alive and continues on therapy.

Conclusion: Intravascular extension from a Wilms tumor is well known. We show that other tumors can also display intravascular extension and therefore initial diagnostic biopsy is essential for appropriate preoperative therapy. Our data suggests that preoperative therapy contributes to safe removal of primary tumor and extension. Further evaluation is being done to examine intracaval extension in other solid tumors.

Poster # 210

REAL WORLD OUTCOMES OF RELAPSED FAVORABLE HISTOLOGY WILMS TUMOR PATIENTS

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Background: The last major cooperative group clinical trial for relapsed favorable histology Wilms tumor (FHWT) completed in 2002. The real world outcomes of patients with relapsed Wilms tumor is unknown.
Objectives: The aim of this study was to assess the efficacy and toxicity of salvage therapies used for patients in first relapse from FHWT.
Design/Method: We performed a retrospective chart review of patients treated for relapse of FHWT from January 2002 through August 2018. Patients who received two drug therapy (dactinomycin, vincristine) for their primary tumor were classified as standard-risk relapse; those who received three drugs (doxorubicin, dactinomycin, vincristine) were classified as high-risk relapse and those who received more than 3 drugs were classified as very high-risk relapse.
Results: We identified 22 patients who received treatment for relapsed FHWT at Texas Children's Cancer Center. Of these patients, 12 (54%) were considered standard-risk relapse, 9 (41%) were high-risk and 1 (5%) was very-high-risk. Nineteen patients (86%) relapsed within 12 months of completing primary treatment, with 100% relapsed within 24 months. Twenty patients had distance relapse; of these 16 had lung metastases. Eleven of the standard-risk patients were treated with Regimen I (etoposide, doxorubicin, cyclophosphamide, vincristine), while one patient had resection only. EFS and OS for standard-risk patients was 84% and 100%, respectively. Eight high-risk patients were treated with NWTS-5 Stratum C (etoposide, carboplatin, cyclophosphamide) and one received ICE therapy (ifosfamide, carboplatin, etoposide). No patient was able to complete therapy per stratum C due to toxicity; median maintenance cycles administered was 2. The very high-risk patient was treated with ICE. The EFS and OS for high-risk patients were both 37.5%, respectively.
Conclusion: Our data suggests that in the real world standard-risk patients had a higher EFS and OS when compared to the results from NWTS-5 (EFS 73% and OS 84%). Inversely, our high-risk patient population had a worse outcome when compared to the results of NWTS-5. A multicenter review is planned to overcome the limitations of small patient numbers.

Poster # 211

INTRATUMORAL GENETIC HETEROGENEITY IN PEDIATRIC ALVEOLAR RHABDOMYOSARCOMA

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Background: Rhabdomyosarcoma is the most common pediatric soft tissue sarcoma with 400 to 500 new cases diagnosed in the United States annually. The alveolar subtype (ARMS) typically has a more aggressive clinical course and portends a worse clinical prognosis than the embryonal subtype (ERMS). Therefore, distinguishing between the two subtypes is necessary for appropriate prognosis. ARMS is characterized by one of three translocation states: the presence of [t(2;13)(p35;p14)] leading to the production of the PAX3-FOXO1 fusion protein, the presence of [t(1;13)(p35;q14)] leading to the production of the PAX7-FOXO1 fusion protein, or a translocation negative status. Multimodality analyses, such as SNP array and RT-PCR, have previously shown that significant heterogeneity regarding the number of translocations exists within tumor tissue samples from rhabdomyosarcoma patients, leading to a variation in clinical outcome.
Objectives: The aim of this study is to investigate the heterogeneity of pediatric ARMS tumor specimens obtained from patients of the Children's Hospital of New Orleans Hematology/Oncology clinic and correlate these findings with clinical outcomes.
Design/Method: We have designed and validated a fluorescence in situ hybridization (FISH) probe in our laboratory which can simultaneously and distinctively tag t(2;13) and t(1;13) translocations. Tumor samples from rhabdomyosarcoma patients ranging in age from 6 months to 18 years were analyzed to determine the presence of these clinically significant translocations and the extent of heterogeneity within each sample. Retrospective chart review was then performed to analyze the 3-year event-free survival of these patients with respect to the translocation status and heterogeneity of the tumors.
Results: Our analysis of the cytogenetic markers for t(2;13) confirms that these translocations exhibit significant numerical variation within these rhabdomyosarcoma samples. Our review of the patient-specific data reveals that there is a correlation between the percent of t(2,13)+ cells within the tumor sample and the patient's clinical outcome. There are 3 ARMS patients that are alive greater than 3 years after diagnosis and of these they had less than 20% t(2,13)+ intratumoral cells by our FISH analysis. Additionally, patients with greater than 80% t(2;13)+ cells were all deceased prior to 3-year follow-up.
Conclusion: Heterogeneity with respect to t(2;13) within alveolar rhabdomyosarcoma tumors may impact response to treatment as evidenced by our findings. This is clinically significant with regards to patient prognosis at time of diagnosis as well as the importance of future treatment strategies targeted to t(2,13)+ alveolar rhabdomyosarcoma.

Poster # 212

CCHE EXPIERNCE IN HIGH RISK RHABDOMYOSARCOMA PATIENTS

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Background: Rhabdomyosarcoma is a rare cancer, but it's the most common type of soft tissue cancer in kids with approximately 350 new cases per year in the U.S. Unfortunately, at least 15% of children with RMS present with metastatic ([IRS] Group IV) disease, and their prognosis has not improved significantly in the last 15 years. Despite the development of more intensive therapies, the overall cure rate remains below 30%. According to COG (IRS IV) Patients with group IV (metastatic) RMS have long-term FFS rates of <30%
Objectives: To study and identify risk factors associated with outcome in children with metastatic rhabdomyosarcoma in a large cohort of patients
Design/Method: Cases presented to Children Cancer Hospital of Egypt (CCHE) with stage IV rhabdomyosarcoma from July 2007 to December 2017 were studied and analyzed
Results: One hundred thirty two patients were analyzed retrospectively. Cases with age from 1 to 10 years were 85 cases, 34 were above 10 years and 4 cases below one year of age.Most of the cases (111 case) were presented with an unfavorable site and 12 cases had a favorable site. Cases had pathology of alveolar RMS (62 cases) in comparison to 61 cases of embryonal pathology. Most of the cases 89 cases had tumor size above 5 cm, 18 cases had tumor less than 5 cm and 16 cases had unknown initial tumor size. Seventy patients had single metastatic site, 45 cases had metastatic sites less than 3 sites and 8 cases had multiple metastatic sites (above 3 sites).Overall survival to all metastatic patients was 26.3% and DFS was 15.4%. Survival was correlated according to tumor size, pathological types, location of the lesion and methods of local control with no significance. Survival comparison was done to patients according to number of metastatic sites number of patients were 8 patients who died all before 2 years so one year survival comparison was insignificant.5-yr OS for 1 metastatic site: 35.5% and for 2-3 sites was 18.8%. 5-yr EFS for 1 metastatic site: 20% and for2 to 3 metastatic sites: 11.6%.
Conclusion: This analysis identified subsets of patients with metastatic rhabdomyosaroma with different outcomes to current therapy and offers a strategy to define patient candidates for experimental approaches to treatment. Increasing the number of patients will improve the study significance

Poster # 213

DETECTION OF RELAPSE BY IMAGING IS ASSOCIATED WITH LONGER SURVIVAL IN RELAPSED RHABDOMYOSARCOMA

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Background: Patients with rhabdomyosarcoma (RMS) who complete therapy are routinely followed with surveillance imaging to monitor for relapse. There is currently no evidence that the surveillance process improves survival after relapse. We hypothesized that there would be no difference in post-relapse survival whether the relapse is detected by imaging alone (Group I) or clinical evaluation (Group S - signs and symptoms, physical exam).
Objectives: To compare overall survival (OS) and mortality between patients with RMS in whom relapse was detected by clinical evaluation versus routine imaging alone.

Design/Method: A retrospective multi-institutional analysis was performed in 129 patients with RMS diagnosed between 1992 and 2016 who relapsed off therapy. OS was calculated from date of relapse to last follow-up or death. Odds ratios (OR) were calculated to compare mortality rates to account for lead time bias. Multivariable analyses were performed using multivariable Cox proportional hazard and logistic regression analyses accounting for potential confounders. All institutions used Children's Oncology Group guidelines for off therapy surveillance imaging frequency.
Results: Relapse was detected in 61 (47%) group I and 68 (53%) group S patients. Most common clinical findings at time of relapse included swelling/palpable mass (n=37, 54%), and pain (n=21, 31%). Median time to relapse in all patients was 1.4 years (range 0.2-8.9 years), with no difference between the two groups. Ninety-seven (75%) patients died with a median 0.9 years to death (range 0.1-6 years); forty-four (72%) in Group I and 53 (78%) in Group S (OR 1.4, P=0.45). Median follow-up in 32 (25%) survivors was 4 years (range 1 to 16.6 years). Mean and median survival after relapse were similar for the two groups (Group I 4.3 and 1.8 years and Group S 4.3 and 1 years, respectively), with similar 4-year OS rates (27% vs. 21%, respectively; P= 0.14). In multivariable analyses accounting for time to relapse, risk group at diagnosis, institution, use of surgery, radiation, and chemotherapy after relapse, patients in Group S were 1.9 (95% CI 1.2-3.0) times more likely to die than patients in Group I (P= 0.004). Logistic regression analyses did not show any difference in mortality between the comparison groups (OR 1.3, P=0.4).
Conclusion: Detection of relapse by routine surveillance imaging is associated with longer survival in patients with relapsed RMS. Lead time bias accounts in part or fully for this finding with no difference in overall mortality.

Poster # 214

PROGNOSTIC FACTORS, TREATMENT AND OUTCOMES OF PEDIATRIC RHABDOMYOSARCOMA: A MULTICENTER STUDY

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Background: Soft tissues sarcomas account for 8% of all pediatric tumors. Soft tissues sarcomas are divided in to Rhabdomyosarcoma (RMS) & Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS). Unfavorable prognostic factors including parameningeal location or alveolar histopathology reduce patient survival rates significantly up to 50%. Combined multi-agent chemotherapy, radiotherapy, and surgery has significantly improved the overall survival. There is scarcity of data specifically on prognostic significance in low and middle income countries especially in Pakistan.
Objectives: To evaluate prognostic factors and outcomes in Pediatric Rhabdomyosarcoma (RMS) at two centers in Pakistan.
Design/Method: Patients 1-16 years from 2005 to 2015 at Aga Khan University Hospital and Indus Children Cancer Hospital. Factors relevant to survival and relapse were analysed.
Results: One hundred fifty-three were identified. Forty-one (27%) left before treatment. Data was analysed from 112, median age five years. Sixty-five (58%) were male. Parameningeal

(n=33, 29%) was the commonest site. Ninety-one were group III (81%), 41 were stage 3 (36%), 20 were stage 2 (18%) and 21(19%) stage 1 and 4 each. Ninety-four (84%) were embryonal. Tumor size was > 5cm in 58 (52%). Eighty-two (73%) had localized disease, 21 (19%) metastatic with lung (n=8, 38%) the commonest site. 96 (86%) were treated. Majority (n=84, 75%) received ARST0531, 3 (3%) received high-risk protocol. 36 (32%) received radiation, 15 (13%) surgery whereas 23 (21%) surgery + radiation. Median follow-up period was 11 months. Improved 5-year overall survival (OS) was associated with age 1-9 years (60%, P=0.029), dose of radiation 50Gy (85%, P=0.004), and local control with surgery + radiation (90%, P=0.001). 70 events occurred; 12 relapsed (11%) and 27 (24%) died; 1 (4%) had progressive disease and 10 (37%) died during treatment, cause remained unknown in 16 (59%) and 31 (28 %) abandoned treatment. Five-year (OS) in both localized and metastatic disease was 58% (95% CI:51.6-70.83) and EFS with relapse was 70% (95% CI:62.93-83.06). Five-year (OS) in patients treated with curative intent was 60% (95% CI:54.71-74.72) and EFS with relapse was 73%(95% CI:63.10-83.66). EFS with relapse + death and treatment abandonment was 35% (95% CI:27.38-44.32).
Conclusion: Favorable site of presentation, effective local control with appropriate doses of radiation correlated well with positive outcomes. 50% of diagnosed patients either did not start or abandoned therapy, a serious concern in our setting

Poster # 215

SPINDLE CELL RHABDOMYOSARCOMA IN INFANTS

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Background: Spindle cell rhabdomyosarcoma (RMS) is a rare variant of RMS, representing 3-10% of all RMS cases. In older children and adults, spindle cell RMS is frequently associated with MYOD1 mutations and poor prognosis. In contrast, congenital/infantile RMS tumors are associated with recurrent fusions involving VGLL2 or NCOA2, and more favorable prognosis.
Objectives: Describe treatment and outcomes of infants with spindle cell RMS treated at Texas Children's Hospital from 1995 to 2018.
Design/Method: After obtaining IRB approval, patients with spindle cell RMS treated at Texas Children's Cancer Center after 1995 were identified through the pathology database. Descriptive statistics, response to treatment and survival analyses were performed.
Results: 5 infants with spindle cell RMS were identified (3 females, 2 males). Four tumors were present at birth, and one was detected at 6 months of age. Primary tumor locations were extremities (2), trunk (2), and para-testicular (1). Three patients were classified as low-risk and two as intermediate-risk. with one having metastatic disease at diagnosis. Surgical resection of the primary tumors prior to chemotherapy was performed with 4 infants. Four patients received vincristine, actinomycin D and cyclophosphamide (VAC) chemotherapy, and one received VAC alternating with vincristine and irinotecan (VAC/VI). The duration of therapy was determined according to risk group assignment. None received radiation therapy. A single patient who received neoadjuvant chemotherapy had stable disease and subsequently underwent gross total resection with microscopic positive margins. All children are alive at a median of 13.3 months follow-up (range 2-17 months). Three of 4 patients with localized disease detected at birth had

t(8;11) TEAD1/NCOA2 fusion, and the fifth patient with metastatic disease detected at 6 months had HRAS mutation.
Conclusion: Infants with spindle cell RMS with NCOA2 fusions tend to have localized disease and excellent prognosis. The need for intensive chemotherapy similar to RMS therapy in these patients should be further investigated.

Poster # 216

DIRECT INHIBITOR TARGETED TO EWS-FLI1 FOR RELAPSED EWING SARCOMA PATIENTS IN PHASE 1 CLINICAL TRIAL

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Background: EWS-FLI1 has been recognized as ideal for targeted therapy to improve survival for Ewing sarcoma (ES) patients for 25 years. This chimeric transcription factor gained the moniker of 'undruggable' that has likely dissuaded attempts at direct inhibition. We developed an unbiased approach to identify small molecules that could lead to novel drugs that directly bind and inhibit EWS-FLI1.
Objectives: Our goal is to create a drug that directly inhibits EWS-FLI1 in order to improve overall survival of patients with ES and reduce morbidity to survivors using targeted, personalized, therapy.
Design/Method: We synthesized full-length recombinant EWS-FLI1 and used an affinity tag for purification. The purified protein was attached to a surface for small molecule screening using surface plasmon resonance. A secondary immunoprecipitation screen validated small molecule lead compounds bound to EWS-FLI1 that disrupted critical protein interactions, including RNA Helicase A. Further tests of transcription (microarray), splicing (RNA-seq), and transformation (anchorage-independent growth, xenografts) were performed to validate direct inhibition of EWS-FLI1. Subsequent chemical optimization was performed to achieve useful pharmacologic properties. IND enabling toxicology and manufacturing led to an FDA issued IND for Phase 1 human testing of a new chemical entity for patients with relapsed ES.
Results: Initial screening led to a panel of compounds followed by a first round of chemical optimization that created the lead YK-4-279. YK-4-279 showed activity in 6 different assays for ES growth, EWS-FLI1 transcript activation, post-transcriptional modification, RNA Helicase activity, and xenograft inhibition. All of these were inhibited by YK-4-279, and specifically, only the S-enantiomer showed activity. These results led to the creation of a company to specifically obtain an IND for Phase 1 testing. Further commercial optimization of YK-4-279 led to the clinical drug TK216. Phase 1 studies (3+3 design) of TK216 are ongoing. Results at this time show manageable toxicity, primarily neutropenia and thrombocytopenia at pharmacologically active blood levels in ES patients with multiply relapsed disease.
Conclusion: This work validates a proof-of-principal that a drug can directly target EWS-FLI1. In addition, financing of a start-up to support the clinical development, establishment of a clinical trial, and broader evaluation of TK216 activity has supported a Phase 1 trial. This paradigm could be considered in other cancers with small numbers of potential patients. The advancement of TK216 to Phase 2 efficacy studies is planned for mid-2019.This project

supported by Oncternal Therapeutics, Inc., Dr. Toretsky is a co-founder and consultant of Oncternal.

Poster # 217

PROGNOSTIC FACTORS FOR SURVIVAL IN PEDIATRIC PATIENTS WITH EWING SARCOMA: A MULTICENTER STUDY

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Background: Ewing sarcoma is the second most frequent bone tumor of childhood and adolescence that can also arise in soft tissue. It is a highly aggressive cancer, with a survival of 70–80% for patients with standard-risk and localized disease and 30% for those with metastatic disease. Early diagnosis and prompt treatment can lead to recovery and aggressive multimodality treatment with chemotherapy, surgery and radiotherapy may translate into better outcome in these patients. There is scarcity of data about prognostic significance and treatment outcomes from developing world including Pakistan.
Objectives: To evaluate prognostic factors and treatment outcomes in pediatric Ewing Sarcoma (EWS) at two major pediatric oncology centers in Pakistan.
Design/Method: All patients 1-16 years from 2005 to 2015 at Aga Khan University Hospital and Indus Children Cancer Hospital. Factors relevant to survival and relapse were analysed.
Results: One hundred-thirty-four patients were identified. Thirty-five (26%) left before treatment. Ninety-seven (72%), median age 11, were analyzed. Fifty-eight (60%) were male. Extremity (n=55, 57%) was the commonest site. Ninety-one (94%) were bone EWS. Tumor size was > 8cm in 40 (41%). EWSR1 translocation was performed in 16(16%). Sixty-seven (69%) had localized disease, 27(29%) were metastatic. Lung (n=12, 44%) was the most common site of metastasis. Majority received EURO-E.W.I.N.G.99 (n=53, 55%), 16(17%) received AEWS0031 protocol, 13 patients (13%) were given different regimens. Twenty-eight (29%) were treated with surgery + radiation, 26 (27%) each received surgery and radiation. The median follow-up period was 13 months. Improved 2-years overall survival (OS) in localized disease was associated with surgery (n=26, 66%, P=0.55), <8cm tumor size 64% (n=15, 60%, P=0.95) and clear surgical margins (n=16, 60%, P=0.86). Fifty-eight events occurred; 19 relapses (19%), 14 (14 %) treatment abandonments and 25 (26%) died. The 5-year OS and EFS for localized and metastatic EWS was 58% (95% CI 8%-40%) and 42% (95% CI: 11%-90%). The 2-year OS for localized EWS was 70% (95% CI: 5%-57%). The 5-year EFS for localized and metastatic EWS with relapse+ treatment abandonment + death was 20% (95% CI: 8%-70%).
Conclusion: Our study demonstrates excellent survival for localized disease. Fifty percent of our patients did not get any treatment because of insufficient resources, one-third had metastasis at presentation because of lack of access to medical care. Although not statistically significant, small tumor size and good surgical results correlated well with outcomes.

Poster # 218

EWING SARCOMA IN ADOLESCENT AND YOUNG ADULTS: EVALUATING OUTCOMES AT ONE ACADEMIC MEDICAL CENTER

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Background: Adolescent and young adult (AYA) patients with Ewing sarcoma (EWS) have inferior survival compared to pediatric patients, even when treated with identical regimens. Possible explanations may include AYA patients having more aggressive tumors at baseline, being treated less aggressively than younger patients, poor compliance with treatment regimens, and lack of participation in clinical trials within this group. Investigation into specific reasons why AYA patients with EWS experience worse clinical outcomes compared to younger patients is unfortunately lacking.
Objectives: The goal of this study was to examine a single institution's experience with EWS over time, with a focus on differences in clinical features at presentation, treatment factors, toxicities of therapy, and outcomes between AYA and younger patients.
Design/Method: A retrospective chart review was performed for patients treated for EWS at Nationwide Children's Hospital in Columbus, Ohio between 1990-2017. Data collected included clinical features at presentation (age, sex, stage, primary location, tumor size, etc.), chemotherapeutic regimens and local control modalities utilized, relapse and mortality rates, toxicities of therapy (infections, fever and neutropenia admissions, ICU admission, delays in treatment, etc.), and other clinical measures related to disease or treatment course. Comparisons between AYA and pediatric patients were completed using nonparametric statistical methods. Overall survival was estimated using Kaplan-Meier method and survival was compared using log-rank tests.
Results: One hundred four patients (59 pediatric and 45 AYA) met inclusion criteria for the study. Median age was 10 and 19 for pediatric and AYA patients, respectively. Statistically significant differences in this cohort were observed between pediatric and AYA patients for stage IV disease (23.5% vs 50.0%, p=0.009), central tumor location (58.9% vs 36.4%, p=0.025), % of male patients (50.8% vs 75.6%, p=0.010), and primary tumor size ≥5 cm (70.0% vs 93.3%, p=0.016). No difference was identified in toxicity or dose adjustments between the 2 groups. Five-year overall survival with 95% confidence intervals were 90.6% (82.2% – 99.8%) and 68.5% (52.4 – 89.6%) for pediatric vs AYA patients. Kaplan-Meier curves showed reduced overall survival probability in AYA patients (p=0.023).
Conclusion: The AYA cohort at our institution demonstrated larger tumor size and a higher likelihood of stage IV disease at presentation, as well as increased mortality compared to younger patients. Similar rates of toxicity and chemotherapeutic dose adjustments suggest that treatment related factors did not play a part in the difference in outcomes between the 2 groups.

Poster # 219

DEFINING PALLIATIVE OPPORTUNITIES IN PEDIATRIC PATIENTS WITH BONE AND SOFT TISSUE TUMORS

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Background: Pediatric patients with cancer have many opportunities for increased primary or specialty palliative care (PC). This is particularly true for patients with solid tumors who often have higher symptom burden and worse outcomes. However, how many opportunities, when they occur, and if these opportunities are correlated with disease or demographic variables are unknown.
Objectives: To define palliative opportunities within pediatric cancer, and explore how these occur in patients with solid tumors.
Design/Method: A priori, nine palliative opportunity categories were defined (disease progression and relapse, hospital admission for symptoms or social concerns, intensive care or marrow transplant admission, phase 1 trial or hospice enrollment, DNR status). A single-center retrospective review was conducted on patients aged 0-17 years at diagnosis with bone/soft tissue tumors who died from 1/1/12-11/30/17. Demographic, disease, and treatment data was collected, and descriptive statistics were performed. Timing of opportunities was evaluated over quartiles from diagnosis to death.
Results: Patients (n=60) had a mean of nine (SD=4) palliative opportunities. Number or type of opportunities did not differ by primary diagnosis or demographic variables. PC consulted on 18 patients (30%) a median of 14.0 months (IQR 25.0) after diagnosis, and 2.6 months (IQR 11.5) prior to death. Likelihood of PC consult did not differ by diagnosis or total opportunities. The opportunities that preceded PC consult were progression/relapse (9/18), escalated hospital level of care (4/18), symptom admission (3/18), and end-of-life concerns (2/18). Hospice was involved for 72% of patients. The majority of opportunities occurred in the last quartile of the disease course (median 5.0, IQR 5.0).
Conclusion: Patients with solid tumors incur many events warranting psychosocial or palliative support, which increase toward the end-of-life. Mean reported opportunities is likely a minimum due to stringent collection methods. No palliative opportunity or demographic variable was associated with PC consultation. Defining palliative opportunities provides an additional framework to assess the disease trajectory for patients suffering from oncologic diseases. Additional work is needed to further refine what qualifies as a palliative opportunity, how to fully capture opportunities, and how those may differ across different cancers.

Poster # 220

BONE ALLOGRAFT AFTER MALIGNANT TUMOR RESECTION IN CHILDREN:10 YEARS AFTER TREATMENT RESULTS

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Background: Limb salvage is key in pediatric malignant Bone tumors treatment. Bone allograft transplant is an alternative to preserve limb function and avoid amputation. In Ecuador, the first National tissue bank was created in 2011. Before this, bone allografts were obtained outside the country. Delay in treatment has been associated with several complications including amputation and infections. The development of a protocol for grafts in Ecuador will improve the outcomes

and reduce complications related to delay of treatment. Studies are necessary to evaluate the impact of new tissue banks on survival and complications in patients with bone sarcomas in developing countries.
Objectives: Evaluate osseous allograft treatment for children sarcoma treatment and long-term complications.
Design/Method: We performed a retrospective study using medical records from 450 pediatric patients diagnosed with malignant pathology in an Ecuadorian Hospital between 1993 and 2003. Twenty-two children with bone malignancy were identified but only patients that underwent resection and bone allograft reconstruction were scheduled for follow up 10 years later.
Results: Twenty-two patients were diagnosed with malignant bone tumors between 1993 and 2003, 15 (68.18%) with osteosarcoma, and 7 with Ewing (31.81%). Most (54.5%) were men with a mean age of 10.9 (range 6-14 years). Only 7(31%) were treated with heterologous bone allograft and member preservation, four of them with osteosarcoma and three with Ewing's sarcoma. All were scheduled for follow up 10 years after surgery and allograft. Four (57%) patients showed remission with preserved function of the limb, three of them diagnosed with osteosarcoma and one with Ewing sarcoma. Two (50%) patients with Ewing sarcoma showed limb shortening and limp. Only one (14.3%) of seven patients required amputation due to vascular complications. The most frequent complication was limb shortening with an average of 5cm disparity when epiphysis was involved.
Conclusion: Bone allograft allowed successful preservation of the limb in 85.7% of patients that suffered bone malignancy during childhood. Long-term complications like limb shortening and limp developed in almost half (45.5%) of patients, being most commonly reported in patients with Ewing sarcoma. No infections after surgery were reported despite it is the most common complication after allograft implantation according to literature. Our study showed that bone allograft is a reliable treatment for limb salvage, however, a new study should be performed after the creation of the first National tissue bank. The development of protocols for grafts in developing countries, like Ecuador, could improve the outcomes and reduce complications related to delay of treatment.

Poster # 221

SURVIVAL OUTCOMES IN PEDIATRIC PATIENTS WITH OSTEOSARCOMA: A TEN-YEAR MULTICENTER STUDY

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Background: Osteosarcoma accounts for approximately 5% of childhood tumors. Approximately 25% of patients present with metastatic disease, with lungs as the most common site. Clinically detectable metastatic disease at presentation is the strongest unfavorable prognostic factor. Multi-agent chemotherapy in neoadjuvant/adjuvant setting along with improved surgical techniques has improved the overall survival of patients with localized osteosarcoma to 55–80%. There is paucity of data regarding demographic characteristics and outcomes of osteosarcomas from the developing world including Pakistan.

Objectives: To evaluate significant prognostic factors and treatment outcomes in Osteosarcoma at two major pediatric oncology centers in Pakistan.
Design/Method: All patients 1-16 years, from 2005 to 2015 at Aga Khan University Hospital and Indus Children Cancer Hospital. Patient characteristics, treatment, outcomes and factors influential to survival and relapse were analysed.
Results: One hundred-thirty-four were identified. Forty-six (47%) left before treatment. Ninety-seven (72%) with median age of 14 were included. Fifty-two (64%) were female. Extremity (n=87, 92%) was the commonest site. Thirty-six (37%) had metastatic disease. Lung (n=24, 66%) was the most frequent site of metastasis. AOST0331 protocol was given in 47(48%), 29 (30%) received Cisplatin/Adriamycin, 3 (3%) were treated on different regimens, 18 (18%) did not receive any chemotherapy. Improved 3-years overall survival (OS) in localized disease was associated with limb salvage (n=34, 56%, P=0.091), clear surgical margins (n=25, 88%, P=0.006), and post-operative tissue necrosis (n=22, 88%, P=0.011). Age 6-10 years (n=21, 75%, P=0.12) and limb amputation (n=29, 64%, P=0.99) showed relatively inferior event free survival (EFS). The median follow-up was 8 months (IQR 3–20 months). Seventy-three events occurred; 14 experienced relapse (14%), 28 (29%) were treatment abandonments and mortality in 31 (40%). The 5-year OS for both localized and metastatic osteosarcoma was 30.8 %(95% CI: 19%-44%). The 5-year OS for localized osteosarcoma was 44% (95% CI: 26%-61%). The 5-year EFS for localized osteosarcoma with relapse as an event was 69 %(95% CI: 47 %-83%) and the 5-years EFS for localized and both localized and metastatic disease with relapse, death and treatment abandonment as an event was 42 %(95% CI: 24%-59%) and 29% (95% CI: 17%-43%).
Conclusion: Limb salvage surgery with good response to chemotherapy were favorable prognostic factors. Poor outcome was associated with treatment abandonment and metastatic disease at presentation.

Poster # 222

PATTERN, MANAGEMENT AND IMPACT OF CHEST METASTASIS ON SURVIVAL OUTCOME OF OSTEOSARCOMA PATIENTS

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Background: Osteosarcoma accounts for about 56 % of all bone cancers under the age of 20 years. Five year overall survival in patients with osteosarcoma is around 70%, while in patients with metastatic disease it is only 10-30%.
Objectives: To find out overall and progression free survival and analyze their relations to different prognostic factors (age, gender, primary tumor size, lung metastases features, management approach of lung metastases and chemotherapy response) in patients diagnosed with metastatic osteosarcoma and treated at department of Pediatric Oncology, NCI - Egypt.
Design/Method: We did a retrospective review of patients' files at the Cancer Epidemiology department from January 2008 To December 2013. Patients with bony metastasis or other extra-pulmonary diseases were excluded. Our study included 61 newly diagnosed patients during the aforementioned period.
Results: Patients' age at diagnosis ranged from 5 to 25 years, with a Median of 15 years, with

male to female ratio was 1.9: 1. The median follow up period was 20 months (2-64 months). Overall survival (OS) and progression free survival (PFS) at 3 years were 19.9% and 3 % respectively. In our study, 16 patients were initially metastatic to lung versus 45 initially non-metastatic but developed pulmonary metastasis later on with 3 year OS 20% versus 23% respectively and 3 year PFS 13% versus 14% respectively, showing no statistical significance. Regarding local control, 32 patients underwent limb salvage versus 28 patients underwent amputation with 3 year OS 32% and 28% respectively, showing no statistical significance. Twenty five patients (25/61; 41%) were completely resected versus thirty two patients (32/61; 51%) were not technically resectable, with 3 year OS were 26 % versus 4% respectively (P value=0.04) and 3 year PFS 19% versus 0 % respectively (p value=0.007). Negative significant correlation was found between 3 year PFS and in patients with more than 5 months delay to local control (P value=0.02). Although median OS of patients who had tumor necrosis at lung nodules >90 % was 35 months and those with tumor necrosis <90% was 18 months, this difference could not prove statistical significance (P value 0.08). Other prognostic factors didn't show any statistically significant relation.
Conclusion: The completeness of surgical resection of all detected tumor metastatic sites has a prognostic impact on both OS and PFS in patients with osteosarcoma with evident lung metastasis. Delayed local control of the primary tumor is a negative predictor of PFS.

Poster # 223

SINGLE CENTER EXPERIENCE WITH HIGH DOSE IFOSFAMIDE (HDI) USE IN REFRACTORY AND RELAPSED OSTEOSARCOMA

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Background: Osteosarcoma is the most common primary malignant bone tumor. The prognosis of patients with osteosarcoma has not significantly changed in the last 40 years after initial improvement associated with the inclusion of chemotherapy alongside surgical resection. Most importantly, no new drugs except ifosfamide showed activity against osteosarcoma since MAP combination (high dose methotrexate, doxorubicin and cisplatin) was introduced. Currently, the MAP regimen remains the standard approach to newly diagnosed osteosarcoma, while conventional dose ifosfamide (9 gm/m2) in combination with etoposide did not improve outcomes in patients with poor histological response to MAP. Escalation of ifosfamide dose to 12-14 gm/m2 as a single agent was reported to have significant activity in patients who failed MAP, although few reports have described the extent of nephrotoxicity seen with HDI use.
Objectives: • To evaluate the response of patients with refractory or relapsed osteosarcoma to HDI therapy. • To evaluate the incidence and extent of nephrotoxicity associated with HDI therapy.
Design/Method: Single institutional retrospective study. All pediatric patients with refractory or relapsed osteosarcoma who received ≥2 cycles of HDI therapy (14 gm/m2 divided in 7 doses every 12 hours) after standard therapy with MAP were included over a duration of 8 years.
Results: Ten patients were included, 4 with recurrent disease and 6 with refractory disease. A total of 52 treatment cycles were administered with a median of 4.5 cycle/patient (range 2-8). Nine patients had measurable disease with 3 PRs, 1 SDs, and 5 PDs observed after 2-4 cycles of

HDI (40% RR). Disease control rate was 50% at 4 months and 20% at 12 months. Moreover, two patients developed isolated pulmonary recurrences after HDI and additional resections lead to prolonged overall survival. Four patients are currently alive without evidence of disease from 4 up to 53 months. Persistent nephrotoxicity was observed in 3/10 patients, with 1 patient developing persistent tubulopathy and electrolyte derangement requiring supplementation, and 2 patients developing asymptomatic creatinine elevation associated with low GFR. All 3 patients who developed renal insufficiency received at least 5 cycles of HDI. Timing of nephrotoxicity was found to be unpredictable, 2/3 occurred simultaneously with treatment while 1/3 occurred at 1 year after completion of therapy. None have required renal replacement therapy.
Conclusion: Consistent with prior published reports, HDI therapy is an efficacious single agent modality in patients with refractory or relapsed osteosarcoma. It is however associated with significant risk of nephrotoxicity which can be both unpredictable and persistent.

Poster # 224

VACCINATION TO ENHANCE ANTITUMOR ACTIVITY OF GD2 CAR EXPRESSING VZV SPECIFIC T CELLS IN OSTEOSARCOMA

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Background: Chimeric antigen receptor (CAR) T cell therapy directed against solid tumors remains a clinical challenge due to multiple immune evasion mechanisms inhibiting the proliferation and persistence of adoptively transferred CAR-T cells. Most CARs are expressed on polyclonally activated T cells whose native antigen specificities are unknown. Our center has compared the use of Epstein-Barr virus (EBV)-specific T cells vs. CD3 and CD28 antibody-activated T-cells (ATCs), both modified with a CAR directed toward the GD2. EBV-specific GD2-CAR T cells circulated with higher frequency than GD2.CAR-ATCs but did not proliferate extensively. We hypothesized that the frequency and persistence of adoptively transferred virus specific T cells could be enhanced using a vaccine against the virus. We therefore generated varicella virus (VZV)-specific T cells to express a GD2 CAR, and these were administered in conjunction with the commercially available VZV vaccine (Zostavax) to patients with relapsed osteosarcoma, which is known to widely express GD2.
Objectives: To determine the safety and efficacy of administering autologous VZV-specific T cells modified with a GD2.CAR (GD2.CAR.VZVSTs) in combination with VZV vaccine in patients with relapsed osteosarcoma
Design/Method: We treated 8 patients with GD2.CAR.VZVSTs in escalating doses, from 1 x 106 to 1 x 108, in combination with varicella vaccination. We measured the frequency of VZV-specific T cells and transgene-positive cells in peripheral blood before and after infusion, using immunoassays and PCR. Clinical responses to therapy were assessed at 6 weeks after infusion.
Results: The therapy was found to be safe with no dose limiting toxicities observed. We observed increases in the frequency of VZVSTs and transgene positive cells after infusion and vaccination, correlating with increases in the frequency of T-cells specific for tumor antigens (epitope spreading). Two patients achieved stable disease after the 6-week observation period.

Two patients received additional doses of GD2.CAR.VZVSTs, and one patient continues to receive cells with no additional therapy and remains with stable disease greater than 2 years after initial treatment.
Conclusion: The combination of GD2.CAR.VZVSTs and varicella vaccine is safe in patients with relapsed osteosarcoma. Further evaluation of this strategy in combination with lymphodepletion is ongoing, and combination with other immunomodulatory approaches to enhance expansion and persistence are warranted.

Poster # 225

DEFINITION OF RISK PROFILE AND TOXICITIES OF HIGH-DOSE METHOTREXATE USE IN PEDIATRIC OSTEOSARCOMA

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Background: Use of high-dose methotrexate (HD-MTX, 12 g/m2) is standard therapy for pediatric osteosarcoma (OS) in North America. In pediatric OS, there is a narrow therapeutic window for HD-MTX, with decreased tumor response rate with MTX concentrations 1500 μM. Risk factors for HD-MTX toxicity have been defined in adults, including body mass index (BMI) and male gender, but such studies have not been conducted in children.
Objectives: To examine the relationship between MTX levels and toxicities during HD-MTX infusion for pediatric OS, thereby identifying risk factors for increased toxicity and providing a framework for therapeutic drug monitoring.
Design/Method: This retrospective chart review included patients treated at Texas Children's Hospital with HD-MTX as first-line therapy for OS from 2009-2015. Data abstracted from electronic records included patient characteristics, BMI and body surface area (BSA), laboratory values, MTX levels 4 and 24 hours after dose given (4h, 24h), hour MTX cleared (MTX <0.1uM) grade 3/4 mucositis, myleosuppression, persistent LFT elevation (CTACE v4.0), and percent tumor necrosis. Correlation between 4h MTX level and other covariates was summarized using generalized linear mixed models.
Results: Thirty-three patient charts were reviewed, totaling 219 HD-MTX infusions. The 4h MTX level was significantly associated with percent tumor necrosis ($p = 0.05$), and was not found to contribute to toxicities or associate significantly with MTX clearance. Female and white patients were more like to clear their MTX at 72 hrs ($p=0.047$ and $p<0.001$, respectively). Males and black patients were more likely to have mucositis ($p=0.046$ and $p<0.001$, respectively). Older age and higher BMI was associated with decreased platelet count post HDMTX infusion ($p=0.05$ and $p=0.035$, respectively). Patients who needed their chemotherapy held secondary to toxicity were more likely to be white, younger, and have a lower BSA ($p<0.001$, $p=0.013$, and $p=0.022$, respectively).
Conclusion: These results suggest that the 4h level does not contribute to toxicities or associate significantly with MTX clearance.

Poster # 226

TREATMENT OUTCOMES IN CHILDREN WITH RELAPSED/REFRACTORY SOLID TUMORS: A SINGLE CENTER STUDY

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Background: Despite recent improvements in overall survival for pediatric cancers, relapsed or refractory disease remains a significant cause of mortality. While survival rates for each therapy have been well-studied, the cumulative effect of multiple relapses and salvage regimens is unknown.
Objectives: To describe the disease trajectory in patients with relapsed/refractory solid tumors, from the time of first relapse to time of death, stable disease for 24 months, or no evidence of disease for 24 months.
Design/Method: We reviewed data from electronic medical records for patients with relapsed or refractory solid tumors treated at Texas Children's Hospital between 2002-2016. Kaplan-Meier survival analysis was used to evaluate time to relapse and death, with Cox regression analysis for each variable described. Log-Rank (Mantel-Cox) p-values are reported. Analysis was performed with SPSS v24.
Results: Of the 80 patients with relapsed/refractory solid tumors reviewed, 38.7% were alive at last contact. Fifty percent were diagnosed with neuroblastoma, 10% osteosarcoma, 9% rhabdomyosarcoma, 9% Wilms tumor, and 7.5% Ewing sarcoma. Patients had a mean of 2.75 (SD=2.16) progressions, 547 (SD=698) days from diagnosis to first relapse, 244 (SD=341) days between first and second relapse, and 500 (SD=577) days from first relapse to death. Of the 48 deceased patients, prolonged survival after first relapse was associated with phase I or clinical trial enrollment, increased number of progressions, increased time between diagnosis and relapse, and increased time between first and second relapse ($p<0.05$). In a multivariate Cox regression model, number of progressions and time between first and second relapse were most significantly associated with increased time from first relapse to death ($p<0.001$). Taking a break from cytotoxic therapy (defined as >21 days between time of relapse and initiation of salvage regimen) (473 vs 576 days, $p=0.565$) and tumor type (range 273-1328 days, $p=0.568$) had no significant effect on time between first relapse and death.
Conclusion: The prognosis for pediatric oncology patients with relapsed or refractory disease is poor. Factors associated with prolonged survival include total number of progressions and increased time between first and second relapse. Delay of cytotoxic therapy after relapse does not appear to impact survival, implying that this option could reasonably be offered to patients to promote quality of life and explore goals of care between treatment regimens.

Poster # 227

THE UTILITY OF PET/CT VERSUS BONE SCAN FOR DIAGNOSIS AND MONITORING OF PEDIATRIC SARCOMA PATIENTS

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Background: Osteosarcoma (OS) and Ewing sarcoma (ES) are the most common pediatric bone cancers. Current imaging guidelines for OS and ES include plain radiographs, CT, and MRI for primary tumor evaluation and CT chest and whole body MDP bone scintigraphy +/- SPECT for metastatic evaluation. In recent years, PET/CT has become more common for disease evaluation yet there are no consensus guidelines for its use in pediatric bone cancers.
Objectives: We aimed to compare identification of osseous metastases using bone scan (BS) versus PET/CT in our patient population. We hypothesized that PET/CT is more likely to detect osseous metastases both at diagnosis and relapse.
Design/Method: We performed retrospective chart reviews of pediatric patients with sarcomas at the Children's Hospital at Montefiore from 2008-2018. Paired BS and PET/CT scans were reviewed by blinded pediatric nuclear medicine physicians and analyzed for presence of osseous metastases at diagnosis and during treatment.
Results: Thirty patients had paired BS and PET/CT during diagnosis or treatment. Fifteen patients presented with localized disease and fifteen had distant osseous metastases. Fifteen patients had OS, thirteen patients had ES, and two patients had undifferentiated sarcomas. In twelve out of fifteen patients with bony metastases, lesions were confirmed on MRI or histopathology. In the OS cohort, eight patients had osseous metastases; 100% of these patients were detected on PET/CT and 75% of these patients were detected on BS. Thirty one bony lesions were seen on imaging in OS patients; 100% of these were identified on PET/CT but only 29% on BS. In the ES cohort, six patients had osseous metastases; 100% of these patients were detected on PET/CT and 50% of these patients were detected on BS. Eighteen bony lesions were seen on imaging in ES patients; 94% of these were identified on PET/CT but only 28% on BS.
Conclusion: For patients in our institution with OS or ES, osseous metastases were more likely detected using PET/CT rather than BS. Our findings add strength to the previous literature and aid in demonstrating that PET/CT may be able to replace BS in future diagnosis and monitoring of bone sarcoma patients.

Poster # 228

TUMOR MARKER SURVEILLANCE FOR EARLY DETECTION OF RELAPSE IN PEDIATRIC EXTRACRANIAL SOLID TUMORS

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Background: Standard surveillance for detection of relapse in hepatoblastoma (HB), hepatocellular carcinoma (HCC) and malignant germ cell tumor (GCT), includes tumor marker (TM) monitoring and serial radiographic imaging. We recently reported on 94 newly diagnosed patients with HB, HCC and GCT and elevated pre-treatment TMs between 2002-2012 at our institution (SIOP 2018). Fourteen patients relapsed; TM elevation preceded radiographic

detection of relapse in 13. The median time from TM elevation to radiographic detection of relapse was 19 days (1-1068). The total TM and radiology costs (2017 Medicare fee schedule) for 93 patients that achieved complete remission prior to relapse were $238,050 and $5,963,126 respectively. The omission of routine radiology surveillance could have potentially resulted in a mean costs savings of $61,560 per patient. These results encouraged physicians at our institution to utilize TM assessment alone for off-therapy surveillance in patients with elevated pre-treatment TMs that normalized at the end of primary therapy. Radiographic imaging was performed per clinical trial requirements or treating physician preference.
Objectives: To determine whether the change in clinical practice has impacted the early detection of relapse in patients with HB, HCC and GCT, and elevated pre-treatment TMs at Children's Hospital Los Angeles.
Design/Method: Retrospective chart review of newly diagnosed patients with HB, HCC and GCT, and elevated pre-treatment TMs between 2012-2018.
Results: Seventy-two patients (43 males, age, 0.01-20 years) with HB(37), HCC(4) and GCT(31) were included. Median serum alpha-fetoprotein(AFP) at diagnosis was 210,000, 13,901, 693 ng/mL for HB, HCC and GCT respectively. Median beta-human chorionic gonadotropin (β-hCG) and lactate dehydrogenase (LDH) at diagnosis in GCT was 2.39 mIU/L (2.39-247,590) and 889 U/L (192-3469) respectively. Fourteen patients experienced a confirmed relapse (HB=5, HCC=3, GCT=6); TM elevation preceded radiographic detection of relapse in all. The median time from TM elevation to radiographic detection of relapse was 24.5 days (0-104). The total number of AFP and β-hCG assays performed off-therapy were 709 and 220 respectively. The total number of radiographic imaging studies performed following completion of primary treatment were 220; chest X-ray=44, computed tomography (CT) chest=70, CT abdomen(A)/pelvis(P)=57, magnetic resonance imaging (MRI) A/P=22, radionuclide bone scan=1, ultrasound A=18, ultrasound P=8. The total TM and radiographic imaging costs were $69,680.88 and $578,691.95 respectively.
Conclusion: TM assessment, without radiographic imaging, is adequate for disease surveillance in patients with HB, HCC and GCT, and elevated pre-treatment TMs that normalize at the end of primary therapy. Surveillance with TMs alone reduces health care costs and radiation exposure.

Poster # 229

OUTCOMES OF PEDIATRIC PATIENTS WITH HIGH RISK SARCOMAS TREATED WITH MAINTENANCE CHEMOTHERAPY

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Background: Pediatric patients diagnosed with metastatic rhabdomyosarcoma (RMS) and Ewing sarcoma (EWS) have inferior outcomes compared to those without metastases at diagnosis. Three year overall survival (OS) and event-free survival (EFS) for patients treated with standard therapy have been reported to be 39% and 25% for metastatic RMS and 34% and 27% for EWS, respectively. There is evidence that metronomic therapy after standard therapy has led to improved outcomes in both adults and pediatric patients with high risk tumors. However, there is limited data on the use of maintenance chemotherapy in pediatric patients with high risk sarcomas.

Objectives: To review cases of pediatric patients with high risk RMS and metastatic EWS treated at our institution with maintenance chemotherapy after standard treatment.
Design/Method: Retrospective chart review and literature review.
Results: Four patients with high risk RMS were treated after standard chemotherapy with combinations of vinorelbine, oral cyclophosphamide with bevacizumab or sirolimus, or pazopanib alone. Three patients with metastatic EWS were treated with temozolomide and irinotecan after standard treatment. OS and EFS were measured from the date of cancer diagnosis. Among patients with RMS, median length of maintenance therapy was 13.5 months (range 11 to 19 months); two patients were continuing on maintenance treatment at the time of this review. All four patients were still living at the time of this review. Three patients were disease-free, while one patient had disease recurrence 33 months after initial diagnosis and two months after completing 19 months of pazopanib. Mean EFS was 35.5 months (range 22 to 63 months) with a mean OS of 40.25 months (range 22 to 63 months). Among patients with metastatic EWS, median length of maintenance therapy was nine months (range nine to 12 months); all patients had completed maintenance therapy. All three patients were alive and disease-free at the time of review. Mean EFS and OS were 81.67 months (range 66 to 104 months).
Conclusion: Maintenance chemotherapy may provide improved event-free survival and overall survival in our patients. This retrospective review is limited by sample size and variety of treatment regimens used. In order to characterize the impact of maintenance chemotherapy, prospective clinical trials in pediatric patients with high risk RMS and metastatic EWS need to be explored.(Breneman, Journal of Clinical Oncology, 2003)(Ladenstein, Journal of Clinical Oncology, 2010)

Poster # 230

CLINICAL CHARACTERIZATION OF LONG-TERM OUTCOMES IN PEDIATRIC EPITHELIOID HEMANGIOENDOTHELIOMA

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Background: Epithelioid Hemangioendothelioma (EHE) is a malignant neoplasm of the vascular endothelium with an estimated prevalence of 1/1,000,000. EHE often affects the lung, liver, bone, and/or soft tissue, but can occur anywhere. An international support group registry reports an overall survival of 73% at 5 years (1). However, the disease course is unpredictable; it may be indolent, slowly progressive, or aggressive from onset. Given the limited clinical trials, there are no standardized approaches to therapy. Although usually diagnosed in adults, it can also present in children. Because of its rarity in pediatrics, little is known about the clinical characteristics and long-term outcomes in this population.
Objectives: This study aims to retrospectively describe the clinical presentation, treatment, and long-term outcomes of 24 pediatric patients with EHE.
Design/Method: An Institutional Review Board-approved retrospective chart review was performed on 24 patients less than 26 years old with pathologically confirmed EHE. Patients were then contacted and surveyed about their disease status.

Results: The mean age at symptom onset was 13.8 years (range: 2.5-25.8). The most common presentations were pain (n=13) and palpable mass (n=7). EHE was an incidental finding in four patients. Multi-organ disease was present in 79% of patients and most commonly involved the lung (79%), liver (46%), and bone (42%). Management included observation, surgery, or medical therapy (interferon alpha, doxorubicin, paclitaxel, thalidomide/celecoxib, sirolimus, sorafenib, sunitinib, bevacizumab, or pazopanib). Sustained stable disease or partial response for >2 years was achieved with sirolimus (n=3), sorafenib (n=1), and thalidomide/celecoxib (n=1). One patient who underwent surgical resection had a complete response. Overall, 12/18 patients progressed with a mean time to progression of 18.4 months (range: 0-53). The average follow-up period was 4.4 years (range: 0.4-13.9). The overall survival at one, two, and five years was 100%, 86%, and 73% respectively.
Conclusion: In our study, patients more commonly presented with multi-organ disease and had an earlier mean time to progression compared to adult studies (1). Moreover, 8/14 patients managed with observation and/or surgery progressed. This data suggests that the pediatric population may have a tumor biology distinct from adults. Additionally, earlier initiation of medical therapy may be warranted. Sirolimus had the most promising treatment response, particularly in stabilizing disease in two patients with continuously progressive EHE. However, further prospective studies and long-term follow-up are needed to determine its role in management. (1) Lau, Chest, 2011

Poster # 231

HEPATOBLASTOMA IN A DEVELOPING COUNTRY: OUTCOME AND PROGNOSTIC FACTORS

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Background: Hepatoblastoma is the most common pediatric liver tumor, a huge progress has been made in management of this disease yet it remains a mystery in developing countries.
Objectives: Our study aimed to assess event free survival (EFS) and overall survival (OS) of de novo pediatric hepatoblastoma (HB) patients and their relation to different prognostic factors including age, initial AFP, tumor stage...etc
Design/Method: This study is a combined retrospective and prospective study that was carried out at the National Cancer Institute, Egypt,and Children Cancer Hospital Egypt during the period of 1/01/2013 – 30/06/2016 with a minimum of 6 months follow up using a modified version of the current COG protocol AHEP 0731(the vincristine/irinotecan chemotherapy was omitted in high risk group).A total of 73 patients were included in this study.Surgery was feasible in 52 patients via partial liver resection ,unfortunately liver transplantation was not feasible in our study.The patients were allocated to 3 treatment groups:very low risk(surgery and observation),low risk group:surgery and 2 adjuvant cycles of chemotherapy,the third group included both intermediate and high risk patients and received 6 cycles of chemotherapy.
Results: The 3 years OS of our study group was 69.2% with a median survival of 23 months with a follow up period from 0.1 to 57 months and 95% confidence interval of (10-57). The 3 years EFS survival of our study group was 60.2%.By the end of this study 23 patients were dead(15 died from disease progression and 8 patients from complications of therapy). Correlation of

OS with different prognostic factors showed poor prognosis in presence of metastatic disease p value (0.025),Lymph node (LN) enlargement(p value < 0.001) ,multifocal disease (p value 0.003), tumor involving both lobes(p value 0.046) and initial AFP level<100(p value 0.024) and good prognosis for those with young age (<36 months)with p value(0.032), PRETEXT stages I&II (p value 0.012)and those with AFP log reduction >1 after first 2 cycles of therapy(p value0.005). Correlation of EFS with different prognostic factors showed poor prognosis with LN enlargement(p value <0.001) ,multifocal disease (p value 0.005), portal vein thrombosis(p value <0.001) and initial AFP level<100 p value(0.044) ,and good prognosis for those with young age(<36 months) p value(0.013), PRETEXT stages I&II (p value 0.034) and those with AFP log reduction >1 after first 2 cycles of therapy(p value0.010).
Conclusion: Early screening, multidisciplinary treatment and adequate supportive care measures are all needed for better outcome.

Poster # 232

A RETROSPECTIVE REVIEW OF THE USE OF SIROLIMUS FOR EPITHELIOID HEMANGIOENDOTHELIOMA IN PEDIATRICS

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Background: Epithelioid hemangioendothelioma (EHE), a malignant vascular tumor, represents less than 1% of all vascular tumors with an estimated prevalence of 1/1,000,000 (1). Adult studies report a mean survival of 4.6 years with wide variability of 6 months to 24 years (2). Due to its rarity there are currently no standard treatment protocols. Of interest is the use of sirolimus, an mTOR inhibitor, for treating advanced EHE. mTOR works via the PI3K/AKT pathway and is linked to the expression of VEGF. Inappropriate activation of this pathway can result in tumor growth and vascular anomalies. It has thus been hypothesized that mTOR inhibitors, such as sirolimus, can be used for the treatment of vascular tumors. Literature of their use in EHE, however, is very limited, especially in the pediatric population.
Objectives: The aim of this case series is to share the experience of two institutions in using sirolimus for the management of advanced EHE in pediatric patients.
Design/Method: A retrospective chart review was performed on pediatric patients younger than 18 years with a confirmed diagnosis of EHE treated with sirolimus at either Boston Children's Hospital or Johns Hopkins All Children's Hospital. Best response to treatment with sirolimus was assessed.
Results: Six pediatric patients were identified with ages 7-16 years. Initial clinical presentations varied, but all were symptomatic from at least 1 of their lesions, which included hemoptysis, abdominal pain, or musculoskeletal pain. Sirolimus was used as initial treatment in 4/6 patients. Two had disease progression, one had disease stabilization, and one demonstrated partial response. The remaining two patients received sirolimus after prior treatment failures. One showed disease stabilization and the other showed a partial response. Three out of six patients have completed treatment and their disease remains stable 1 year off therapy. Initial sirolimus doses ranged from 1mg-15mg and were adjusted based on variable trough goals (6-10ng/dL or 10-15ng/dL). Duration of treatment ranged from 4-37 months. The average follow-up has been about 5 years since diagnosis. Overall, therapy was well tolerated with minimal side effects.

Conclusion: Results for the use of sirolimus in pediatric patients with EHE are promising with 4/6 patients demonstrating partial response or disease stabilization as the best response to therapy. Dosing regimens, trough goals, and duration of treatment are currently not established. Additional prospective studies are warranted to further investigate the use of sirolimus in treatment of EHE.1. Wassef, Pediatrics, 20152. Sardaro, Oncol Rev, 2014

Poster # 233

A MULTICENTER RETROSPECTIVE REVIEW OF PEDIATRIC DIFFERENTIATED THYROID CANCER

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Background: In 2015, the American Thyroid Association (ATA) developed management guidelines for children with differentiated thyroid cancer (DTC) based upon literature reviews and expert opinions. While providing a framework to care for children with DTC, these recommendations warrant validation.
Objectives: Identify the general practices and outcomes in children with DTC prior to the introduction of the ATA guidelines.
Design/Method: Patients less than 21 years of age diagnosed with DTC between 2000 and 2015 at Texas Children's Hospital, Seattle Children's Hospital, or Children's Healthcare of Atlanta were included. A retrospective chart review was used to extract clinical information.
Results: Seventy-nine patients were eligible. Diagnoses include papillary thyroid carcinoma (PTC) (49), PTC-follicular variant (18), PTC with classic and follicular variants (2), PTC-diffuse sclerosing variant (2), papillary microcarcinoma (2), follicular thyroid carcinoma (5), and Hurthle cell carcinoma (1). The median age at diagnosis was 15.5 years (range 9 - 20.9 years). Median follow-up was 43 months. Sixty-two (78%) patients were female. Patients identified as non-Hispanic white (27), Hispanic white (15), white with ethnicity not specified (11), black (6), Asian (4), and other (16). Sixty-three patients underwent a total thyroidectomy, and 14 had a lobectomy of which 12 underwent a completion thyroidectomy. Two underwent a surgery not specified. Twenty-one patients had central lymph node dissection (LND) and 11 had a lateral LND. Forty-three (54%) had regional lymph node involvement; 11 (14%) had lung metastases. Using the ATA pediatric risk classification, there were 46 low-risk, 7 intermediate-risk, and 23 high-risk patients. Seventy-two (91%) underwent an I-123/I-131 whole body scan. Thirty-six (78%) of the low-risk, and all of the intermediate and high-risk patients received radioactive iodine (RAI). None of the patients received chemotherapy or targeted therapy as part of the initial treatment. Relapse or progression of disease was noted in 5 (11%) ATA low-risk, 3 (43%) intermediate-risk, and 13 (57%) high-risk patients. The cervical lymph nodes were the most common site for relapse/progression (81%). Of the 7 tumors evaluated for genetic changes, BRAFv600E mutations were noted in 4 patients, and ATM and NRAS mutations were noted in one patient. Five patients had a prior history of cancer (AML, CML, Hodgkin Lymphoma, medulloblastoma, neuroblastoma); of these, 4 patients had radiation prior to DTC diagnosis.
Conclusion: Prior to the introduction of the ATA guidelines, a majority of patients underwent a

total thyroidectomy followed by RAI. However, selective use of RAI for low-risk disease as recommended in the current guidelines may be appropriate.

Poster # 234

DENOSUMAB FOR CENTRAL GIANT CELL GRANULOMA: A REPORT FROM TEXAS CHILDREN'S RARE TUMOR REGISTRY

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Background: Central giant cell granuloma (CGCG) is a rare locally aggressive tumor that occurs in the maxilla/mandible of affected children. It is characterized by high rates of recurrence after surgical curettage. Various medical interventions have been tried in the past in the adjuvant and neoadjuvant setting with varying degrees of success including interferon alpha, intralesional steroids, calcitonin and zoledronic acid. Denosumab is a monoclonal antibody that inhibits RANK ligand and is approved for treatment of giant cell tumors in skeletally mature individuals.
Objectives: To describe our experience treating children with CGCG using denosumab
Design/Method: Retrospective review of medical records of children treated with denosumab for CGCG at Texas Children's Hospital.
Results: Three children with CGCG were treated with denosumab. First patient, 12 year old male, presented with prognathic chin and redness. Imaging showed 4.5 X 3.1 X 3.2 cm craniocaudal expansile multiseptated mass centered in the symphysis of mandible. Second patient, 11 year old male, presented after incidental finding of a 1.5 X 2 cm lesion in the left anterior mandible displacing the mandibular incisors detected during routine dental visit. Third patient, 6 year old female, presented with rapidly enlarging 4.5 cm mass in the ramus of mandible with trismus, tenderness and pain. The two male patients received 120 mg dose (standard dose) while the female patient was started on 60 mg (decreased dose due to age and weight). All patients received supplemental calcium and vitamin D. The three patients have received 10, 6 and 1 cycles of denosumab respectively. There was immediate improvement noticed during the first cycle in the two symptomatic patients with resolution of redness and pain. In the two male patients, the lesions showed new bone trabeculae formation and decrease in size after 3 cycles. All patients developed asymptomatic hypocalcemia requiring adjustment of calcium supplementation. No other side effects were noted and the bone age is stable in two patients who completed at least 6 months of therapy. A total of one year therapy is planned in all three patients.
Conclusion: Denosumab shows activity in children with CGCG and may be helpful in avoiding deforming surgery and loss of teeth. Long term follow-up is needed to ascertain efficacy and side effects, especially in children with immature skeletons.

Poster # 235

INFLAMMATORY MYOFIBROBLASTIC TUMOR IN CHILDREN: A REPORT FROM TEXAS CHILDREN'S RARE TUMOR REGISTRY

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Background: Inflammatory myofibroblastic tumor (IMT) is a rare locally aggressive tumor of intermediate malignant potential. Surgical resection is often curative for localized tumors, however, up to 25% of tumors recur.
Objectives: In this study, we describe the presentation, treatment and outcome of children with IMT at Texas Children's Hospital.
Design/Method: A retrospective chart review was conducted on patients diagnosed with IMT between August 1994 and March 2018.
Results: Eighteen patients were identified, ten males (55.6%) and eight females (44.4%), with a median age of 7.4 years (0-16 years) at diagnosis. Primary site included abdomen (38.9%, n=7), lung (33.3%, n=6), bladder (11.1%, n=2), neck (5.6%, n=1), larynx (5.6%, n=1) and heart (5.6%, n=1). Patients presented with symptoms related to the site of involvement, such as abdominal pain and hematuria for abdominal masses, and cough and hemoptysis for lung masses. Up front surgery was attempted in fifteen patients (83.3%); complete resection (CR) was achieved in six patients (33.3%), gross total resection (GTR) in seven (38.9%), and partial resection (PR) in two (11.1%). Two patients with GTR received adjuvant celecoxib. Three patients (16.7%) received neoadjuvant therapy (chemotherapy in 2, NSAID- 1); two of them developed disease progression. 1/7 patients with GTR had relapse and 1/2 patients with PR has disease progression. 3/4 patients who had relapse/progression had lung primary. All the patients with CR remained disease-free at last follow-up. One patient with an abdominal mass who progressed on celecoxib died due to post-operative hemorrhage. The 3-year event free and overall survival for the entire group was 76.4% and 94.1% respectively. Of the 15 patients assessed for ALK expression by immunohistochemistry, nine were positive (60.0%); of the 13 patients assessed for ALK gene rearrangement, seven were positive (53.8%). Only one patient screened for both tumor characteristics showed a discrepancy between results, testing positive for ALK expression but negative for ALK mutation.
Conclusion: Children with IMT who undergo complete resection have excellent prognosis. Intrathoracic IMT may be associated with increased recurrence risk due to difficulty in achieving complete resection.

Poster # 236

PEDIATRIC DESMOPLASTIC SMALL ROUND CELL TUMOR PATIENTS ARE HIGH RISK FOR CLOSTRIDIOIDES DIFFICILE

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Background: Clostridioides difficile infection (CDI) is one of the leading causes of hospital- and antibiotic-associated gastrointestinal illness in children. Recently, incidence of CDI in pediatrics has been increasing, currently 2-12 patients per 1000, and is associated with an increased risk of adverse outcomes or death. Pediatric oncology patients, who are frequently

immunosuppressed, exposed to medications associated with CDI, and frequently hospitalized, constitute a population at substantial risk for CDI. Patients with desmoplastic small round cell tumor (DSRCT), a rare non-neural solid tumor, are treated with intraperitoneal cisplatin combined with debulking surgery and abdominal radiation, which could disrupt the native microbiome, allowing pathogens to flourish, and may be at particularly high risk. Certain ribotypes, genotypes of C. difficile, have been identified in adults and associated with more severe infections; this association has not been described in children.
Objectives: To study the epidemiology of CDI in pediatric patients at a cancer center to identify oncology-specific risk factors for infection and poor clinical outcomes and describe the C. difficile ribotypes at our institution.
Design/Method: We conducted retrospective chart review of all patients treated at The University of Texas M. D. Anderson Children's Cancer Center in Houston, Texas age 0-18 years with positive C. difficile testing and exhibiting symptoms of CDI from 2000-2017. Patients without oncologic diagnosis were excluded from analysis. We cultured C. difficile from stool samples and used PCR to identify ribotypes.
Results: : Incidence of CDI in our pediatric oncology population was 37 patients per 1000. DSRCT patients experienced particularly increased risk (incidence 300 per 1,000 patients; $P<0.0012$). All non-neural solid tumor patients were more likely to have severe and recurrent disease than other oncologic diagnoses (11 and 20%, respectively, versus 5 and 14%). Ribotype distribution in our pediatric oncology population was similar to that reported for the general public, 50% F014-020 or F106, without increased incidence of ribotypes previously associated with severe infection.
Conclusion: Incidence of CDI was higher in our pediatric oncology population than in the general pediatric population, especially among patients with DSRCT, suggesting treatment modalities associated with DSRCT may constitute previously unidentified risk factors for CDI. Overall, close monitoring for CDI during antineoplastic treatment may be indicated for pediatric oncology patients. Despite being a single institution study, our findings will enhance CDI treatment guidelines in pediatric oncology.

Poster # 237

"MEK-ING" A PLAN TO TREAT NF: SAFE DELIVERY OF MEK INHIBITORS FOR INOPERABLE PLEXIFORM NEUROFIBROMAS

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Background: Patients with type 1 neurofibromatosis (NF1) who have progressive, unresectable plexiform neurofibromas (PN) have limited therapeutic options to help slow or reverse tumor growth. Uncontrolled tumor growth frequently results in significant co-morbidities including pain, disfigurement, and impaired motor function. Based on promising results of MEK inhibitor (MEKi) efficacy in an early phase pediatric clinical trial for inoperable PN, our institution has adopted this therapy for this indication. When offered to patients who are ineligible for a therapeutic clinical trial, they are prescribed in tandem with an institutional screening and surveillance protocol, described here.
Objectives: To implement a protocolized screening and treatment plan to safely prescribe MEKi

to pediatric patients with type 1 neurofibromatosis with inoperable PN.
Design/Method: At our institution, patients who are ineligible for a therapeutic clinical trial and with significant morbidity from PN are prescribed a MEKi: selumetinib tablets (AstraZeneca, dosing: 25 mg/m2 BID) or trametinib suspension (Novartis, dose: 0.025 mg/kg/d, max: 2 mg). In conjunction, regimented screening and surveillance studies are performed prior to enrollment (month 1) and prior to each monthly cycle as follows: serum chemistries, creatine kinase, and complete blood counts (at month 2 and 3, then every 3 months); vision exam and echocardiogram (at month 3, 6, and 12, then at least annually); disease evaluation (at month 6 and 12, then annually); a complete dermatologic evaluation (as needed, but at least annually). History and physical exam visits are performed at two-week intervals for the first month, again at month 2, then every 3 months.
Results: Two patients are being treated with selumetinib tablets (ages: 5 and 10 years) and one with trametinib suspension (age: 6 years). Ongoing lengths of treatment are 2, 6 and 3 months, respectively. There have been no dose limiting toxicities or grade 2-5 adverse events (per CTCAE criteria). One patient has developed grade 1 gingival hypertrophy while on therapy, which is previously unreported as a MEKi toxicity. No patient has had progressive disease-related morbidity while on therapy.
Conclusion: We have implemented an institutional screening and surveillance regimen for pediatric patients with NF1 being treated with a MEKi for morbid PN. The inclusion of frequent, comprehensive, and multi-disciplinary surveillance is key to ensuring that MEKi are safely prescribed to patients when given outside of a therapeutic clinical trial.

Poster # 238

SURVIVAL AND FACTORS AFFECTING THE OUTCOME OF SYNOVIAL SARCOMA IN CHILDREN AND ADOLESCENTS

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Background: Synovial sarcoma (SS) is a malignant soft tissue tumor. They are termed SS because of their histologic resemblance to the synovium, but they rarely involve a synovial structure and are thought to arise from pluripotent mesenchymal cells .Synovial sarcoma (SS) is a rare sarcoma driven by a translocation between SS18 and SSX 1, 2, or 4. With approximately 800 to 1,000 cases a year in the United States.
Objectives: To evaluate the impact of the clinical and pathologic features at diagnosis and prognosis, study the outcome of synovial sarcoma in children and adolescents assess the different methods of management including chemotherapy radiotherapy and suurgery
Design/Method: Retrospective analysis of patients below 18 years old with pathological diagnosis of synovial sarcoma and treated at Children Cancer Hospital Egypt 57357 (CCHE) between July 2007 and December 2016. Clinical characteristics, pathological information, treatment modalities and survival data were reviewed. survival was correlated with different clinical factors
Results: Thirty one patients were included with a median age at diagnosis 14.8 years. They constituted 5.2% of soft tissue sarcoma patients.The most common affected primary site was the

extremities in 20 cases (64.6%). Most of the patients were categorized into intermediate risk 27 patients (87.2%) 2 patients of low and 2 patients with high risk. Patients were treated according to CHILDREN'S ONCOLOGY GROUP COG (ARST0332) Study. The estimated 5 –year overall survival and failure free survival rates for the entire group were 84.4 ± 7.2 % and 63.8 ± 9.7 % Overall survival and disease free survival were correlated according to age, site of the tumor, method of local control, initial tumor size and pathological types .Twenty cases had only surgery as local control method , 10 cases had both surgery and radiotherapy as local control method and only one had radiotherapy only.Patients who had surgery as local control method 19 cases had initial surgery and 11 cases had delayed surgery
Conclusion: Results indicate that a younger age, a smaller tumor size, a distal limb location, and negative resection margins are correlated with improved outcomes but statistically were not significant may be due to small nomber of patients. Preoperative chemotherapy can help for delayed excision in patients presented initially with unresectable tumors.

Poster # 239

A WEB-BASED TUMOR BOARD FOR RARE PEDIATRIC SOLID TUMORS: THE TEXAS CHILDREN'S HOSPITAL EXPERIENCE

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Background: Pediatric tumors classified as rare include those with a very low incidence, for which no standard of care has been established, as well as adult-type tumors, usually of epithelial origin, which are rarely seen in children. As only a small number of children are affected by these diseases, for any single provider or pediatric cancer treatment center to have expertise in all of these diagnoses is a challenge. Additionally, reviewing the medical literature for each individual patient with one of these tumors can be difficult and time-consuming.
Objectives: To analyze the number and types of cases presented in a web-cast tumor board for rare pediatric solid tumors and to describe its participants
Design/Method: We retrospectively reviewed our experience running a monthly, web-based tumor board for the presentation of cases of rare pediatric tumors to be teleconferenced to institutions across North America. Providers at all institutions are invited to request cases for review. For each case, a detailed review of the clinical presentation, relevant laboratory values, imaging, and pathology is presented by the requesting provider. Subsequently a review of the pediatric medical literature is presented by an expert solid tumor provider, followed by an examination of standard of care guidelines for adult-type cancers, if available. The discussion is then opened to all participants to raise inquiries or to elaborate on their own experiences. Periodically, updates on past cases are presented. Past presentations are archived for future reference. A log of cases and participants are kept.
Results: Since the inception of the Texas Children's Hospital Rare Tumors Tele Tumor Board in April 2018 until December 2018, 27 cases of pediatric rare tumors with 21 distinct diagnoses have been presented, each with an accompanying review of the medical literature. The only repeated diagnoses presented were alveolar soft part sarcoma, paraganglioma, recurrent nasopharyngeal carcinoma, and inflammatory myofibroblastic tumor; all other cases had unique diagnoses. 69 participants from 34 institutions accepted participation in the tumor board.

Participants included pediatric oncologists, surgeons, pathologists, geneticists, advanced practice providers, and medical trainees.
Conclusion: The creation of a forum for the presentation and discussion of rare childhood tumor cases creates an avenue for providers to learn more about the types and evidence-based management of these diseases. This collaborative effort allows sharing of rare tumor expertise across institutions and has the potential to improve patient care and provider comfort when patients with these tumors are encountered.

Poster # 240

PEDIATRIC RARE TUMOR CONSULTS: ANALYSIS FROM THE RARE TUMORS PROGRAM AT TEXAS CHILDREN'S HOSPITAL

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Background: Pediatric rare tumors include both diagnoses that are primarily malignancies of childhood, such as pancreatoblastoma, as well as those that are common in adults but uncommon in children, such as melanoma or colorectal cancer. The infrequency of these tumors has resulted in a lack of standardized workup and treatment regimens for many diagnoses. The Rare Tumors Program at Texas Children's Cancer Center was established in 2015 and offers free consultations for physicians worldwide to help guide management for pediatric patients with rare tumors.
Objectives: To analyze the scope of pediatric rare tumor consultations requested at a single tertiary care pediatric cancer center over a four year period.
Design/Method: A retrospective review of outside consultation requests to Texas Children's Rare Tumors Program over a four year period (February 2015-December 2018) was performed.
Results: The total number of consults fielded over a four year period was 226, with the mean of 66 consults per year over the last three years of the review. The majority of these consults originated from within the United States (140, 62%), compared with those from international locations (86, 38%). International consults were received from a variety of locations, including India, Germany, New Zealand, Armenia, Uganda, and China. Patients ranged from newborn to 56 years of age; however, only 7 were older than 21 at the time of consult. Over 50 distinct diagnoses were assessed, and the top 10 most common diagnoses made up less than half of the cohort (103, 46%). The top three diagnoses for consultations included neuroendocrine tumor (25, 11%), rhabdoid tumor (14, 6%), and papillary thyroid carcinoma (11, 5%). The vast majority of consults requested advice regarding treatment recommendations (201, 89%), often in the context of relapsed/refractory disease or metastases; a much smaller subset inquired about targeted therapy (8, 3.5%), treatment in the context of genetic predisposition syndromes (5, 2.2%), and surveillance (3, 1.3%).
Conclusion: We present analysis of consultations performed by the Rare Tumors Program at Texas Children's Hospital over a four year period. These services were employed not only by other physicians in North America, but also frequently by international physicians as well. The large number of diagnoses discussed during this time highlights the wide spectrum of rare pediatric solid tumors; while the stable number of yearly consults demonstrates the utility of this service for physicians managing rare pediatric cancers.

Poster # 241

GEOGRAPHY OF SKIN CANCER IN CHILDREN: A REVIEW IN THE EQUATORIAL LINE

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Background: Melanoma is one of the most common skin tumors in young adults, however, less than 2% of cutaneous melanoma in the United States occurred in childhood. Risk factors for skin cancer in children include UV radiation, xeroderma pigmentosum, and familial predisposition. Clusters with a higher incidence of Skin cancer lead to the association of tumors to Geographic location, altitude, and UV radiation. A better understanding about these could help prevention efforts in areas with higher UV radiation in the United States. We investigated the distribution of skin tumors in Quito, Ecuador, where UV index exceeds 24UV when the maximum tolerable level of radiation has been established by WHO as 11UVI. A deeper knowledge of geographic variability could reveal underlying risk factors that should be the target for prevention of skin cancer.
Objectives: Evaluate the incidence and distribution of malignant and benign skin tumors in Children that live in Quito and compare the outcomes to determine if the incidence changes when UV radiation index superior to 11.
Design/Method: A retrospective study was performed with pathology data from 660 samples obtained between 2009-2013 at a Children Hospital. We obtained the distribution of malignant and benign tumors in children between 0-14. These results were compared with the worldwide incidence.
Results: From a total of 660 samples, 167 (25%) were diagnosed as skin tumors. Rate male: female was 1,2: 1 and the mean age was 5 years old. Of them, 2.4 % were malignant skin tumors and 97.6 % benign tumors. Benign tumors were classified as follows: Haemangioma (31.7%), Lymphangiomas (2.6%), Pilomatrixoma (20.8%), Melanocytic naevi (7.8%), Neurofibroma (4%), Granuloma (7.8%) others (15.3%). Malignant skin tumors were classified as non-Hodgkin lymphoma (0.6), Cutaneous Lymphoma (0.6), Malignant Melanoma (0.6) and Neuroblastoma (0.6), being the lymphomas the most common of malignant tumors (1.2%). All of them were found in children under 6 years, in non-exposed to sun skin areas.
Conclusion: Our results coincide with the 2% of malignant skin tumors incidence in children reported. However, Melanoma incidence was not higher in Quito despite the high UV radiation of the equatorial area. Also, the majority of malign tumors were found in the areas of skin non-exposed to the sun. This supports the hypothesis that melanoma is associated with genetic predisposition rather than cumulative UV dose. Literature shows a higher incidence in some geographical clusters of the United States, however, other risks factors related to education, chemicals exposure and socioeconomic factors could explain the geographic variability rather than UV exposure or altitude.

Poster # 242

COLORECTAL CARCINOMA IN CHILDREN AND ADOLESCENTS, LEADING LMIC EXPERIENCE FROM CCHE

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Background: Colorectal carcinoma (CRC) is common in adults, but extremely rare in children and presents with a poor prognosis. Surgical management and long-term follow-up of this entity are still obscure because of lack of data.
Objectives: to evaluate the clinical characteristics of childhood CRC and determining the predictors of poor outcome
Design/Method: This study was retrospectively done on all Colorectal Carcinoma patients, less than 18 years of age, treated in Children's Cancer Hospital of Egypt (CCHE, 57357 hospital) in the period between 2007 and 2016. The Patients' information including age, sex, predisposing factors, positive family history, and clinical characteristics, and diagnostic procedures, extent of disease, treatment methods, histological types, and survival outcome were collected from the files after patients' approval.
Results: There were 15 cases less than 18 years of age with median age of 15 years treated in CCHE in the period between 2007-2016. All patients had unfavorable CRC histopathology types (mucinous adenocarcinoma) and 10 cases had metastatic disease at presentation. Initial surgical resection was complete in 8/15 cases, and all patients received adjuvant chemotherapy. Four patients were diagnosed with rectal adenocarcinoma and all were treated with upfront chemo-radiotherapy. Family history was positive in 3 cases; 2 cases had both predisposing syndrome (Adenomatous Familial polyposis) and Neurofibromatosis type 1 (NF1) and one case had NF1 syndrome only. Ten patients had tumor progression or relapse, while 12 cases died at the end of the follow up period; overall survival (OS) and event free survival (EFS) was 17.8 % and 16.5 % respectively at 3 years.
Conclusion: Delayed diagnosis, advanced stages of disease, and, most importantly, mucinous type of histology are the major determinants of poor outcome in childhood colorectal carcinoma. Surgery remains the mainstay of treatment of pediatric CRC as in adults. Preoperative radiotherapy for rectal adenocarcinoma, offers better prognosis. Chemotherapy plays role in the metastatic disease and is able to down stage the primary tumor for better local control.

Poster # 243

CANCER PREDISPOSITION SYNDROMES DETECTED IN PEDIATRIC CANCER PATIENTS THROUGH SOMATIC TUMOR TESTING

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Background: Somatic tumor testing is now widely being used to identify genomic alterations in tumors for treatment with targeted therapies. These somatic panels can reveal pathogenic variants in genes that if found in the germline would indicate a cancer predisposition syndrome (CPS). While somatic tumor testing is not meant to directly inform germline genetic testing, we review 5 cases that led to germline testing. Interestingly, the tumors were not known to be

associated with the CPS identified.
Objectives: To review genomic alterations identified by pediatric tumor panels and determine if these alterations represent germline pathogenic variants that would be consistent with a CPS.
Design/Method: Since beginning the hereditary cancer risk program, all newly diagnosed patients in our pediatric oncology clinic received genetic profiling of their tumor through next-generation sequencing technology for detection of genomic alterations in 324 genes and select rearrangements. If a pathogenic variant in a gene associated with a known CPS was identified in the tumor, regardless of whether the patient's cancer type was one related to that gene/syndrome, the patient and parent(s) received a hereditary cancer risk assessment and the patient received germline genetic testing by a board certified genetic counselor. The germline testing consisted of a panel ranging from a 27 gene pediatric tumor panel to a 64 gene pediatric and adult-onset cancer panel.
Results: Five patients tested positive for a germline pathogenic variant consistent with a CPS that was initially identified by their tumor testing; these germline variants were not previously associated with that tumor type. The five cases included: an APC mutation in a parameningeal embryonal rhabdomyosarcoma and in a testicular sertoli leydig cell tumor, BRCA2 in a desmoplastic small round cell tumor, RET in a paraspinal Ewing sarcoma, and ATM in a renal Ewing sarcoma. Subsequent parental testing confirmed that all were inherited from a parent, except one whose parents have not been tested.
Conclusion: We report the benefit of incidentally diagnosed CPS by way of somatic tumor testing. These CPS likely would not have otherwise been detected until an associated cancer was diagnosed in another family member. Early identification allows these families to benefit from surveillance that will either prevent the cancer or detect it at an early, potentially more treatable, stage. The question remains whether these are truly incidental findings, or are we at a precipice of identifying additional cancer types that are caused by or associated with these hereditary cancer genes.

Poster # 244

CANCER GENOMICS IN AN ETHNICALLY DIVERSE PATIENT POPULATION

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Background: There is a growing body of literature in pediatric oncology regarding the utility of cancer gene panels. Genomic sequencing can help in diagnosis and guide the selection of targeted therapy when significant somatic mutations are identified. However, such sequencing also often reveals variants of unknown significance (VUS) with unclear implications. Most data on mutation frequency is derived from patients of Caucasian descent; the incidence of both somatic and germline VUS in other ethnic groups is not well described. Our center cares for a widely diverse patient population and oncology patients with high-risk tumors routinely undergo genomic sequencing with the UCSF500, a comprehensive cancer panel that screens for mutations in 500 cancer genes.
Objectives: To describe the results of a comprehensive cancer gene panel in our oncology patient population at UCSF Benioff Children's Hospital Oakland (BCHO) with regard to mutation type and frequency in an ethnically diverse population

Design/Method: Retrospective chart review of BCHO oncology patients for whom the UCSF 500 cancer gene panel was sent. All data was collected from the electronic medical record.
Results: 89% of patients had at least 1 somatic mutation with an average of 2 mutations. 86% of Latino patients had at least 1 somatic mutation with an average of 2.8 mutations. 88% of Caucasian patients had at least 1 somatic mutation with an average of 1.94 mutations. 35% of the patients had at least 1 VUS with an average of 1.3 mutations. Average number of VUS in Caucasians was 1.64 compared to 1.18 in other ethnicities. We also looked at the percentage of tumors which had isolated somatic mutations (not seen in any other tumors in the study) and found 39% of tumors had a unique somatic mutation with a higher percentage noted in Caucasian Latino (80%) and Caucasian African American (50%) than in Caucasian population (46%).
Conclusion: This gene panel is a valuable tool in characterizing mutations found in a variety of cancers in a diverse oncology patient population. Although there was no significant difference in frequency of somatic or VUS mutations between ethnicities, several unique somatic mutations were discovered in the mixed racial groups, thus adding to the genomic data available for diagnosis and elucidating potential new therapeutic targets.

Poster # 245

PEDIATRIC NEURONCOGENOMIC MAP DEFINES MEDULLOBLASTOMA HETEROGENEITY & PREDICTS TREATMENT RESPONSE

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Background: Medulloblastoma is a heterogenous group of tumors which collectively are the most common malignant brain tumor of childhood. Advances in treatment are required as one third of patients die from the disease, and those who survive suffer severe long-term side effects from therapy. The ability to sequence entire genome, methylome, and transcriptome of tumors provides the opportunity to identify underlying drivers of malignancy, predict treatment response, and develop novel therapies. A lack of reproducibility when comparing identified genetic mutations with treatment response is challenging because a single genetic change does not reflect the cellular state of a cancer cell in its entirety, which is expressing a multitude of genes. Computational methods allow for the creation of oncogenomic mapping systems which may more accurately describe the cellular state and thereby more reproducibly predict treatment response
Objectives: We used Pediatric Neuro-Oncology Oncogenomic Mapping (PNOM) to define medulloblastoma heterogeneity and predict treatment response using patient derived xenografts (PDX).
Design/Method: RNA transcription abundance from medulloblastoma samples published by Cho et al. were used to create a PNOM tool. This was accomplished by analyzing the distribution of transcriptional abundance for each gene across all samples in order to select the genes that display the most asymmetric and non-Gaussian behavior. This delineated a "context score" for each gene emphasizing those over and under expressed allowing for the creation of a unique signature to model cellular states. The medulloblastoma samples from Cho et al. were then

plotted onto the map based upon their RNA transcriptional abundance signatures creating clusters of similar cellular states. Likewise, RNA transcription abundance from 20 PDX samples, for which drug response was known, was then mapped.
Results: PNOM identified six cellular states for medulloblastoma by which to define patient samples; SHH, WNT, Photoreceptor/MYC (in which Group 3 medulloblastoma falls), Neuronal differentiation (in which Group 4 medulloblastoma falls), oxidative phosphorylation/AKT and Inflammatory pathways. The patient samples clustered into these states as follows; SHH, WNT, Photoreceptor/MYC, Neuronal differentiation, and oxidative phosphorylation/AKT pathways. PDX samples for which drug response was known clustered similarly onto the map.
Conclusion: PNOM using RNA transcriptional abundance from medulloblastoma samples could be used to predict drug response

Poster # 246/Early Career Travel Stipend Award Recipient

CIRCULATING HYBRID CELLS IN PEDIATRIC PATIENTS WITH GLIOMA

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Background: Central nervous system (CNS) tumors are the leading cause of death from childhood cancer. Pediatric gliomas are the most common CNS tumor of childhood, a subgroup of which is characterized by an aggressive, recurrent, and highly lethal clinical course. Despite a decade of revolutionary advances in understanding the molecular biology driving pediatric gliomas patient outcomes have not improved, in part due to crude measures of disease. Disease assessment is limited by tumor location and risk of serial biopsy as well as under-developed circulating analytes. Recent research identified a unique circulating tumor cell (CTC) derived from fusion of macrophages and tumors cells results in a tumor hybrid cell harboring hematopoietic and tumor properties (called circulating hybrid cell, CHC). In solid tumors CHCs correlate with disease burden and overall survival. In pediatric gliomas, detection of circulating cells with tumor characteristics, such as CTCs, are seldom reported and there are not yet reports of CHCs. The development of noninvasive circulating biomarkers in pediatric gliomas is critical to detecting disease evolution, progression and recurrence allowing investigations into the biologic processes underlying these phenomena and associated therapeutic opportunities.
Objectives: The purpose of this project is to detect and delineate the role of CHCs as a liquid analyte of disease status in pediatric patients with glioma.
Design/Method: Peripheral blood was obtained from 8 pediatric patients with: H3K27M mutant midline glioma (n=3), glioblastoma (n=2), anaplastic astrocytoma grade III (n=1) and astrocytoma grade II (n=2) at initial resection/biopsy (n=2) or disease progression/recurrence (n=6). Peripheral blood mononuclear cells (PBMCs) were isolated, adhered to poly-d-lysine–coated slides, fixed, permeabilized and stained with antibodies to CD45 and Glial Fibrillary Acid Protein (GFAP) and DAPI. Discrete cellular populations were identified by protein expression using a Zeiss AxioObserverZ.1 microscope, then digitally scanned using an Ariol digital scanner/Leica DM600 B, and processed with ZEN software.
Results: CHCs, defined as cells expressing CD45 and GFAP, were identified in 7 of 8 samples evaluated including high and low grade glioma. This pilot study established an isolation and immunofluorescence detection platform for measuring CHCs in pediatric patients with glioma.

Conclusion: CHCs are detectable in pediatric patients with glioma. We are investigating the immune, phosophotome and molecular profile of CHC using a multiplexed immunofluorescence imaging technique. Based on these findings we will perform longitudinal study of CHCs in pediatric patients with newly diagnosed high and low grade glioma to determine their role as a biomarker of disease status.

Poster # 247

SURVIVAL OF PEDIATRIC HIGH-GRADE GLIOMA TREATED WITH A THREE-DRUG MAINTENANCE CHEMOTHERAPY REGIMEN

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Background: Beyond focal radiation, there is no consensus standard therapy for children with high-grade glioma (HGG) and diffuse intrinsic pontine glioma (DIPG), yet with all current therapies outcomes remain dismal. We initiated an institutional standard 3-drug maintenance chemotherapy regimen for children with HGG/DIPG in 2009.
Objectives: To describe treatment and survival of children with HGG/DIPG treated at Seattle Children's Hospital (SCH) with multi-modality outpatient therapy consisting of focal radiation with concurrent temozolomide followed by maintenance chemotherapy with temozolomide, irinotecan, and bevacizumab.
Design/Method: We retrospectively reviewed the records of 36 pediatric patients treated at SCH between 2009-2017. Survival was analyzed using the Kaplan-Meier method. The log-rank test was used to compare factors potentially associated with survival.
Results: Thirty-six patients (50% male) were treated with this regimen, including 26 HGG and 10 DIPG, 4 of these with biopsy-proven H3 K27M-mutations. Other histologies included anaplastic astrocytoma (8), diffuse astrocytoma/gliomatosis cerebri (4), glioblastoma multiforme (9), HGG not otherwise specified (4), and giant cell glioblastoma (1). Common molecular alterations included TP53, NF1, and CDKN2A mutations. Median age at diagnosis was 10.9 years (range: 18 months – 18 years). All patients completed radiotherapy, 15 patients (42%) completed all 12 cycles of maintenance chemotherapy, 14 (39%) discontinued therapy due to progressive disease, and 7 (19%) discontinued due to toxicity or patient preference. Dose limiting toxicities included thrombocytopenia (9) and nausea/vomiting (7). The majority of patients (83%) experienced at least one chemotherapy delay or omission, with temozolomide the most commonly held drug. Median progression-free (PFS) and overall survival (OS) was 15.9 and 18.5 months for HGG and 9.4 and 13.5 months for DIPG. Survival at 1, 2 and 5 years was 85, 30, and 19% for HGG and 80, 30 and 0% for DIPG. PFS, but not OS, was associated with gender with earlier progression observed in girls ($p=0.03$).
Conclusion: Our single center experience demonstrates tolerability of this 3-drug regimen. Prolonged survival in DIPG was observed compared to prior series of patients treated with single-agent temozolomide, but cure was rare for HGG and absent for DIPG. Children with HGG and DIPG remain excellent candidates for study of novel therapeutics combined with standard therapy.

Poster # 248

PREDICTIVE AND PROGNOSTIC SIGNIFICANCE OF MRI IN PEDIATRIC LOW GRADE GLIOMAS

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Background: Pediatric low-grade gliomas (pLGG) account for 35% of all central nervous system (CNS) tumors. Though the overall prognosis is good, unresectable and progressive tumors remain a major therapeutic challenge. MRI is the preferred imaging modality for the diagnosis and treatment assessment.
Objectives: This study aims to evaluate if radiographic characteristics of pLGG at diagnosis are prognostic and predictive of treatment response.
Design/Method: Medical records of 567 pediatric LGG (pLGG) patients were reviewed at MD Anderson Cancer Center from 1998 to 2018. Summary statistics were provided to describe patient demographic and clinical characteristics. Chi-square test or Fisher's exact test, whichever the more appropriate, was used to compare categorical variables among surgery type. Wilcoxon rank sum test was used to compare continuous variables among surgery type. Kaplan-Meier method was used to evaluate the impact of radiographic characteristics including contrast enhancement on survival.
Results: 523 patients were ineligible because of unavailability of MRI at diagnosis or during treatment, no chemotherapy treatment after diagnosis or lack of histological conformation if underwent surgery. 44 patients were eligible, 23 male (52.3%) with the mean age of 5.3 years at diagnosis. 41 patient (93.2%) had a single lesion and 84% had cystic lesion (s) at presentation. The most common tumor location was optic/suprasellar (52%) and the most common line of chemotherapy used was carboplatin and vincristine (85%). Seventy percent of the studied tumors have contrast enhancement (low 36%, moderate 23% and high 11%). No statistically significant difference in outcome was found on the imaging characteristics including contrast enhancement, presence of cyst, tumor infiltration, tumor size, tumor location on the MRIs of the pLGG patients at diagnosis.
Conclusion: MRI is an essential tool in diagnosing LGGs. In the current study, the outcome was not significantly different between patients with (low, moderate, or high) versus without contrast enhancement. Collaborative multi-institutional studies are warranted to delineate consensus and investigate prognostic factors to improve the outcome of pLGG.

Poster # 249

MEK INHIBITOR FOR PEDIATRIC LOW-GRADE GLIOMAS (LGGS): A SINGLE-INSTITUTION EXPERIENCE

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Background: LGGs are the most common type of pediatric brain tumors; classified as World Health Organization Grade I or II. In General, LGGs are slow-growing tumors, regarded as chronic disease with excellent prognosis if completely resected. However, they tend to progress when incompletely resected, posing therapeutic challenges. LGGs can occur sporadically or as part of syndromes; most commonly neurofibromatosis 1 (NF1). Recently, Mitogen-activated-protein-kinases (MAPK) pathway has been identified as a major contributor to development of LGGs, offering an alternative therapeutic target in patients with progressive disease despite conventional therapies.
Objectives: Review our experience with Trametinib therapy in patients with LGGs who failed conventional therapies to determine clinical and/or radiological responses, and inhibitor-related adverse events.
Design/Method: We describe six children with sporadic or NF1-associated LGGs, treated with Trametinib (MEK inhibitor) at our institution after failing conventional therapies, through performing a retrospective chart review from January 2010 till September 2018.
Results: The median age at diagnosis with LGGs was 12.5 months with mean of 30 months (range: 5-84 months). The median age at starting Trametinib was 128 months with mean (130 months (range: 57-228 months). There were 3 males and 3 females. Three patients diagnosed with NF1, 1 patient with Down syndrome, 1 patient with autism spectrum disorder, and 1 patient with no associated syndrome. BRAF V600E was identified in two patients. Testing was not done in 4 patients (3 patients with NF1 and 1 patient with autism-spectrum disorder). All patients received prior therapies including surgery and/or chemotherapy. Five patients received Trametinib at starting dose of 0.035mg/kg/day. Overall, 4 patients had evidence of partial response at 3 months following initiation of therapy with two patients had stable disease. 1 patient died due to disease progression. Five patients had Grade I/II toxicities mainly involving skin and GI systems. The most frequent toxicities were mild-moderate skin rash and diarrhea. 1 patient tolerated Trametinib therapy without any side effects, and 1 patient who died had severe skin toxicity with scalp-wound dehiscence requiring discontinuing therapy despite partial response noted at 3 months following starting Trametinib.
Conclusion: Targeted individualized treatments with fewer toxic profiles are developing. Tissue biopsy at diagnosis with genomic testing is warranted to identify patients who would benefit from specific targeted therapy. Trametinib appears to be well tolerated in pediatric patients and effective in patients with refractory/ progressive LGGs who failed conventional therapies. Further prospective trials are needed to determine the optimal dosage and duration of therapy.

Poster # 250

TREATMENT-RELATED TOXICITIES DURING INDUCTION CHEMOTHERAPY FOR PATIENTS ON HEAD START IV PROTOCOL

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Background: The Head Start (HS) protocols have been one of the most commonly used regimens for the treatment of young children with central nervous system malignancies. HS I-III protocols utilized absolute neutrophil count as a marker of bone marrow recovery and initiation of subsequent cycles of chemotherapy. The ongoing HS IV protocol differs by utilizing absolute

phagocyte count (APC) as a measure of bone marrow recovery.
Objectives: The purpose of this study was to determine if utilization of APC resulted in greater number of treatment-related toxicities during induction chemotherapy for patients enrolled on HS IV.
Design/Method: Review of the RedCap database was conducted for duration of each induction cycle, and treatment-related CTCAE grade 3 and 4 toxicities as reported within the spectrum of "possible" to "definite". Data were summarized descriptively and nonparametric statistical methods were used for comparisons.
Results: At the time of this analysis, a total of 160 induction cycles were completed for the 56 patients enrolled, with a median of 34 days per cycle (range: 14-77 days). There were 666 grade 3 toxicities and 260 grade 4 toxicities documented. The most common toxicities were febrile-neutropenia (68%), mucositis (64%), anorexia (52%), and electrolyte abnormalities (52%). The most frequent grade 4 toxicity was hematologic (94%). Of the 56 patients, 9 (19%) voluntarily discontinued induction therapy after completing a median of 3 cycles each. These patients had a higher number of documented infections (52% versus 18%, p=0.0004). Veno-occlusive disease (VOD) occurred in 5 patients; 3 of whom voluntarily discontinued therapy. Since the protocol addendum utilizing milligram/kilogram dosing for patients less than 6 years of age, there have been no documented episodes of VOD. All other toxicities were observed to be similar between both groups of patients. Other serious grade 4 adverse events occurred only in patients that remained on study and include 2 episodes of thrombotic angiopathy, 1 of acute respiratory distress syndrome, 1 of pericardial tamponade, and 1 of aortic insufficiency. There were no toxic deaths in either group. The overall toxicities for this cohort were comparable to those reported for induction chemotherapy in HS I-II where febrile neutropenia was also the most common (69-77%).1
Conclusion: The higher rate of infections in those who discontinued therapy may possibly be associated with shorter duration of the immediately prior cycles. The use of APC as part of a dose-compression/intensification strategy in HS IV does not appear to result in more significant toxicities.Chi, JCO, 2004

Poster # 251

SINUSOIDAL OBSTRUCTION SYNDROME ON HEAD START IV REGIMEN IN YOUNG CHILDREN WITH EMBRYONAL TUMORS

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Background: The Head Start (HS) regimens include intensive chemotherapy protocols developed to treat young patients diagnosed with CNS embryonal tumors. Sinusoidal obstruction syndrome (SOS) is a potentially serious complication associated with intensive multiagent chemotherapy.
Objectives: We hereby describe the clinical characteristics and the predisposing factors of SOS in three patients at our institution who developed SOS during induction therapy with multiagent chemotherapy as per HS IV guidelines.
Design/Method: A PUBMED search was conducted for queries including SOS, HS. Relevant

papers were selected for literature review.
Results: Case 14-year-old male diagnosed with MYC amplified group 3 non-metastatic medulloblastoma. Following gross total resection, treatment was started as per HS IV protocol. Three weeks after initiation of the first cycle of chemotherapy on meter square dosing, the patient developed significant weight gain, ascites, and hyperbilirubinemia consistent with grade II SOS. Defibrotide was initiated for 21 days. Subsequent chemotherapy cycles and single autologous transplant were reduced based on weight dosing with prophylactic defibrotide.Case 2 3-year-old female diagnosed of medulloblastoma with leptomeningeal disease. After tumor resection, the patient was started on HS IV protocol. Cycle 3 was given based on the square meter dose as she turned three at that time. Two weeks later, she was diagnosed with a full-blown picture of grade III SOS and had a complicated hospital course from severe liver toxicity and pancytopenia. Case 3 5-year-old female diagnosed with cerebellar embryonal tumor with extensive spinal metastasis. Following partial resection of the primary and metastatic lesions, she started therapy as per HS IV regimen with weight-based dosing. Post cycle 4; she developed legionella sepsis and was noticed to have weight gain, edema, and elevated bilirubin that met the criteria of grade II SOS. She received 3 weeks of defibrotide and proceeded with cycle 5 of HS IV with a reduction in the chemotherapy and single autologous transplant along with defibrotide prophylaxis.
Conclusion: A low index of suspicion of SOS should be taken into consideration in young patients with brain tumors on HS regimens. Square meter dosing of chemotherapy in young patients and successive chemotherapy cycles resulting in liver toxicity, profound pancytopenia, and potentially serious infections might be inciting factors for the development of SOS in these young patients' populations.

Poster # 252

METHOTREXATE LEVELS IN CSF AFTER DIRECT INTRAVENTRICULAR INJECTION IN CHILDREN WITH EMBRYONAL TUMORS

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Background: Methotrexate has been used for intrathecal administration in leukemia as well as embryonal CNS tumors in children. Achieving adequate CSF levels has been difficult due to the blood brain barrier. Combining systemic chemotherapy with intrathecal therapy may provide the best approach to manage these tumors.
Objectives: To measure CSF methotrexate levels and tumor response in children receiving intra-Ommaya Methotrexate along with systemic Topotecan and Cyclophosphamide.
Design/Method: Patients with recurrent embryonal tumors after standard treatment including radiation were enrolled on this IRB approved phase 2 study. An Ommaya reservoir was inserted in the lateral ventricle and used to administer 4 daily doses of methotrexate (2 mg/dose) along with 5 days of intravenous topotecan (0.75mg/m2/day) and cyclophosphamide (250 mg/m2/day). Methotrexate was administered in a volume of 2 mL infused over 5 minutes and flushed with 2 additional mL of preservative free saline. Ventricular CSF methotrexate levels were measured on day 2, 3, and 4 of the first or second cycle before administration of IT methotrexate. MRI responses were assessed after two cycles.

Results: Three patients (age range 3-21) received 2 cycles of intra-Ommaya methotrexate and topotecan /cyclophosphamide – Two patients had recurrent metastatic medulloblastoma and one had a BCOR mutated metastatic posterior fossa tumor. Methotrexate levels in CSF were obtained 24 hours after dose administration and ranged from 0.97 to 33.00 mcmol/L (mean 14.5 mcmol/L). The mean methotrexate levels on the 2nd, 3rd, and 4th day were within the same range. These levels were significantly higher than what has been reported with high-dose methotrexate (5gm/m2) given intravenously in children with ALL. No adverse neurologic toxicity was seen. No systemic methotrexate toxicity was observed. Hematologic toxicity was seen as expected with this systemic chemotherapy regimen. No MRI white matter changes were seen. One patient had stable disease and 2 had a mixed response after two cycles.
Conclusion: Intraventricular administration of daily low dose methotrexate can achieve sustained meaningful CSF levels and could be considered as an alternative to systemic high-dose methotrexate in the management of recurrent embryonal CNS tumors in children.

Poster # 253

PEGYLATED INTEFERON-ALPHA TREATMENT FOR RECURRENT ADAMANTINOMATOUS CRANIOPHARYNGIOMA: A CASE SERIES

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Background: Craniopharyngioma is a rare, benign neoplasm that arises from the epithelial remnants of the craniopharyngeal duct or Rathke's pouch in the sellar or suprasellar region. These can be cystic or solid with cystic components, otherwise known as adamantinomatous type. Clinical signs and symptoms may include sequelae of increased intracranial pressure, visual abnormalities, and panhypopituitarism. Treatment options for craniopharyngioma include primarily surgical resection, with radiation therapy for symptomatic residual tumor or recurrences. Chemotherapeutic trials have employed pegylated interferon-alpha for recurrent, refractory craniopharyngiomas. Pegylated interferon- (peginterferon) is a convalent conjugate of recombinant interferon alpha and polyethylene glycol.
Objectives: Recurrent, refractory adamantinomatous craniopharyngioma can be treated with radiation and/or surgery. While these options carry significant morbidity with lifelong endocrine abnormalities, peginterferon may offer a less invasive adjunctive option.
Design/Method: This is a retrospective, case-series of three patients diagnosed with recurrent or refractory adamantinomatous craniopharyngioma from 2006-2018 who were treated with peginterferon.
Results: The median age at diagnosis was 12 years (range: 12 years – 20 years). All of the patients were female, labeled as Patient A, Patient B, and Patient C, and all had multiple endocrine abnormalities, such as hypothyroidism, diabetes insipidus, delayed puberty, and short stature. All of the patients had neuro-ophthalmologic abnormalities. None of the patients underwent radiation therapy prior to peginterferon therapy initiation. At 3 months post-initiation of peginterferon, Patient A had 60% decrease in tumor volume, but noted to have progression at 12 months. Patient B had no change in tumor volume at 3 months post-initiation of peginterferon, but 96% reduction in tumor volume at 12 months. Patient C had clinical response to peginterferon, and is awaiting tumor evaluation via imaging. Peginterferon was administered

once weekly, with duration of 12 months for Patient A, 5.5 years for Patient B, and 4 months for Patient C. All patients were initially monitored every 4-6 weeks while undergoing peginterferon therapy, with minimal toxicity observed.
Conclusion: Pegylated interferon-alpha presents a less invasive treatment option for recurrent, refractory adamantinomatous craniopharyngioma. The minimal toxicity profile and weekly administration allows for better compliance. While previous studies have shown no objective response to peginterferon in cases of craniopharyngioma with prior exposure to radiation therapy, our small radiation-naive cohort seems to suggest reduction in tumor volume.

Poster # 254

SURVEY ON THE RESOURCES AVAILABLE FOR PEDIATRIC NEURO-ONCOLOGY IN CHILE

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Background: Survival outcomes improved for children with cancer in Chile after establishing a unified public cancer health program, "Programa Infantil Nacional de Drogas Antineoplásicas" (PINDA) in 1988. We were interested in learning about the Chilean experience in treating children with central nervous system (CNS) tumors in public and private sectors.
Objectives: To collect data of the current state of human and material resources available in Chilean institutions providing pediatric neuro-oncology services.
Design/Method: A cross-sectional survey was distributed to 16 oncologists representing 16 hospitals providing pediatric neuro-oncology services between February – July 2018.
Results: Response rate was 75% (n=12; 8=PINDA, 4=private). Hospitals are primarily located in metropolitan centers (82%). Majority of pediatric services were provided within general hospitals (67%). The median number of pediatric beds for oncology was 12 (range, 4-17) and intensive-care was 10 (range, 2-18). All institutions have a registry for children with CNS tumors, and 67% have a registry for toxicity-associated with chemotherapeutic agents. Children with CNS tumors were treated by pediatric oncologists in all of the institutions. None of the pediatric oncologists were formally trained in pediatric neuro-oncology. The median number of pediatric neurosurgeons per institution was 2 (range, 0-8); complete resections for posterior-fossa tumors was 83%. Neuro-radiologists were available in 83% of institutions. All private institutions had an official report on the same day of the order compared with none of the PINDA centers (50% within 2-7 days). Pathology specimens were sent to pediatric neuropathologists (33%), general neuropathologists (25%), general pathologist (25%), and pediatric pathologist (16.7%); with a report generated 67% of the time within 1-2 weeks. In-house pediatric radiation oncologists were available in 25% of centers. Intensity-modulated radiotherapy was utilized by 67%, conformal radiotherapy by 58% and cobalt radiotherapy by 42%. Only one center (private) performed autologous hematopoietic cell transplant in children with CNS tumors, 16.7% in other tumors, 75% did not have experience. Centers reported that

83% of children with CNS tumors completed therapy. Majority of centers (58%) stated interest in a second opinion and in conducting teleconferences with a center abroad to discuss clinical cases. Multidisciplinary tumor boards are available in 58% of centers.
Conclusion: Chile is a high-income country with a population of ~18-million spanning over a geographically challenging 292,993mi2. These results give us a glimpse into the pediatric neuro-oncology services available in Chile providing coverage primarily in the metropolitan region. Implementing multidisciplinary teleconferencing programs may provide an innovative tool to continue to improve pediatric neuro-oncology patient care.

Poster # 255

PITUITARY ADENOMA IN PEDIATRICS: NONSURGICAL MANAGEMENT

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Background: Pituitary tumors are unusual in children and are associated with significant morbidity. The most common intrasellar tumors are craniopharyngiomas and pituitary adenomas. Craniopharyngiomas emerge from low-grade embryonic malformations of the sellar/parasellar region and typically grow very slowly, infiltrating and causing subtle symptoms associated with damage to nearby structures. Pituitary adenomas are typically benign expansions of well differentiated pituicytes, which also generally demonstrate slow growth and expansion over time, although they tend to be less invasive. Both tumor types can cause profound morbidity, with similar clinical and imaging findings. However, because the tumors are derived from entirely different cell types, there are important differences in their behavior and clinical management.
Objectives: We describe our observations in a contemporary series of children with prolactinomas and compare them to baseline features in children with craniopharyngiomas. We aim to describe the clinical presentation, biochemical, and imaging abnormalities which allowed us to determine the true diagnosis of a pituitary adenoma and describe their clinical response to therapy.
Design/Method: This is a retrospective, case-series describing six children evaluated in our institution since 2016 who were diagnosed with prolactinomas.
Results: The mean age of subjects was about 15.7 years (range 14- 19 years) at time of diagnosis and 66% were female. The most common presenting symptoms included growth failure (17%), delayed puberty (17%), irregular menses (66%) and galactorrhea (50%). Lab studies demonstrated elevated prolactin (median: 434.1ng/mL]) and other pituitary hormone deficiencies in 17% of subjects. No subjects had diabetes insipidus. MRI findings were consistent with a solid intrasellar lesion in 66% while 33% had mixed solid/cystic composition. 50% of tumors abutted or displaced the optic chiasm. Subjects were treated with cabergoline and 83% had a biochemical response with reduction in prolactin by >50% within 6 weeks. Follow-up MRI imaging demonstrated >20% reduction in size of the tumor in 33% of subjects by 6 months and complete resolution of tumor in 17% within 18 months. All subjects treated for more than 3 months with cabergoline tolerated therapy well and experienced resolution of pituitary dysfunction.
Conclusion: Pituitary tumors are uncommon in children and, while craniopharyngiomas are the most commonly recognized sellar mass in children, it is important to consider pituitary adenomas

as alternative diagnoses. Confirming the diagnosis of a prolactinoma may drastically alter the treatment approach and substantially reduce morbidity associated with the disease process.

Poster # 256

DIAGNOSTIC DELAY AND MORBIDITY OF CENTRAL NERVOUS SYSTEM TUMORS IN CHILDREN AND YOUNG ADULTS

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Background: Central nervous system (CNS) tumors are the leading case of cancer-related death in children, with a substantial increase of disability in survivors. A high index of suspicion, with an appropriate understanding of symptomatology and onset timeline, is needed to decrease the diagnostic delay that can lead to morbidity and mortality.
Objectives: Identify barriers existing within the local healthcare system that may result in diagnostic delay.
Design/Method: A retrospective chart review was conducted of patients with newly diagnosed CNS tumors between January 1, 2008 and December 31, 2017. Data collected included age at diagnosis and year at diagnosis, gender, race, zip code, PCP, tumor type and location, presenting symptoms, total number of healthcare visits prior to diagnosis, symptom interval, any associated tumor predisposition syndrome, and outcome (alive or deceased).
Results: 235 patient cases were reviewed. 34 (14.5%) had an associated tumor predisposition syndrome. Median (IQR) age at diagnosis was 9 years (4.0 - 14.0), with median (IQR) number of days from symptom onset to definitive diagnosis of 42 days (14 - 120). Delays $\geq$ 60 days occurred in 95 (40%) patients. There were 31 (13.2%) patients reported as deceased at the time of data collection. 115 of 235 (48.95%) patients were reported to have tumor or treatment related complications, including neurocognitive/neuropsychiatric disorders (93; 80.9%), growth hormone deficiency or pubertal delay (32; 27.8%), vision changes/loss (19; 16.5%), hypothyroidism (19; 16.5%), and diabetes insipidus (12; 10.4%).
Conclusion: Our institution had a shorter symptom interval of 42 days than currently reported in the literature, which may be due to quicker referrals following primary healthcare provider visits. In addition, only 31 (13.2%) patients were deceased at the time of data collection, with less than half (115; 48.9%) of all 235 patient reporting long term tumor or treatment related complications, suggesting that a shorter symptom interval may be crucial in providing patients with the best quality of life. Larger scale research is prudent to identify barriers needed to overcome the unacceptable delay in 47% of our patients. In the meantime, as the general pediatrician is pivotal in appropriate diagnosis and management of long term complications, we aim to further improve education and awareness in our community by offering educational seminars for community pediatric providers, as well as students and trainees. With this, we hope to continue to improve the time to diagnosis as well as the long term complications in children with CNS tumors.

Poster # 257

USE OF ACTH STIMULATION TEST TO DIAGNOSE ADRENOCORTICAL INSUFFICIENCY IN CHILDREN WITH BRAIN TUMORS

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Background: Childhood cancer survivors with brain tumors are at high risk of developing adrenocortical insufficiency (AI).
Objectives: Primary objective of this study was to determine prevalence of AI in children with brain tumors.
Design/Method: Under an IRB approved study, we performed retrospective chart review to identify children treated for brain tumors. Adrenocortical function was evaluated by ACTH stimulation test ("stim test"). Low-dose stim test was performed by giving 1 mcg cosyntropin intravenously and measuring serum cortisol levels at 0, 10, 20 and 30 minutes. A high-dose stim test was performed by giving 15 mcg per kg (max 250 mcg) cosyntropin and measuring serum cortisol levels at 0, 30 and 60 minutes. AI was diagnosed if peak serum cortisol levels were below 18 mcg/dL. AI was classified as (1) central AI due to direct effect on hypothalamic-pituitary (HP) region by tumor, surgery, or cranial radiation therapy; (2) adrenal suppression from the effects of exogenous glucocorticoids or other medications on hypothalamic-pituitary (HP) axis; and (3) primary AI due to adrenal gland pathology.
Results: Four-hundred-one children, median age 8 years (range: 0.1 – 19) were diagnosed with brain tumors between 2006-2017 at our institution. Adrenocortical function testing was performed on 56 patients. A total of 72 stim tests were performed, and no adverse effects were noted. Of these 52 were high-dose, 13 were low-dose, and 7 were low-dose followed by high-dose. AI was observed in 16/56 (29%) cases. All cases (16/16, 100%) were considered to be central, related to direct tumor effects on HP region, cranioradiation therapy and / or surgery. Exogenous glucocorticoids or megestrol causing adrenal suppression contributed in 4 (25%) cases. Amongst those undergoing stim testing, other endocrinopathies were common (43/56, 77%). We observed a higher rate of AI in patients with direct involvement of HPA by tumor (41% vs. 21%), and those undergoing surgery in HPA region (63% vs. 21%), and those with other endocrinopathies (33% vs. 18%).
Conclusion: We observed a high prevalence of AI in pediatric patients with brain tumors. Children with tumors involving the HP region are at high-risk and should have adrenal function evaluated early especially prior to intracranial surgery. Children with medulloblastomas who received cranial radiotherapy, and those with multiple endocrinopathies should be screened for late onset central AI. ACTH stim test is a useful and objective measure of hypothalamic-pituitary-adrenal axis function and should be considered in routine practice in management of this high-risk population.

Poster # 258

RETHINKING MIBG: PERSISTENT POSITIVITY 6 YEARS AFTER CESSATION OF HIGH RISK NEUROBLASTOMA TREATMENT

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Background: Neuroblastoma (NB) is the most common extra-cranial solid tumor in the pediatric population. These neuroendocrine tumors have widely heterogeneous clinical behavior, ranging from spontaneous regression (eg. stage 4S) to aggressive metastatic disease that leads to death despite aggressive, multi-modality therapy (e.g., Stage 4). MIBG imaging is a sensitive and specific marker for NB. Persistently positive MIBG despite therapy is currently accepted as a negative prognostic factor for survival. There are currently no case reports of patients with Stage 4, high-risk NB with persistently positive MIBG despite therapy, who had prolonged survival despite cessation of all interventions. A recent retrospective analysis in Japan of 15 patients with stage 4 NB showed 4 patients who had persistently positive(albeit improving) MIBG status-post PBSCT with 100% continued complete remission(CCR), while those with negative MIBG had 18% CCR(2 in 11).
Objectives: We report a case of a fourteen-year-old boy who survives 10 years after his initial diagnosis of stage 4 high risk NB despite persistently positive MIBG.
Design/Method: Case report and review of literature.
Results: Previously healthy four-year-old Caucasian male presented with 2 month history of musculoskeletal pain with intermittent fevers, refusal to walk, and 5-pound weight loss (4/2009). Imaging revealed a 7.9x5.9 heterogenous right suprarenal mass with extensive lymphadenopathy and osseous and pulmonary metastasis. Bone marrow was involved, histology unfavorable, but MYCN not amplified. Patient was diagnosed with stage4 NB and treatment initiated after biopsy and partial resection per COGA ANBL0532 x5 cycles, but taken off study due to progression of bony disease. Patient thereafter underwent successful primary tumor resection and intraoperative radiation therapy (1/2010), post-op EBRT, autologous HSCT (3/2010), one course cis-retinoic acid (5/2010), and therapeutic MIBG (6/2010) with suboptimal response. Despite these interventions, repeat MIBG scans showed continued diffuse metastatic disease (involving calvarium, spine, pelvis, acetabulum, humerus, femurs, scapulae, manubrium, ribs). Family elected palliative care at this time (11/2010) and refused further interventions unless symptoms developed. Approximately 18 months later, patient developed new headaches and was started on oral Irinotecan and Temozolomide, but due to difficulty with medication administration and family preference, treatment was stopped after two cycles (12/2012). Thereafter, patient received no further interventions. Most recent MIBG (completed 1/2019), was notable for Total Curie Score of 17(unchanged from 2012).
Conclusion: Our case demonstrates the need for future studies to better identify why some patients have good outcome despite poor prognostic factors and to examine meaning of persistently positive MIBG. This may save patients from unnecessary cytotoxic chemotherapy which can lead to many negative long term consequences.

Poster # 259

CASE REPORT: A CONGENITAL NEUROBLASTOMA PATIENT WITH BRAIN METASTASES

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Background: Neuroblastoma (NB), the most common extracranial tumor of childhood, accounts for more than 7% of malignancies in patients younger than 15 years and around 15% of all

pediatric oncology deaths. Congenital neuroblastoma is rare with less than 100 cases described in the literature. The central nervous system (CNS) is an uncommon site for dissemination and accounts for 0.7% of cases. Crizotinib is an anaplastic lymphoma kinase (ALK) inhibitor therapy that is currently undergoing clinical trials for treatment of NB.
Objectives: We detail the clinical course, including diagnostic workup and treatment plan, of a four-month-old boy with congenital, stage IV NB.
Design/Method: Prenatal ultrasound at 37 weeks and 5 days detected a mass above right kidney and labor was induced. Computed tomography (CT) showed right adrenal neoplasm with hepatic metastases. Metaiodobenzylguanidine scan and elevated urine catecholamines were consistent with NB. Patient was enrolled in the Children's Oncology Group Protocol ANBL1232 for non-high-risk NB. Repeat CT after two cycles of chemotherapy showed decreased in size of right adrenal mass and liver lesions. Third cycle was postponed for wound healing as a result of right adrenalectomy. Biopsy of tumor revealed positive ALK and amplified N-Myc. Patient developed a seizure and CT of the brain found masses suggestive of metastases, confirmed by magnetic resonance imaging (MRI). Given the ALK and N-Myc status, patient was switched to the Protocol ANBL1531 for high-risk NB.
Results: According to the Protocol ANBL1232, the patient was treated under group C. The first two cycles were Carboplatin/Etoposide and Carboplatin/Cyclophosphamide/Doxorubicin, respectively. After the transition to the Protocol ANBL1531, the regimen included Cyclophosphamide/Topotecan along with Crizotinib for the ALK positive status. Our patient was the youngest to receive Crizotinib. Despite the change in therapy, his clinical course continued to worsen, and the patient passed a month after the diagnosis of brain metastases.
Conclusion: Although NB accounts for a significant portion of pediatric oncology deaths, congenital NB remains exceedingly rare. The incidence of CNS metastases at diagnosis and at recurrence are also considerably low. Our patient was a stage 4 congenital NB at diagnosis, and subsequently had CNS involvement. He was also the youngest case to receive Crizotinib therapy for NB.

Poster # 260

EXTRASKELETAL MESENCHYMAL CHONDROSARCOMA OF THE KIDNEY IN A CHILD WITH HISTORY OF RIGHT ADRENAL NEUROBLASTOMA FOLLOWING REMISSION

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Background: Chondrosarcomas compose a heterogenous group of malignant tumors that share in common the production of chondroid matrix and are the third most common primary malignancy of bone after myeloma and osteosarcoma. Mesenchymal chondrosarcomas are rare and highly metastatic tumors with average age of onset in 25 to 30 years of age and commonly involve the meninges, craniofacial bones, ribs, ilium, and vertebra. Extraskeletal involvement of this tumor is extremely rare and few cases have been described without a definite treatment protocol available.
Objectives: To describe a case of mesenchymal chondrosarcoma of kidney in a child following neuroblastoma remission.

Design/Method: Case report.
Results: An 13-year-old male with history of right adrenal neuroblastoma diagnosed in 2010, who received chemotherapy with vincristine, doxorubicin, cyclophosphamide, etoposide and cisplatin along with radiotherapy, autologous stem cell transplant and monoclonal antibody therapy; with right adrenalectomy in 2011 and regular follow up every 3 months with primary oncologist. Patient presented on May 2018 with episodes of fever, right costovertebral tenderness and right back pain that worsened with voiding. The patient was admitted for IV antibiotics due to clinical diagnosis of pyelonephritis. Following initial evaluation, the patient was found with a right abdominal mass with demarcated borders measuring 2 cm x 2 cm, for which an abdominopelvic CT scan with IV contrast was performed. This study revealed the presence of a large right renal upper pole mass with irregular walls and associated thickening of the renal fascia, fat stranding and small amount of retroperitoneal and pelvic free fluid, findings worrisome for renal cell carcinoma. Following initial stabilization and symptom improvement, the patient was taken to OR for right radical nephrectomy with inter-aortocaval, right hilar and precaval lymph node dissection. Pathology was positive for a high-grade sarcoma with chondroid differentiation, consistent with extraskeletal mesenchymal chondrosarcoma.
Conclusion: To our knowledge, there are no previous reported cases of mesenchymal chondrosarcoma of the kidney following initial chemotherapy and radiotherapy for patients with high-grade neuroblastoma. Despite the challenging clinical presentation and rarity of the diagnosis, it might be an important consideration in pediatric patients exposed to radiotherapy and various chemotherapy agents in their early years.

Poster # 261

SPINAL CORD COMPRESSION IN RELAPSED FAVORABLE HISTOLOGY WILMS TUMOR

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Background: Wilms tumor occurs predominantly in children and is highly responsive to treatment with event-free survival approaching 90%. Patients with favorable histology have low risk of recurrence such that that current studies focus in treatment reduction to avoid long term effects. Spinal cord compression is a rare presenting feature in relapse of favorable histology Wilms. These patients represent a unique cohort with biologically aggressive tumors. We present a case of spinal cord relapse in a patient with favorable histology Wilms' tumor.
Objectives: This case report describes a clinical presentation, imaging, and therapy approach in a patient with relapsed favorable histology Wilms' tumor who presented with spinal cord compression.
Design/Method: A literature search was conducted using queries for Wilms tumor, spine, and spinal cord compression. Relevant papers were selected for review.
Results: A 6-year-old female had a history of Stage II Wilms tumor, treated with left nephrectomy and chemotherapy with vincristine, doxorubicin, and daunorubicin per AREN0533, regimen DD-4A. Tumor histology was favorable, and there was no loss of heterozygosity of 1p and 16q. Patient did not receive abdominal radiation therapy. A year after completion of treatment, she presented with gradually progressive lumbosacral pain. Lumbar XR and

abdominal ultrasound were normal. Her pain progressed to paraplegia with bowel and bladder incontinence. Magnetic resonance imaging of the spine was obtained and demonstrated large metastatic epidural lesions involving L1 through L3 vertebral bodies with partial encasement of the thecal sac and severe central canal narrowing. She was noted to have tumor extension beyond the anterior and lateral borders of L2 with extension into the IVC just below the porta hepatis. Patient underwent T12-L4 laminectomy for decompression. Immunohistochemistry expressed WT-1, confirming metastatic nephroblastoma with no anaplastic features. She subsequently received T12 to L4 radiation therapy [Cumulative dose= 2160 cGy] and chemotherapy with ifosfamide, etoposide, and carboplatin (ICE). She underwent stem cell harvest after Cycle 2 of ICE but did not undergo autologous stem cell transplant given only marginal evidence of survival benefit in the literature for standard-risk Wilms tumor at relapse. Spine, chest, abdomen, and pelvis imaging following Cycle 4 of ICE demonstrated no evidence of disease.
Conclusion: To our knowledge, our patient is the first report of recurrent favorable histology Wilms tumor presenting with spinal cord compression. This should alert providers to consider spinal imaging in patients with history of Wilms tumor who present with neuropathies. These patients may further benefit from evaluation of tumor gene expression evaluation.

Poster # 262

WILMS TUMOR AND CONGENITAL ANOMALIES: DISCOVERY OF A PIK3CA MUTATION AND DIAGNOSING CLOVES SYNDROME

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Background: CLOVES syndrome is a constellation of abnormalities (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal anomalies) that is caused by a postzygotic activating mutation in phosphoinositide-3 kinase (PIK3CA). Due to the mosaic nature of the PIK3CA mutation, it is often diagnosed by sequencing abnormal or affected tissues and not germline DNA. The clinical phenotype also varies, making diagnosis of this syndrome challenging. This mutation leads to PI3K-AKT-mTOR pathway activation, leading to cell proliferation and growth. Overgrowth syndromes, such as CLOVES, have been associated with developing Wilms tumor (WT).
Objectives: Describe a unique presentation of WT with multiple congenital anomalies and its association with a PIK3CA mutation and CLOVES syndrome
Design/Method: Case report
Results: A 9-year-old girl has a history of coarctation of the aorta, mid-aortic syndrome, tethered cord, severe scoliosis, epidermal nevus, café au lait spot, multiple neurofibromas, adrenal rest, and bilateral nephroblastomatosis. At the age of seven, she had a left upper pole nephrectomy due to dysplasia on imaging. It revealed favorable histology (FH), epithelial predominant WT arising from hyperplastic perilobar nephroblastomatosis. Due to the indolent nature of this area seen on imaging for the prior 6 years, she was observed without further treatment as if she had very low risk WT. A year later, a spleen mass was identified. Splenectomy revealed recurrence of triphasic, FH WT. She was treated with 28 weeks of vincristine, doxorubicin, and

dactinomycin without radiation. Six months after completion of chemotherapy, she relapsed in her operative bed, liver, lung, and peritoneum. Gross resection of her intra-abdominal disease revealed FH WT. She is currently receiving etoposide, cyclophosphamide, and carboplatin and will receive whole lung and abdomen radiation. Chromosome microarray as well as germline analyses of genes causative for RASopathies and cancer predisposition were negative. Genomic analysis on the recent relapsed specimen revealed a somatic activating KRAS mutation and a pathogenic missense mutation in PIK3CA, p.H1047R with an allelic frequency of 39%. This mutation fits with the diagnosis of PIK3CA-related overgrowth spectrum (PROS) and her clinical features are consistent with the subgroup, CLOVES.
Conclusion: This case highlights the difficulty of diagnosing somatic mosaic disorders like CLOVES and the importance of tumor tissue sequencing. While this diagnosis does not change the chemotherapy plan, PIK3CA inhibitors are in trials to treat congenital anomalies associated with CLOVES. Additionally these inhibitors may offer another treatment option for her refractory disease.

Poster # 263

ATYPICAL ANGIOMYOLIPOMA IN TUBEROUS SCLEROSIS COMPLEX MIMICKING METASTATIC WILMS TUMOR: A CASE REPORT

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Background: Wilms tumor (WT) is the most common malignant renal tumor in childhood. Renal angiomyolipoma (AML) is another renal mass that is often asymptomatic and commonly occurs in association with tuberous sclerosis complex (TSC). Renal AMLs are typically comprised of fat, vasculature and muscle tissue. About 5% of renal AML are reported to be fat-poor. Distinguishing radiographically between atypical AML and WT will allow clinicians to identify these entities in the absence of histologic diagnosis and may eliminate the need for tissue biopsy. While it is possible for WT to occur in patients with TSC, this is a rare phenomenon with only two published cases.
Objectives: To expand the differential diagnosis of the pediatric patient presenting with a renal mass and concomitant pulmonary nodules. To radiographically distinguish WT from atypical AML.
Design/Method: Case report.
Results: A 4-year-old boy presented with abdominal pain and intermittent vomiting. Initially a parasitic infection was suspected related to recent travels in Africa. Abdominal ultrasound showed a 2x2x1.6 cm mass involving the lower pole of the right kidney. A computerized tomography (CT) scan of the abdomen showed a 2.3x2.3x1.8 cm lobulated exophytic heterogenous mass in the lower pole of the right kidney concerning for WT. CT obtained in evaluation for metastatic disease demonstrated three pulmonary nodules. CT head was performed due to concern for spells of seizure-like activity and showed multiple bilateral calcified subependymal nodules and subcortical cerebral calcifications suggestive of tuberous sclerosis. MRI of the abdomen showed increased signal intensity in the lower pole of the right kidney, without loss of signal intensity on the out-of-phase imaging to suggest significant fat content. These findings were suggestive of differential considerations of Wilms tumor and atypical

angiomyolipoma. Serial renal ultrasounds were monitored for interval growth and showed a stable mass, supporting the diagnosis of atypical AML. Genetic testing confirmed Q797X nonsense mutation in the TSC1 gene, establishing the diagnosis of TSC.
Conclusion: Differentiating incidental renal masses in pediatric patients with overlapping signs and symptoms is a diagnostic challenge. MRI offers the most diagnostic utility. WT presents as hypointense on T1-weighted images compared with kidney parenchyma and hyper- or isointense on T2-weighted images. Fat-poor AML demonstrates a relative T2 hypointensity compared to renal cell carcinoma or WT. Additionally, homogeneous signal loss on T1-weighted gradient-recalled echo opposed-phase chemical shift imaging is a proposed finding that is suggestive of fat-poor AML. Clinicians could consider these diagnostic clues when evaluating new renal masses.

Poster # 264

A NOVEL GERMLINE TP53 MUTATION IN A PATIENT WITH LI-FRAUMENI SYNDROME

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Background: Li-Fraumeni syndrome (LFS), a cancer predisposition syndrome resulting from germline TP53 mutations, is characterized by early and multiple malignancies including CNS tumors, adreno-cortical adenomas, sarcomas, and premenopausal breast cancer. Over 440 germline mutations affecting approximately 1200 families have been catalogued in the International Agency for Research on Cancer (IARC) TP53 database.
Objectives: We identified a novel TP53 germline mutation responsible for a clinical presentation of Li Fraumeni syndrome.
Design/Method: Case report, literature review, and genomic database search.
Results: An African-American female presented at 2 years of age with localized, alveolar rhabdomyosarcoma of the shoulder treated with chemotherapy and radiation. She was disease-free until age 11 when she developed a local recurrence that required forequarter amputation after progression on salvage chemotherapy. The tumor was 95% viable at resection. She received adjuvant chemotherapy and was disease-free at end-of-therapy. At age 17, biopsy investigating a right breast mass demonstrated phyllodes tumor and ductal carcinoma in situ (DCIS). Imaging revealed an additional mass in the contralateral breast. Further metastatic work up was negative. She underwent double mastectomy, with pathology from the left breast demonstrating invasive ductal carcinoma grade 3 and DCIS. She received adjuvant chemotherapy and remains disease-free.Family history included a PGGM, PGM, and MGGM with breast cancer in their 30’s, 40's, and 50’s respectively. Several other family members had single cancers in their 50’s or above. Neither parent has had cancer.Despite not having a classic family history for Li Fraumeni syndrome she did meet one of the four Chompret/Bougeard diagnostic criteria: early-onset breast cancer. Germline TP53 analysis showed a missense mutation in exon 5 (c.476C>T), resulting in a valine substitution for alanine at codon 159 (p.A159V).There are no prior reports of TP53 p.A159V in LFS in the IARC germline database and this variant is not described in population germline databases (GnomAD). However, identical missense mutations are reported as variants in both the COSMIC and IARC TP53 somatic databases, with 32 mutations noted in a variety of

malignancies, including breast cancer. She is being monitored with physical exams every three months and annual whole-body MRI's.
Conclusion: TP53p.A159V is a novel Li Fraumeni syndrome germline variant associated with soft tissue sarcoma and breast carcinoma.

Poster # 265

EMBRYONAL RHABDOMYOSARCOMA WITH AN UNUSUAL PRIMARY SITE AS INITIAL PRESENTATION OF DICER1 SYNDROME

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Background: DICER1 syndrome is an inherited cancer predisposition syndrome that predisposes individuals to the development of tumors, both benign and malignant. Mutations in the gene encoding the endoribonuclease, DICER, lead to the disruption of microRNA processing and subsequent disruption of gene expression. This dysregulation seen in DICER1 syndrome has classically been linked to the development of pleuropulmonary blastomas. However, other tumors have been found to be associated with DICER1 syndrome including rhabdomyosarcomas, cystic nephromas, multinodular goiters, thyroid cancer, and ovarian Sertoli-Leydig cell tumors. Rhabdomyosarcomas associated with DICER1 are characteristically embryonal in origin.
Objectives: To discuss the case of a patient with primary embryonal rhabomyosarcoma (ERMS) of the colon, an unusual location for this particular tumor, and how the diagnosis of DICER1 syndrome unfolded.
Design/Method: Here we describe the case of a 3-year-old male with a large abdominal mass, along with the workup that led to the diagnosis of ERMS. We also describe the patient's course on and off therapy which led to the diagnosis of DICER1 syndrome.
Results: Initial imaging revealed a large heterogeneous abdominal tumor compressing the bladder. Metastatic workup was negative. Imaging of the chest revealed pulmonary blebs. The patient underwent gross total resection of the primary tumor. Pathology revealed ERMS. Pulmonary blebs were biopsied and there was no evidence of tumor on pathology. He was treated with chemotherapy. Two months after his diagnosis, he was found to have abdominal distention and recurrence of his tumor; he underwent a second resection. Subsequent therapy included high-dose chemotherapy, autologous stem cell transplant, and radiation therapy. Follow-up scans two years after diagnosis demonstrated increased size of the pulmonary blebs. A wedge resection was done and there was no evidence of tumor. Approximately six years after diagnosis, follow-up scans were significant for renal cystic lesions. These new lesions, in the setting of pulmonary blebs and ERMS, raised the question of DICER1 syndrome. Genetic workup was significant for a DICER1 mutation.
Conclusion: The colon is a rare presenting location for ERMS and can potentially be explained by DICER1 syndrome. To date, there are no published case reports of ERMS associated with DICER1 that present in the colon. This case supports evaluating for DICER1 mutations not only in patients who develop tumors classic for DICER1 syndrome in common locations, but also in those who present with those classic tumors in unusual locations, as there may in fact be a link to a DICER1 mutation.

Poster # 266

OPTIONAL PET SCAN UPSTAGING PEDIATRIC RHABDOMYOSARCOMA

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Background: The standard staging imaging protocol for cases of pediatric rhabdomyosarcoma (RMS) includes CT, MRI, and bone marrow aspiration, but not PET (optional). In addition, insurance does not reliably pay for PET scans. Standard imaging may not be sufficient for staging RMS due to the possibility of under-staging, subsequently following a protocol suited for a lower level diagnosis and leading to a less aggressive treatment plan and poorer prognosis.
Objectives: The objective is to report cases that highlight the value of incorporating PET scans into the standard imaging for evaluating/staging RMS.
Design/Method: We reviewed PubMed and Google Scholar using the following phrases/words: "rhabdomyosarcoma, staging, and PET scan". The search was limited to cases of Rhabdomyosarcoma in the last 15 years and the English language.
Results: Three case reports of patients with RMS in addition to our case were found. The first case was a 38-year old woman had alveolar rhabdomyosarcoma from breast primary tumor. A PET/CT scan revealed hepatic and pancreatic metastases along with multifocal bone marrow involvement which a CT scan did not detect (Luporsi et. al). The second case was of a 26 year-old man with alveolar Rhabdomyosarcoma that had a 18F-FDG PET/CT scan that detected a significant level of bone metastases that were not detected in bone scintigraphy (Yang et, al, 2013). The third case was of a 9-year old male with paratesticular rhabdomyosarcoma. The PET/CT scan yielded positive findings of lymph node metastasis while the CT scan revealed negative results (Burnette et al., 2013). In each case, the PET scan upstaged the patient.We report a case of a 22-year old female originally evaluated as a stage II anterior mediastinal embryonal rhabdomyosarcoma. The standard imaging protocol of MRI, bone marrow, CT and bone scan showed no evidence of diffuse disease (Fig. 1a & 2a), but PET-CT revealed high risk metastatic disease with primary anterior mediastinal embryonal rhabdomyosarcoma with mets to the supraclavicular node, spine, and pelvis (Fig. 1b & 2b). This led to the patient being upstaged from II to IV.
Conclusion: Without the optional PET scan imaging, the patients would have been under-staged and treated with a less effective protocol that was not suited for metastatic RMS. These cases emphasize the importance of incorporating PET imaging into the standard protocol for evaluation and diagnosis of RMS as well as advocating for medical insurance to cover these scans(currently are not), rather than offering them as an optional supplement.

Poster # 267

CASE REPORTED OF OSTEOSARCOMA ISOLATED RELAPSE TO THE PHARYNGEAL TONSIL

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Background: A 27-year-old male diagnosed with osteosarcoma relapse isolated to the tonsils after an isolated bone relapse and after initial diagnosis. He was originally treated off protocol (COG AOST0031) following the standard neoadjuvant chemotherapy protocol "MAP" (methotrexate, doxorubicin, and cis-platinum) to complete 29 weeks of therapy. He remained disease free, until an isolated condyle relapse was identified by biopsy and treated with an en bloc resection. The second relapse occurred 13 months after to the first recurrence. He presented with an enlarged right tonsil that was thought to be strep throat. The tonsillar swelling persisted which prompted an ENT evaluation and biopsy, identifying it as relapse of osteosarcoma. PET scan, bone scan, CT of head showed no other detectable disease. He was treated with resection, high-dose chemotherapy, and proton beam radiation therapy.
Objectives: Recurrent osteosarcoma (OST) occurs in 30-50% of cases of initial localized disease and 80% of metastatic disease (Recurrent Osteosarcoma, 2016). Common sites of recurrence include lungs and bones (80% respectively) (Recurrent Osteosarcoma, 2016). With the introduction of intensive, high-dose chemotherapy for the treatment of Osteosarcoma, changes in the pattern of metastases observed at relapse have been reported (SN, 2004). The unusual sites of recurrence include the kidney, brain, muscle, subcutaneous tissue, stomach, duodenum, and penis (Kabnurkar, 2015). Recurrence in the tonsils has not been previously reported. We present the case what we believe to be the only known reported case of osteosarcoma relapse isolated in the tonsil.
Design/Method: We reviewed PubMed and Google Scholar using the keywords: "Osteosarcoma", "Relapse of Osteosarcoma", "Osteosarcoma relapse in tonsils", "Unusual patterns of relapse in OS", and "Unusual sites of metastatic reoccurrence of osteosarcoma." The search was limited to the English Language.
Results: Forty-three reports of osteosarcoma recurrence cases to the head and neck region were reported. Of that forty- three reported, no similar cases were reported to our case of an osteosarcoma recurrence isolated to the tonsil.
Conclusion: Osteosarcoma relapse in sites other than the lungs and bones are extremely rare outside of widespread early life recurrences. Based on our literature review, we believe this is the only known reported case of osteosarcoma relapse isolated to the tonsils. We want to emphasize the importance of understanding that OST can occur in other parts of the body to avoid misdiagnosis, undertreatment/overtreatment, and/or no treatment at all. There has been an emerging pattern of unusual relapses after wide spread adoption of multiagent chemotherapy. In this case, the recurrence of osteosarcoma to the right pharyngeal tonsil resembled swollen lymph nodes in the neck mimicking strep throat. Early recognition of this relapse prevented further distant metastasis.

Poster # 268

CLINICAL RESPONSE TO RE-EXPOSURE TO HIGH DOSE MTX IN MULTIPLY RELAPSED OSTEOSARCOMA PEDIATRIC PATIENT

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Background: Methotrexate (MTX), an anti-folate antineoplastic agent, has been used since 1986 as a standard of care to treat osteosarcoma (OST). Relapsed OST cases have limited systemic treatments no standard second or third line therapies.
Objectives: In general, practitioners try one of a handful of agents (interferon, doxorubicin, cis-platinuum, MTX, ifosfamide, etoposide,) that have shown efficacy in OST and avoid repeating previous agents. However in a multiply relapsed patient, retreatment with an agent proven previously successful when other options have been exhausted may be reasonable. We report a case of multiply recurrent, progressive OST, retreated with two doses of HD-MTX with a demonstrable clinical and palliative objective response.
Design/Method: We reviewed PubMed and Google Scholar using keywords: "osteosarcoma," "retreatment," "methotrexate." The search was limited to the English language.
Results: There found no reported cases of response or non-response to HDMTX re-exposure for relapsed OST found. Case Report: At the time of diagnosis, our patient was a 17-year-old female with metastatic osteosarcoma to the lungs and bone. The presenting alkaline phosphatase (ALP) level of 1880 u/L. The patient was successfully treated with "MAPIE" and aggressive surgical resection of primary, bone and lung tumors and achieved radiological and clinical remission with an ALP level of 42 u/L. Twelve months post-chemotherapy, the patient relapsed in the lungs, presenting with an ALP level of 162 u/L. The patient was treated with denosumab for 6 cycles, doxorubicin and also nivolumab, but still progressed to which her ALP level rose to over 1200. The patient requested to're-try' MTX. After a difficult approval process, it was approved and the patient experienced elimination of pain, dramatic decrease in the size of bony vertebral mass and decrease in ALP from 1248 to 889 with the first dose and from 889 to 571 after the second dose. The patient tolerated the therapy without any adverse effects. Unfortunately no further doses of MTX were approved and the patient died 3 months later.
Conclusion: In a setting of limited or no options of treatment of relapsed osteosarcoma, retreatment of MTX is worthy of consideration. In our particular case, there was an objective response to the retreatment of MTX including alleviation of pain, decrease in size of vertebral mass, and decrease in ALP levels. Retreating osteosarcoma was successfully explored and provides a plausible palliative treatment option for cases of relapsed, progressive OST.

Poster # 270

INFANT BRONCHIOLITIS OR MORE? A CASE OF SUPERIOR MEDIASTINAL INFANTILE FIBROSARCOMA

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Background: Infantile fibrosarcoma (IFS) is a rare malignant soft tissue neoplasm of fibroblastic lineage that represents less than 1% of childhood tumors. IFS is diagnosed at birth or during infancy and commonly presents in the extremities, less commonly the trunk. Due to its rarity, there is often delay in diagnosis and consequently treatment of these patients.
Objectives: Unusual clinical presentation of rare tumors can pose a diagnostic and therapeutic challenge. Herewith, we report a case of IFS that occurred in the superior mediastinum.
Design/Method: The patient underwent an ultrasound guided needle core biopsy (USBX) following radiologic evaluation initially by a chest radiograph followed by Computed Tomography (CT). Routine histologic evaluation was conducted supplemented by immunohistochemical stains (IHC) and fluorescent in-situ hybridization (FISH).
Results: A 3-month-old Caucasian male presented with one-week of worsening respiratory distress without fever or constitutional symptoms. He was initially managed for bronchiolitis without clinical improvement. A chest radiograph showed a mediastinal mass, which on CT was confirmed to be a 10.2cm superior mediastinal mass with mass effect on the heart, great vessels, and lungs. Serum AFP, b-HCG and urine catecholamines were normal. Ultrasound guided biopsy showed a malignant spindle cell neoplasm. The neoplastic cells were negative for desmin, myogenin, cytokeratins, and SALL-4 IHCIHC. Cytogenetic testing with FISH demonstrated an

showed ETV6 rearrangement, confirming the diagnosis of IFS.Neoadjuvant systemic therapy was urgently initiated given the size of the mass and compression of the great vessels. Patient received Vincristine [0.05 mg/kg/dose], Dactinomycin [0.025 mg/kg/dose], and Cyclophosphamide [25 mg/kg/dose] for 12 weeks per ARST03P1. Imaging after Cycle 1 demonstrated a 25% reduction in tumor volume with complete resolution of respiratory symptoms and 50% reduction in tumor volume following Cycle 3. Thoracoscopic resection was performed after Cycle 3 with negative margins. The tumor extended into thymus and demonstrated ~60% necrosis.
Conclusion: To our knowledge, this is the first report of IFS presenting as a superior mediastinal mass with thymic involvement. This should alert providers of the mediastinum as a possible primary site of fibrosarcoma in an infant presenting with respiratory distress. Cytogenetic testing on even a limited sample can assist in timely diagnosis and management.

Poster # 271

TREATMENT OF YOUNG ADULT PATIENT WITH MULTIFOCAL DESMOPLASTIC SMALL ROUND CELL TUMOR

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Background: Desmoplastic small round cell tumor (DSRCT) is a rare tumor that occurs in children, adolescents and young adults. Ninety percent of cases have been reported in males. DSRCT has an aggressive course and the 5-year overall survival is currently estimated at 15%. Only 200-450 cases have been reported in the literature to date. Of those cases, most patients present with disease in the peritoneum. We report a rare case of a patient that presented with multifocal DSRCT, including cardiac and cerebral involvement and outline his clinical course.
Objectives: To review the clinical, pathological features and radiological findings as well as treatment outcome in patients with DSRCT and to evaluate the evidence for treatment options available.
Design/Method: We report a clinical case from our center and have conducted a review of the literature from Medline (Pubmed) database from 1989-2017.
Results: A 19 year old male presented with a three month history of headaches. Imaging revealed 3 cerebellar tumors. Initial diagnosis was undifferentiated carcinoma, possible primitive neuroectodermal tumor (PNET). Further staging revealed a 5.2 cm x 4.9 cm intracardiac mass, a right sided soft tissue lesion in the flank measuring 2.3 x 1.7 cm and a small nodule noted in the right lower lobe of the lung. Cardiothoracic surgery was consulted but did not recommend upfront surgery without a trial of systemic therapy to control other areas of disease. Due to the unclear pathology, a second biopsy was pursued of his flank mass. Pathology revealed DSRCT with EWSR1 rearrangement. He was treated with MSKCC's P6 5-drug Ewing-like regimen. He also received further radiation therapy for progression of brain disease. During his final cycle of chemotherapy, he had a V-fib cardiac arrest, prompting a cessation of chemotherapy. He completely recovered and was able to later be restarted on treatment with Pazopanib and cardiac radiation therapy. However, he died of progressive cardiac failure two years post-diagnosis.
Conclusion: Our patient survived approximately two years from the time of diagnosis of DSRCT with a combination of surgery, chemotherapy, radiation and targeted therapy with

Pazopanib. Pazopanib only provided brief clinical benefit and may have contributed to progression of cardiac failure. Larger studies and clinical trials are needed for this rare disease to study optimal strategies for staging and treatment.

Poster # 272

DENOSUMAB FOR RECURRENT METASTATIC GIANT CELL TUMOR OF THE BONE

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Background: Giant cell tumor (GCT) of the bone is an uncommon bone tumor, usually localized, and rarely presents at less than 20 years of age. Only two to three percent of patients have pulmonary metastases. Denosumab, a fully human monoclonal antibody against RANKL, is approved for treatment of unresectable GCT in skeletally mature individuals.
Objectives: To present a case series of two children with GCT of the bone with pulmonary metastasis.
Design/Method: Retrospective review of medical records of two pediatric patients with metastatic GCT who underwent treatment with Denosumab at Texas Children's Hospital.
Results: Our first patient, a 14 year old Asian male, presented with bilateral leg pain and neurogenic bladder secondary to a large sacral mass, measuring 4.2cm x 6.5cm x 4.5cm. He underwent biopsy and surgical debulking at another institution which confirmed GCT. He presented to us two months later with an 8.7cm x 7.9cm x 8.2cm recurrent mass with tumor thrombus in the left internal iliac vein. CT chest revealed five nodules ranging from 2mm to 8mm in diameter. Therapy was initiated with Denosumab at 120mg subcutaneously once weekly for three weeks and then monthly. In addition, single session of radiofrequency ablation at the periphery and two sessions of transarterial embolization centrally by interventional radiology were administered starting second cycle. After 2 cycles, mass size decreased to 7.1cm x 8.3cm x 6.4cm and largest pulmonary nodule decreased from 8mm to 5 mm. He has completed 8 cycles of Denosumab without major complications with continued reduction in size of the mass.The second patient, a Hispanic male, presented at age 16 with a left proximal tibial pathological fracture and a 6cm x 3.9cm x 4.5cm mass. He underwent intralesional excision. Local recurrence with an 11.9cm x 12.6cm x 9.6cm mass and numerous pulmonary nodules were discovered nine months post-surgery. He underwent above the knee amputation and pulmonary nodule sampling which confirmed GCT. Denosumab therapy was initiated due to progression of pulmonary lesions after a period of observation. He completed 26 cycles of Denosumab with resolution of a majority of the pulmonary nodules and is alive 4 years from initial diagnosis.
Conclusion: Denosumab is active in pediatric patients with giant cell tumor and should be considered in patients with unresectable or metastatic disease.

Poster # 273

SYSTEMIC BEVACIZUMAB IN CHILDREN WITH RECURRENT RESPIRATORY PAPILLOMATOSIS

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Background: Recurrent respiratory papillomatosis (RRP), caused by the human papilloma virus, is the most common pediatric neoplasm of the larynx. Patients often present with hoarse voice and typically require frequent surgical debridements. Bevacizumab, a vascular endothelial growth factor antibody, has been described in case reports to control recurrent papilloma growth and decrease surgical procedures.
Objectives: To present a case series of two pediatric patients with RRP managed with systemic bevacizumab.
Design/Method: Case series.
Results: We report two pediatric patients with RRP managed with systemic bevacizumab. The first patient, a 6-year-old male, presented with a raspy voice in infancy and was noted to have bulky sessile papillomas of the vocal folds at 3 years of age. He underwent ablation of the papillomas and pathology showed squamous papilloma. He had multiple recurrences necessitating 16 surgical ablations within a 29-month period. Additionally, 4 doses of intralesional bevacizumab were ineffective in preventing recurrence. Intravenous bevacizumab was initiated at 10 mg/kg every 4 weeks. He was noted to have improvement in voice quality and resolution of papillomatosis except for one minimal papilloma growth on the right vocal cord after two cycles. He has received 6 doses of bevacizumab (now administered every 6 weeks) and has not required further surgical debridement. The second patient, an 8-year-old female with RRP, has required surgical debridements every 3 months between 8 and 33 months of age. She has needed 37 additional surgical debridements in the past 5 years. She developed respiratory distress, snoring, and worsening of voice quality with interval growth of lesions. She received intralesional bevacizumab on 2 occasions with recurrent growth. She started on systemic bevacizumab at 10 mg/kg and has completed three cycles with no respiratory distress or snoring in the past 3 months. Parents have noticed mild improvement in her voice quality. Both patients continue to tolerate bevacizumab well with no hypertension, proteinuria, or significant bleeding.
Conclusion: Systemic bevacizumab is effective in RRP and reduces surgical procedures and exposure to anesthesia, and improves quality of life. Further investigations are necessary to determine length of treatment and the long-term effectiveness.

Poster # 274

AVASTIN THERAPY AS AN ADJUNCT TREATMENT MODALITY FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

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Background: Recurrent respiratory papillomatosis (RRP) is a rare, benign disease characterized by repeated growth of benign, exophytic lesions both in the upper and lower respiratory tracts. Unfortunately, over time these lesions can convert into malignant disease, most commonly squamous cell carcinoma. Currently, there is no cure for the disease, and treatment is primarily focused on maintaining airway patency and voice quality. The current standard of care is

periodic surgical excision, with adjunct therapies used as needed.
Objectives: This case report aims to demonstrate the effectiveness of Bevacizumab (Avastin) as an adjunct treatment for RRP in childhood.
Design/Method: The patient is a 9 year old boy who was diagnosed with respiratory papillomatosis when he initially presented with cough, difficulty breathing, and voice changes. The patient required at disease onset direct laryngoscopies with surgical debridement every 6 weeks for removal of papillomas which affected his breathing, and ability to speak clearly. He was started on pegylated interferon therapy in an effort to stabilize the progression of RRP. This therapy kept the disease stable for 1 year and decreased the frequency of direct laryngoscopies to every 3 months. He went on to develop rapid progression of papillomatosis, especially in the lungs with two episodes of respiratory distress requiring hospitalization. At this time, his treatment modality changed to serial direct laryngoscopies with surgical excision and injections of cidofovir every 2-4 months depending on when he was symptomatic. CT imaging noted overall progression of the disease especially in the lower airways. It was decided to start monthly treatments with Bevacizumab. After his first treatment and subsequent direct laryngoscopy, the patient was noted to have a drastic decrease in disease burden and his voice is now back to normal. Direct laryngoscopies are now performed every 6 to 9 months as surveillance.
Results: Bevacizumab was shown to be an effective adjunct therapy for recurrent respiratory papillomatosis. Our patient's quality of life has markedly improved with decreased overall procedures in the last 12 months. He continues to receive Bevacizumab every 4 to 6 weeks as maintenance therapy. The direct laryngoscopies are performed every 6 to 9 months as surveillance.
Conclusion: This case report concludes that Bevacizumab is an effective adjunct therapy for recurrent respiratory papillomatosis.

Poster # 275

PEMBROLIZUMAB-INDUCED TYPE 1 DIABETES IN A PEDIATRIC PATIENT

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Background: Immunotherapy is increasingly being tested for Pediatric malignancies. There are at least 25 active clinical trials involving pembrolizumab for patients <18-years-old. Endocrinopathies are known complications of anti-PD-1 therapy, including primary thyroid dysfunction and type-1 diabetes (T1DM). No T1DM cases have been reported in pediatric patients receiving PD-1 inhibitors.
Objectives: To describe a pediatric case report of PD-1 inhibitor-induced T1DM, its presentation, management and evolution.
Design/Method: Case Report
Results: We present a 15-year-old male who developed T1DM secondary to pembrolizumab treatment for metastatic alveolar soft part sarcoma (ASPS) of the right thigh. His medical history includes asthma, ADHD and obesity. Family history is significant for rheumatoid arthritis. Patient underwent surgical excision of his primary ASPS, but was found to have multiple lung nodules. He was initially treated with Sunitinib. Due to acanthosis and obesity, he was started on Metformin. Hemoglobin A1C prior to treatment was <5%. His side effects to Sunitinib included

nausea and pain despite dosage reductions. Patient was enrolled on a Dendritic Cell Vaccine clinical trial, completing the protocol without major complications and with stable disease. However, he developed Kikuchi-Fujimoto disease shortly after completion, which resolved spontaneously. He received Pazopanib for 4-months but had disease progression. Patient was then enrolled on a clinical trial of Axitinib/Pembrolizumab after permission to treat a patient under 16-years-old was obtained from the trial sponsor. He experienced grade-4 liver toxicity attributed to the axitinib, leading to removal from trial and cessation of medication. Once LFTs normalized, he was continued on Pembrolizumab monotherapy. Two weeks after, patient developed hyperglycemia >300mg/dL. Hemoglobin A1C of 5.5% excluded long-term hyperglycemia. C-Peptide was undetectable 12 days after insulin was initiated. Anti-GAD65 (glutamic acid decarboxylase 65 antibody) was strongly positive with levels >250, which confirmed autoimmune T1DM. High-dose insulin was started with recent transition to an insulin pump, leading to improved glycemic control.
Conclusion: It is unknown if our patient had previous anti-GAD65 antibodies and Pembrolizumab enhanced the autoimmune process, or if it was caused by therapy alone. This case highlights the importance of delineating genetic and immunologic biomarkers to help identify at-risk patients and incorporating appropriate guidelines for early identification. New evidence has linked HLA-DR4 with development of immunotherapy-induced T1DM, but further studies are needed to determine whether prescreening should be considered. Our case emphasizes that as the role of immunotherapy in pediatric malignancies is being elucidated, a new crop of toxicities will also emerge.

Poster # 276

5-FLUOROURACIL INDUCED CARDIOMYOPATHY IN A PEDIATRIC PATIENT: A RARE EVENT

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Background: 5-fluorouracil (5-FU) is a commonly used chemotherapy agent in adult solid tumor patients but is less frequently used in pediatrics. In adults, 5-FU is a well-recognized inducer of cardiotoxicity, particularly among patients with underlying cardiovascular disease. 5-FU mediated cardiotoxicity has rarely been reported in the pediatric population. 5-FU mediated cardiotoxicity may present as myocardial infarction, coronary vasospasm, arrhythmias or cardiomyopathy. The mechanism is not fully understood, however may be due to a combination of ischemia related to coronary vasospasm and direct myocardial cell toxicity. Uridine triacetate is FDA approved as a 5-FU reversal agent for the emergency treatment of patients with life-threatening toxicity.
Objectives: We report a rare case of 5-FU induced cardiomyopathy in a pediatric patient with nasopharyngeal carcinoma (NPC), successfully managed with milrinone and uridine triacetate, underscoring the need for awareness and prompt recognition and medication administration for this potentially reversible condition.
Design/Method: A literature search was conducted for 5-FU induced cardiomyopathy in pediatric patients. We identified 2 previously reported cases.
Results: A 16 year old female diagnosed with stage IVA NPC began treatment with a regimen of

Cisplatin and 5-FU. She had no significant PMH besides one year of migraine headaches preceding her diagnosis and recent left sided cranial nerve VII palsy secondary to tumor compression. Echocardiogram prior to chemotherapy demonstrated normal cardiac function.Planned initial chemotherapy regimen consisted of 3 cycles of Cisplatin (80mg/m2) on day 1 and 5-FU (1,000 mg/m2/day continuous infusion) on days 1-4. On day 3 of cycle 1, she acutely developed hypotension and tachycardia. Electrocardiogram demonstrated sinus tachycardia and echocardiogram showed significantly compromised cardiac function, with LV ejection fraction (EF) of 33% (previously 68%). She was transferred to the pediatric ICU and milrinone drip was initiated. Chemotherapy was continued and the 5-FU infusion was completed.Cardiac function continued to decline. Due to the temporal relationship, 5-FU cardiotoxicity was considered as the etiology of the patient's cardiomyopathy. At hour 60 past the completion of 5FU infusion, uridine triacetate therapy was initiated. Within 48 hours, LV EF had improved to mid-40%. By 96 hours, EF normalized and milrinone was weaned off. She completed the full regimen of uridine triacetate (10 grams q6 hours; total of 20 doses).
Conclusion: Although rare, 5-FU mediated cardiotoxicity is life-threatening and underappreciated as a potential complication for pediatric patients. Prompt recognition and appropriate management is essential to achieve favorable outcomes, and normalization of cardiac function is possible following an event.

Poster # 277

CONTROVERSY IN THE MANAGEMENT OF THYROGLOSSAL DUCT CYST CARCINOMA: A REPORT OF TWO CASES

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Background: Thyroglossal duct cysts (TGDCs) are a common congenital neck mass. Carcinomas occur in only 1% of diagnosed TGDCs, with less than 200 cases reported in the literature. TGDCs are routinely excised via the Sistrunk procedure. The diagnosis of TGDC carcinoma is usually made post-operatively, with pathology demonstrating histology most frequently consistent with papillary thyroid cancer (PTC). Currently, there is no consensus on the best management of TGDC carcinomas, which has ranged from Sistrunk procedure alone to therapy including total thyroidectomy and radioactive iodine.
Objectives: To describe two cases of TGDC carcinoma, highlight the ambiguity in recent management recommendations, and propose a conservative treatment approach.
Design/Method: Case report with literature review.
Results: Patient 1 was a 22-year old female who presented with a painful neck mass consistent with TGDC with microcalcifications on ultrasound. Sistrunk procedure was performed. Pathology showed a 0.7 cm multiloculated mass consistent with PTC with negative margins. Patient 2 was an 18-year old female who presented with a 4 cm painless neck mass described on MRI as an atypical-appearing multilobulated TGDC with nodular enhancement. During the Sistrunk procedure, the cyst was adherent to surrounding structures. Pathology showed a 1.5 cm mass consistent with PTC with soft tissue and hyoid bone involvement. Following discussion at tumor board, the mass was determined to be non-invasive and ultimately low-risk. For both patients, labs and imaging indicated normal thyroid function and no concerning lymph nodes.

Total thyroidectomy and radioactive iodine were not recommended or performed for either patient. Surveillance with thyroid studies and ultrasound was planned for 3 months post-operatively and at 6-month intervals thereafter for a minimum of 1 year.
Conclusion: We report 2 cases of TGDC carcinoma with varying gross and microscopic features. Both masses were treated conservatively. Recent literature suggests this approach for patients with low-risk features including patient age < 45 years, size < 2 cm, absence of invasion of local structures, absence of thyroid function abnormalities, and absence of lymph node involvement. Despite this, management still varies, likely because the interpretation of invasive features is controversial. Given that the overall prognosis for patients with TGDC carcinoma is excellent, a less invasive treatment plan is reasonable for these patients.(Rayess, Otolaryngol Head Neck Surg, 2017; Thompson, Head Neck Pathol, 2017; Wood, Ann Otol Rhinol Laryngol, 2018)

Poster # 278

MYELOID SARCOMA OF THE PANCREAS IN PEDIATRICS: A DIAGNOSTIC CONUNDRUM

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Background: Pancreatic masses are rare in pediatrics and the differential diagnosis can be broad. We present a case of a 13-year-old boy who presented with jaundice and abdominal pain and was found to have myeloid sarcoma of the pancreas without bone marrow involvement, an atypical presentation.
Objectives: Highlight the importance of having a broad differential diagnosis as well as obtaining adequate tissue specimens for evaluation and diagnosis of pancreatic malignancy in pediatrics.
Design/Method: Case report.
Results: A 13-year-old previously healthy boy presented with jaundice and abdominal pain found to have hyperbilirubinemia and transaminitis. Initial evaluation included an abdominal ultrasound which revealed an obstructive mass at the head of the pancreas measuring 2.7 x 3.2 x 4.2 cm. Findings were concerning for malignancy, Magnetic Resonance Cholangiopancreatography (MRCP) and Computed Tomography (CT) scans of the chest, abdomen, and pelvis were performed confirming a solid pancreatic head mass with no evidence of metastasis. The pancreatic mass was found to be encased by the hepatic artery, portal vein confluences, and superior mesenteric vein and artery. To relieve biliary obstruction via stent placement and to obtain a fine needle aspiration (FNA) biopsy for further diagnosis an Endoscopic Retrograde Cholangiopancreatography (ERCP) was performed. FNA showed the presence of malignant cells but further delineation of the form of pancreatic cancer was undetermined. Repeat ultrasound guided FNA was inconclusive. Positron Emission Tomography (PET) scan demonstrated fluorodeoxyglucose (FDG) activity in and around the pancreas with no evidence of activity in soft tissues or osseous structures. A laparoscopic pancreatic biopsy was attempted and converted to an open laparotomy to obtain adequate tissue specimens. Histology showed pancreatic tissue with extensive involvement by large immature appearing infiltrates, positive for myeloid markers, consistent with myeloid sarcoma. A subsequent bone marrow

aspiration showed trilineage hematopoiesis with normal flow cytometry and cytogenetics.
Conclusion: In adults with pancreatic masses, if FNA shows malignant cells treatment for adenocarcinoma is often initiated, however, due to the rarity of pancreatic masses in children the same assumption cannot be made. This case highlights the rarity of pancreatic neoplasms in children as well as the importance of obtaining adequate tissue for biopsy to identify the type of cancer and illustrates that although rare, myeloid sarcoma should be included in the differential of a pancreatic mass. In addition, it highlights the need for more studies on myeloid sarcoma to guide treatment and intervention.

Poster # 279

SUCCESSFUL TREATMENT OF DISSEMINATED NEUROENDOCRINE CARCINOMA OF PULMONARY ORIGIN IN A CHILD

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Background: Neuroendocrine carcinoma is a subgroup of neuroectodermal malignancies that is extremely rare in children. Extra-appendicial tumors are particularly aggressive, present with metastatic disease, and have an extremely poor prognosis with a 2 year overall survival of less than 5%1. While metastatic disease to the liver and bone is common, diffuse bone marrow involvement is exceedingly rare. Secretion of vasoactive substances and typical symptoms of carcinoid symptoms are not seen in these cases, making the diagnosis a challenge in the pediatric population.
Objectives: To describe our experience in achieving complete remission in a child with metastatic high grade neuroendocrine carcinoma of primary pulmonary origin who had an unusual presentation with widespread bone marrow involvement.
Design/Method: Case Review
Results: A 9 year old female presented with three weeks of worsening right lower extremity pain and intermittent fevers. Lower extremity MRI revealed diffusely abnormal heterogeneous signal in the bone marrow, concerning for malignancy. CT of the neck, chest, and abdomen showed diffuse lymphadenopathy in the supraclavicular, mediastinal, hilar, and peribronchial regions. There was compression of the right middle and lower lobe bronchi due to significant lymphadenopathy, leading to complete middle lobe collapse. MRI brain and spine also revealed a dural based metastatic lesion as well as multiple cervical, thoracic, and lumbar spine metastasis with an extradural lesion causing severe compression of the thecal sac. These lesions were FDG avid on PET scan. Left cervical node biopsy revealed metastatic high-grade neuroendocrine carcinoma (positive for CD56, chromogranin, synaptophysin, TTF-1, and MIB-1). Bone marrow biopsy showed extensive marrow involvement, (> 80%). As the patient presented with such disseminated disease, the primary site was unknown, presenting a diagnostic conundrum. With immunostains positive for TTF-1, a pulmonary primary origin was favored, and therapy was started with Cisplatin (Day 1) and Etoposide (Days 1-3), which is the accepted first line therapy for small cell lung cancer. PET/CT after two cycles of therapy showed significant improvement, with approximately 70% reduction in size of all involved lymphadenopathy. Bone marrow showed significant improvement with only mild avidity remaining. After six cycles of therapy, the patient had no radiographic evidence of active disease.

Conclusion: Bone marrow involvement as a manifestation of metastatic neuroendocrine carcinoma is exceedingly rare. Our case illustrates that bone marrow disease in metastatic neuroendocrine carcinoma responds favorably to platinum based therapy. REFERENCE: 1 Govindan R, et al.. J Clin Oncol. 2006;24:4539–4544.

Poster # 280

HIGH DOSE ACETAMINOPHEN WITH N-ACETYLCYSTEINE RESCUE FOR UNRESECTABLE HEPATOBLASTOMA

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Background: One third of patients with hepatoblastoma (HBL) present with unresectable tumors at diagnosis. Complete surgical resection is required for cure of HBL, but only 50% of hepatoblastomas can be fully resected at diagnosis. The outcome of children with unresectable HBL that fail primary chemotherapy is dismal. It was been suggested that acetaminophen's toxicity enhances efficacy of cisplatin in HBL and hepatocellular carcinoma cell lines1. High dose acetaminophen (30g/m2) with N-Acetylcysteine rescue (HD-AAP/NAC) has been previously reported for the treatment of adult malignancies and in one pediatric case with HBL.
Objectives: To report a case of a refractory HBL treated with chemotherapy and HD-AAP/NAC.
Design/Method: Case Report
Results: A 2-year old Hispanic male, with history of prematurity (23 weeks) presented with large liver mass extending into the inferior vena cava, mesenteric veins and the right atrium. No pulmonary metastasis were noted. His Alpha-fetoprotein (AFP) was 987,000 ng/mL. A liver biopsy proved HBL with mixed epithelial and mesenchymal pattern. Patient received seven cycles of alternating Cisplatin/Vincristine/5FU; and Cisplatin/Doxorubicin resulting in a decrease of AFP level to 500 ng/mL, and 75% reduction of tumor size. Surgical resection was attempted but deemed unresectable by partial hepatectomy. In light of a report on the use of HD-AAP/NAC in HBL, patient received four cycles of HD-AAP/NAC and cisplatin. HD-AAP/NAC was well tolerated with transient grade 3 elevation of liver enzymes. AFP decreased to 15 – 30 ng/mL range. On CT scans liver tumor was persistently visible but calcified. An orthotopic liver transplant was considered feasible, however, after tumor dissection, splenectomy and partial pancreatectomy, several collateral mesenteric veins containing tumor thrombus were noticed forcing to abort orthotopic liver transplantation. Surprisingly, post-surgery AFP remained within normal levels. Due to fears for tumor progression the patient received 12 cycles of Ifosfamide/Etoposide/Carboplatin every 4 weeks. Patient is alive eleven years later he continues to have evidence of calcified residual liver tumor with normal AFP level, but is otherwise doing well with hearing loss and short stature.
Conclusion: HD-AAP/NAC was well tolerated with grade 3 elevation of liver enzymes. We believe the addition of HD-AAP/NAC to conventional chemotherapy contributed to the elimination of viable HBL cells obviating the need of surgical resection and/or liver transplantation; and allowing long term survival.1 Newelt, Neoplasia, 2009.

Poster # 281

A CURIOUS CASE OF BECKWITH-WIEDEMANN SYNDROME

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Background: Beckwith-Wiedemann Syndrome (BWS) is an epigenetic disorder associated with genomic imprinting. It is classified as a congenital overgrowth disorder with variable expressivity, characterized by a predisposition toward tumorigenesis. In particular, patients are at increased risk of developing Wilms tumor and hepatoblastoma, although neuroblastoma, rhabdomyosarcoma and adrenocortical carcinoma have also been reported. Other classical features include pre- and postnatal constitutional and organ overgrowth, neonatal hypoglycemia, macroglossia, anterior abdominal wall defects and hemihyperplasia. Patients are also at risk for developmental delay. Congenital hepatoblastoma, defined as diagnosis within the first 3 months of life, is rare. Less than 15 cases of antenatally-diagnosed hepatoblastoma have been described in the literature. Congenital hepatoblastoma exhibits several distinct features when compared with cases diagnosed beyond the neonatal period, including the risk of tumor rupture during vaginal delivery, fatal polyhydramnions and/or non-immune hydrops fetalis.
Objectives: This case report presents a phenotypically normal female infant found to have a liver mass on routine antenatal ultrasound and was diagnosed with congenital hepatoblastoma shortly after birth. Methylation testing revealed BWS.
Design/Method: Following the discovery of a fetal hepatic tumor, labor was induced at 38 weeks, and a phenotypically normal female was delivered vaginally. A serum alpha-fetoprotein (AFP) level at birth was 373,170ng/ml. A post-natal MRI confirmed a mass in the right lobe of the liver, and a percutaneous core biopsy revealed an epithelial type hepatoblastoma with predominantly embryonal histology. Methylation testing revealed hypomethylation at imprinting center 2 (IC2), consistent with a diagnosis of BWS. Recent literature suggests a correlation between epigenetic changes and risk of tumorigenesis with the greatest tumor prevalence in those with IC1 epimutations. Interestingly, IC2 epimutations confers the lowest risk.
Results: The infant received 2 cycles of chemotherapy per Children's Oncology Group protocol AHEP0731 regimen T, followed by operative resection with negative surgical margins. She then completed an additional 4 cycles of adjuvant chemotherapy, identical to the first 2 cycles. At 7 months off therapy, she remains in a continued complete remission with a normal AFP for age (20 ng/ml).
Conclusion: Congenital hepatoblastoma is rare, however should be considered in any antenatally- detected fetal hepatic mass as it may impact mode of delivery, and allows for prompt diagnosis and treatment. Even in the absence of classical phenotypic stigmata, all patients with hepatoblastoma should undergo diagnostic testing for BWS to optimize targeted, risk-based cancer screening, and provide ongoing developmental surveillance.

Poster # 282

MICROWAVE ABLATION AS PRIMARY THERAPY FOR PRETEXT II HEPATOBLASTOMA

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Background: Hepatoblastoma (HB) is the most common primary liver malignancy in children. Standard of care in resectable disease includes a combination of CTH and surgical resection or transplantation. In some cases, comorbidities preclude standard therapy and few options are available. Microwave ablation (MWA) is form of thermal ablation, commonly used as primary therapy in adult liver tumors that uses electromagnetic waves to produce tissue necrosis and is a potential therapeutic option for appropriately sized pediatric liver tumors.
Objectives: To describe a case of a 21-month-old patient with PRETEXT II HB treated with percutaneous MWA with significant clinical, laboratory, and imaging response.
Design/Method: Case Report
Results: A 14-month-old girl born at 36 and 5/7 weeks with trisomy 18, VSD, PDA, dysplastic/bicuspid aortic valve, pulmonary hypertension, OSA, and CPAM was found to have an elevated alpha-fetoprotein (AFP) of 85 ng/mL during workup for transaminitis attributed to Bosentan therapy. MRI demonstrated an indeterminate 0.8 cm lesion in segment VII. The lesion was followed with MRI five months later which showed the segment VII lesion had grown to 3.1 cm and a new 1.0 cm segment VIII lesion had appeared. Concomitant AFP was 434 ng/mL. Ultrasound-guided percutaneous biopsy of the segment VII lesion showed an INI-1 negative HB of almost entirely fetal origin. CT of the chest revealed no metastases. A multidisciplinary conference including oncology, surgery, interventional radiology, and hepatology was convened. Despite localized disease amenable to surgical resection, the patients elevated mean pulmonary arterial pressures (46 mmHg) and extensive comorbidities were thought to carry a significant a peri-operative risk of mortality. CTH alone was offered as was MWA with CTH. In light of the patient's overall prognosis and potential side-effects of CTH, the family opted for ablation alone. The patient subsequently underwent technically successful percutaneous MWA of both lesions simultaneously and was treated with a 14-day course of prophylactic antibiotics. Mild, expected post-intervention ileus and fever resolved within 7 days. An MRI two months following ablation demonstrated complete tumor response. AFP decreased from a pre-intervention peak of 660 ng/mL to 10 ng/mL. Four months following MWA ablation, the AFP was 5 ng/mL. The patient will continue to be monitored with serial MRI and AFP and the addition of CTH will be discussed.
Conclusion: Percutaneous MWA was efficacious in this patient with PRETEXT II HB. This therapy is another option to be considered for treatment of HB in patients with localized tumors and comorbidities that preclude standard therapy.

Poster # 283

MIXED EPITHELIAL AND STROMA TUMOR (MEST) IN A 12 YEAR OLD MALE KIDNEY TRANSPLANT RECIPIENT

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Background: Mixed epithelial and stromal tumors (MEST) of the kidney are a benign group of tumors with rare incidence of malignant transformation. The tumor develops from Mullerian-like stromal cells and typically has cystic and solid components characterized by a biphasic proliferation of stromal cells with an epithelial component (1).
Objectives: As the current literature reports ten malignant cases in adults, the objective of this case report is to describe the first case of MEST in a child and the first case of MEST in a transplanted kidney.
Design/Method: This is a case report discussion of the first case of MEST in a pediatric male transplant recipient.
Results: A 12-year-old male presented four years after his second living donor kidney transplant with multiple masses in his transplanted kidney on ultrasound. In this patient, the MEST was likely donor derived. This case is unique as the tumors developed in a transplanted organ from a perimenopausal adult female. The donor had normal renal imaging and function at time of donation, which raises the importance of donor selection. It is unknown if there was microscopic disease present at transplantation that progressed over time. The MEST lesion was discovered after resolved acute cellular rejection and BK nephropathy. Based on pathology, the tumor was determined to be benign. There is some thought that perhaps acute cellular rejection or perhaps his prior history of BK viremia with exposure to immunosuppressant therapy led to an immunomodulating event that precipitated the natural progression of MEST (2). Although there are too few cases to determine a standard of care, oncologists recommend immediate surgical resection. In this case, the risk of loss of renal function with removal of any kidney tissue outweighed the risk of potential enlargement or metastases of MEST. Given the limited lifespan of this transplanted kidney, resection was deferred to avoid dialysis. Instead, the patient is undergoing serial ultrasound and MRI imaging to monitor for growth of the tumor. This is the first example in the literature of an individual with MEST to opt for watchful waiting.
Conclusion: This report highlights the first case of MEST in a transplanted organ and the first known report of a non-surgical approach for the management of MEST. When the patient is ready to be placed back on dialysis, he will undergo transplant nephrectomy and only if there is absolutely no malignancy will he be considered for a repeat transplant.

Poster # 284

ATYPICAL SPITZOID TUMOR RECURRING AS RAPIDLY PROGRESSIVE FATAL METASTATIC MELANOMA

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Background: Atypical spitzoid tumors represent a controversial diagnostic category of cutaneous lesions with features ranging between Spitz nevus and spitzoid melanoma usually found in younger patients. The majority of these neoplasms have a favorable prognosis and only a small proportion of patients develop distant metastases and succumb. There has been a trend toward less aggressive management although specific features predicting those cases that are likely to have progression or disease mortality are not clearly defined.
Objectives: Describe a case of death due to metastatic melanoma in an Adolescent and Young

Adult (AYA) patient originally diagnosed with atypical spitzoid tumor three years prior.
Design/Method: Case report
Results: A 21-year-old previously healthy female presented with an evolving 7 x 7 millimeter brown nevus of her left upper extremity which was evaluated by punch biopsy. Original dermatopathology diagnosis was of atypical spitzoid lesion. Two additional secondary expert pathology consultations were obtained, given atypical features including deep mitotic activity, incomplete maturation, and loss of p16 expression on immunostaining, with concordance favoring atypical spitzoid tumor over melanoma. The lesion was non-ulcerated, lateral margins were involved by tumor, and thickness of the tumor was not reported. Additional FISH and CGH testing was not performed. A re-excision was performed with gross measurement of 30 x 12 x 8 millimeters and no evidence of residual tumor. Sentinel node biopsy was not performed. Twenty-eight months later the patient presented with a subcutaneous local recurrence of metastatic melanoma, BRAF and NRAS wildtype. Staging scans revealed local skin and left axillary nodal involvement. Wide local excision and left axillary dissection was completed with clear margins and 2 out of 13 nodes positive for metastatic melanoma. The patient began adjuvant therapy with anti-PD-1 therapy. After 2 cycles she presented with new distant subcutaneous nodules and imaging revealing widespread metastatic disease of the left breast, left axilla, lungs, liver and bones. She began combination checkpoint inhibitor therapy with anti-PD-1/anti-CTLA-4 and experienced dose limiting colitis requiring multiple rounds of anti-TNF therapy. She died from pulmonary disease progression 10 months after her initial relapse.
Conclusion: The majority of spitzoid neoplasms in children and AYA patients are clinically indolent. However, a subset of patients is at risk for aggressive clinical behavior. Given this risk and the rarity of the disease, it is important that pediatric oncologists and providers have familiarity with these potential outcomes and seek appropriate consultation and clinical investigations at the time of diagnosis of ambiguous melanocytic tumors.

Poster # 285

SYNCHRONOUS COLORECTAL ADENOCARCINOMA AND ANAPLASTIC ASTROCYTOMA DUE TO CMMRD-POLE GENE VARIANT

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Background: Mismatch repair syndromes, such as Lynch syndrome and constitutional mismatch repair deficiency syndrome (CMMRD), encompass familial multi-tumor neoplastic syndromes caused by germline mutations in mismatch repair (MMR) genes POLE germline variant is a more recently described entity
Objectives: To Highlight the underlying genetic cause of synchronous presentation of Invasive colonic cancer along with Anaplastic astrocytoma and elucidate the clinical course and outcome of an adolescent female.
Design/Method: A 17-year-old female with a past medical history of café au lait macules and seizures in infancy presented with 2 months of abdominal pain, intermittent bloody diarrhea, and anemia with a hemoglobin of 7.3 g/dL. A colonoscopy with biopsy revealed invasive adenocarcinoma of the cecum with tubulovillous adenomas of the rectum. She underwent a colectomy for removal of the mass. Rectocolectomy with ileorectal anastomosis was

recommended; however, the patient and her family declined as she did not wish to have an ileostomy bag. The patient subsequently began to complain of lower extremity paresthesias and weakness following anesthesia events. A brain MRI revealed a well-defined cortical lesion of the frontal lobe. She underwent craniotomy with complete resection of the tumor. Pathology results revealed high-grade anaplastic astrocytoma
Results: Since she showed phenotypic and clinical evidence for a mismatch repair defect, a gene panel was sent to assess for pathogenic variants in mismatch repair genes along with a reflexive full colon cancer panel. No pathogenic variants were detected in mismatch repair sequences MLH1, MSH2, MSH6, PMS2. The results revealed only a variant of the POLE gene c. 1307C>G (p.Pro436Arg). A karyotype and chromosomal microarray were normal. To date, she has undergone 6 cycles of Oxaliplatin chemotherapy along with Capecitabine for colon cancer and 12 cycles of Temozolomide chemotherapy with cranial radiation therapy for Anaplastic strocytoma. Surveillance MRIs are obtained every 4 months showing no interval progression. Surveillance colonoscopies every 4 months showing no new pathologic change. She is currently kept on low dose aspirin as chemoprevention.
Conclusion: While our patient lacked a germline mutation in one of the known mismatch repair genes, evaluation of an expanded colorectal cancer panel showed a de novo variant of uncertain significance, POLE variant may cause deficient proofreading repair during DNA replication. While the genetic basis of our patient's disease continues to be elucidated, her clinical presentation fits that of CMMR-D and genetic analysis of POLE may need to be considered in the evaluation of patients with similar phenotypes.

Poster # 286

ATYPICAL TERATOID RHABDOID TUMOR IN A NEWBORN: DIAGNOSIS BY GERMLINE TESTING

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Background: Atypical Teratoid Rhabdoid Tumors (ATRT) are rare, malignant tumors of the central nervous system diagnosed via surgical biopsy/resection. ATRTs most commonly occur in children less than age three and account for approximately 2% of all pediatric brain tumors. Metastatic disease is present in 30% of cases, and the median age of survival is 12 months. Greater than 90% of ATRTs are associated with autosomal dominant loss of function mutations in SMARCB1 or SMARCA4, which constitute rhabdoid tumor predisposition syndrome (RTPS). To our knowledge, this is the first reported case of ATRT diagnosed by germline testing without surgical biopsy. We report a novel pathogenic variant identified in SMARCB1: c.233-2A>G (splice acceptor).
Objectives: To report the case of a newborn with inoperable ATRT; to discuss diagnosis using germline testing without surgical biopsy, and its implications for family members; and to describe the patient's clinical course.
Design/Method: Retrospective review of the electronic medical record and review of the literature.
Results: A girl was born at 39 weeks gestation via caesarean section due to profound

macrocephaly. Physical exam revealed widely separated cranial sutures, a bulging anterior fontanelle, sun-setting eyes, bilateral lower extremity clonus, bradycardia, and lethargy. Magnetic resonance imaging (MRI) of the brain demonstrated a large, highly cellular, hemorrhagic tumor of the fourth ventricle, effacing the third ventricle and extending to the foreman magnum. There was extensive hydrocephalus and mass effect with displacement of the brainstem and thalami. MRI of the spine demonstrated diffuse leptomeningeal metastatic disease; bilateral kidneys were unaffected. A diagnosis of ATRT was suspected. The tumor was deemed inoperable and terminal, and the family elected to discharge home on hospice on day 8 of life without diagnostic surgical biopsy, following placement of a palliative ventriculoperitoneal shunt. Germline testing of peripheral blood identified a novel heterozygous pathogenic variant in SMARCB1: c.233-2A>G (splice acceptor), confirming a diagnosis of ATRT and RTPS. The patient died at day 50 of life. The patient's 18-month-old brother was negative for the same germline mutation; parents declined testing for themselves.
Conclusion: The use of germline testing to diagnose RTPS should be considered in cases of suspected ATRT when invasive biopsy/resection is not recommended or performed, such as in patients with incurable disease. Germline testing is accessible and reliable, provides an opportunity for important genetic counseling and family planning, and may provide closure to family members in cases where invasive surgical diagnostics are not pursued.

Poster # 287

ATYPICAL TERATOID/RHABDOID TUMOR ARISING FROM GIANT CELL GLIOBLASTOMA: A CASE REPORT

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Background: Atypical teratoid/rhabdoid tumors (ATRT) are highly malignant primary CNS tumors with a poor prognosis and are most often diagnosed in children less than 3 years of age. Reported adult and pediatric primary CNS tumors that have progressed/transformed to ATRT are rare and include low grade ganglioglioma (both pediatric cases), pleomorphic xanthoastrocytoma (PXA) (2 pediatric and 1 adult case), and 4 high grade gliomas (HGGs) (2 pediatric and 2 adult cases) for a total of 9 reported cases. Initially, BRAF V600E mutations were thought to play a role as 5/9 of these cases carried the mutation, but none of the 4 HGG cases harbored a BRAF V600E mutation.
Objectives: Present a case of ATRT arising from a giant cell glioblastoma (GBM).
Design/Method: A review of the literature was performed on PubMed using keywords "Atypical teratoid/rhabdoid tumor of CNS" which yielded 384 results. Nine cases were identified as relevant to this review. Locally we have a single case to report of an ATRT arising from a giant cell GBM.
Results: A male patient presented at five years of age with fatigue, vomiting, and headaches. Imaging showed a mass with cystic and solid components in the left parietal lobe. The patient underwent a complete resection and pathology review showed a giant cell GBM. The patient received radiation therapy (proton) which was completed approximately 2 months post-resection for a total dose of 59.4 Gy. Radiation was well tolerated but the patient developed worsening headaches and right-sided weakness. Imaging revealed a mass that had doubled in size with new

dural-based lesions outside of the radiation field. The patient underwent a craniotomy, had another complete resection, and pathology revealed an ATRT. Pathology from the first and second resections was sent to St. Jude for review. Review confirmed giant cell GBM and ATRT as previously diagnosed. The patient remains on treatment; he has received 3 cycles of induction chemotherapy as per ACNS 0333/334 followed by 3 cycles of high dose chemotherapy with Carboplatin and Thiotepa.
Conclusion: This case supports growing evidence that ATRT can arise from other tumors and the importance of repeat biopsy in the setting of recurrence. One notable difference in these patients is the age of patients with transformation is older than the average age of diagnosis in ATRT. Additional areas of future research should focus on gathering a larger cohort of similar cases and investigation of epigenetic drivers of ATRT arising from other primary CNS tumors.

Poster # 288

A CASE OF PEDIATRIC ADAMANTINOMA WITH BONY METASTASIS, RAPID PROGRESSION AND LOW MUTATIONAL BURDEN

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Background: Adamantinomas are rare malignant bone tumors which typically present in adulthood. Most present with localized disease in the tibia, however some develop metastasis in regional lymph nodes or the lungs. Adamantinomas are unresponsive to chemotherapy and radiation, thus gross total resection remains the mainstay of care. While recurrences do occur, overall these are slow growing tumors with a very good prognosis. Here we present a case of adamantinoma in a pediatric patient who presented with multi-focal bony metastasis and rapid progression.
Objectives: To describe a unique case of adamantinoma in a pediatric patient.
Design/Method: Clinical, pathologic, and radiographic data was collected using the electronic medical record.
Results: A twelve-year-old Hispanic female presented for a new consultation for a left tibial bone tumor. She initially presented to a local hospital in Mexico 15 months prior with ankle pain and was found to have a left tibial bone tumor on xray. Her medical care there included several reassuring biopsies as well as bone curettage and grafting. Due to poor wound healing, she had a third biopsy which was read as osteosarcoma. At the time of presentation to the US, four months later, she had not received any therapy but had notable left ankle swelling, pain, and inability to bear weight. Imaging demonstrated a large, destructive left tibial tumor and a lytic lesion in her left glenoid. Biopsy of both her tibia and glenoid were consistent with spindle cell adamantinoma. During her work-up, she was also found to have latent mycobacterium tuberculosis and disseminated mycobacterium gordonae. One month after biopsy, she underwent below the knee amputation with 5.5 cm negative margins. A repeat PET done five days post-operatively showed progressive disease in her left glenoid, as well as new lesions in her L2 and L4 vertebral bodies, L2 spinous process, and left posterior acetabulum. Given her progressive bony disease, Sunitinib was started to attempt systemic control. After one cycle, a repeat PET showed further progression of all sites of disease as well as new disease in her tibial stump and

left fourth rib. Genomic profiling of her tumor through Foundation Medicine demonstrated several mutations, including microdeletion in NF1 with an NF1 rearrangement.
Conclusion: We report the first case of adamantinoma in a pediatric patient with extensive bony metastasis, rapid progression, and tumor sequencing results. More research is needed to understand the biology of this rare tumor.

Poster # 289

RARE CASE OF OPTIC NERVE MEDULLOEPITHELIOMA-TYPE EMBRYONAL TUMOR WITH MULTILAYERED ROSSETES (ETMR)

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Background: World Health Organization 2016 classification defines medulloephitelioma-type embryonal tumors with multilayered rosettes (ME-ETMR) as a set of central nervous system primitive neuroectodermal tumors. ME-ETMR arising from the optic nerve are extremely rare in children.
Objectives: We describe a case of an optic nerve ME-ETMR successfully treated with chemo-radiation in order to avoid exenteration or enucleation.
Design/Method: Case Report
Results: A 9-year-old female presented with one-week history of progressive vision loss in her right eye, proptosis and diplopia. Imaging showed a 3.1 x 2.5 x 1.8 cm, heterogeneously enhancing mass in the right intraconal soft tissue, partially encasing and displacing the right optic nerve sheath complex. Biopsy revealed small round blue tumor cells positive for SOX2, SOX10 and NB84, BAF47/INI1 and LIN28, suggesting ME-ETMR. Genetic sequencing analysis demonstrated a truncating frameshift mutation in the ARID1B gene with gains of chromosomes 1q 2, 3, 5, 8, 11, 13, 16, 20 and 21.To avoid enucleation, patient received chemotherapy as per Children's Oncology Group (COG) protocol ARET0321 for extraocular retinoblastoma in combination with radiation therapy (45 Gy), with remarkable immediate regression of her proptosis. She then underwent lateral orbitotomy with complete tumor excision. Post-operatively, she maintained her baseline vision acuity with mild residual abduction deficit. She then pursued consolidation with high-dose chemotherapy followed by autologous stem cell rescue.
Conclusion: Intraocular ME-ETMRs most frequently arise from the ciliary body and are typically benign. Optic nerve medulloepitheliomas are very rare and appear to be a distinct entity as they are usually malignant in nature, but rarely metastasize. Optimal treatment for this tumor is not yet standardized. Prior reports describe aggressive multimodal therapy mainly based on radical surgical enucleation or exenteration in combination with chemotherapy and radiotherapy. Chemotherapy regimens are typically based on neuroectodermal tumor protocols using multiple alkylating agents with a synergistic topoisomerase inhibitor. Recent delineation of medulloepitheliomas as ETMR has facilitated identification of genomic markers and potentially actionable drug targets fort this entity. However, as a greater number of tumors undergo genetic sequencing, new challenges arise in classifying rare tumors that are histologically similar but carry distinct gene mutations. Our case, for example, presented morphologic features consistent

with medulloepithelioma but found to have genetic mutations not been previously described in this malignancy. We highlight some of the challenges in diagnosis and a novel treatment approach with the main goal of avoiding radical surgery in order to preserve vision functionality.

Poster # 290

CBFB-MYH11 GENE FUSION: A POTENTIAL CONNECTION BETWEEN CLIVAL CHORDOMA AND ACUTE MYELOID LEUKEMIA

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Background: While several cancer predisposition syndromes have associated solid malignancies with acute myeloid leukemia (AML), the spectrum of genetic mutations that can induce tumors is largely unknown. Identifying specific cancer causing genetic alterations is vital to understanding development of specific tumors. There are no previously described associations between chordoma and AML.
Objectives: We report a case of AML in a patient receiving maintenance chemotherapy for chordoma of the clivus and explore a potential association as a consequence of a CBFB-MYH11 gene fusion.
Design/Method: A literature search was conducted for queries including "acute myeloid leukemia AND chordoma," "chordoma," and "secondary malignancies." Relevant papers were selected for review.
Results: A 20-month-old Caucasian-Hispanic male was diagnosed with poorly differentiated chordoma of the posterior clivus after presenting with an antecedent history of torticollis, neck discomfort, and prodromal symptoms. Diagnosis was based on histopathological findings including positive CAM5.2, negative AE1/AE3, loss of INI-1, and positive for brachyury. The patient received systemic chemotherapy based on COG AEWS0031 after review of the chordoma literature. Cycle A consisted of vincristine [2 mg/m2/cycle], doxorubicin [75 mg/m2/cycle], and cyclophosphamide [1200 mg/m2/cycle] alternating with Cycle B which consisted of ifosfamide [900 mg/m2/cycle] and etoposide [500 mg/m2/cycle], followed by surgical resection, and a seventh cycle of vincristine, actinomycin D, and ifosfamide. He began an oral maintenance regime consisting of imatinib mesylate and etoposide. Fifteen months after chordoma diagnosis, he presented with fever and neutropenia. Peripheral blood counts noted pancytopenia and severe neutropenia with a white blood cell count of 4.1 cells/mm with an absolute neutrophil count of 190 cells/mm, platelet count of 75,000 cells/mm, and hemoglobin of 7.4 g/dL with myeloblasts noted on a subsequent smear. Immunohistochemistry confirmed inv(16) acute myeloid leukemia with CNS 2a involvement. Peripheral blood cytogenetics indicated a germline CBFB mutation. FoundationOne from bone marrow was notable for a CBFB-MYH11 fusion. Genomic testing was not obtained from chordoma due to insufficient DNA extraction from specimen slides. Patient achieved remission after two cycles of FLAG therapy and proceeded with haploid BMT. Neutrophil engraftment occurred on Day +15 with 100% donor chimerism noted on Day +24.
Conclusion: This rare case of a young child developing acute myeloid leukemia during maintenance therapy for chordoma suggests a potential cancer predisposition resulting from the CBFB-MYH11 gene fusion. In the era of precision medicine, this presentation should alert

pediatric oncologists to consider genomic sequencing in children with chordoma to screen for variants that may be related to cancer predisposition.

Poster # 291

MALIGNANT TRANSFORMATION OF A DESMOPLASTIC INFANTILE GANGLIOGLIOMA

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Background: Desmoplastic infantile ganglioglioma (DIG) is a WHO grade I pediatric brain tumor occurring primarily in children under two years of age and found most commonly in the frontal and parietal lobes. Generally, these partially cystic and partially solid tumors, comprised of neuro-epithelial and fibroblastic elements, are benign with gross total resection often being curative. However, there are recent case reports of DIGs having malignant transformation in patients with TP53 gene mutations.
Objectives: To describe a case of malignant transformation of a DIG with a BRCA 2 mutation, without a TP53 gene mutation.
Design/Method: Case Report
Results: An 8 month old female was noted to have increasing head circumference and underwent subtotal resection of a left frontotemporal mass, determined to be a DIG with associated cyst. Subtotal resection was deemed necessary due to involvement of the sylvian fissure and significant risk for vascular injury. Four months following subtotal resection, the infant presented again with ongoing signs of mass effect, including hearing loss and ptosis. A cysto-peritoneal shunt was placed. Eleven months following shunt placement, the patient began exhibiting mild right hemiparesis and the decision was made to perform secondary resection. Follow up imaging showed stable disease and six years later, the cystoperitoneal shunt was converted to a ventriculoperitoneal shunt (VPS). Unfortunately, almost nine years following the secondary resection, the patient presented with persistent vomiting associated with headache. A CT scan at that time demonstrated a new left temporal mass which was determined to be recurrence of the DIG and gross total resection and repeat VPS placement was completed. Histopathology of the newly resected DIG demonstrated high-grade neuro-epithelial tumor, most consistent with a CNS embryonal tumor. Foundation One testing revealed BRAF deletion at exons 3-10 and a concurrent BRCA2 mutation at K1549fs*18. The patient underwent radiation therapy and received temozolamide, followed by 4 cycles of ICE chemotherapy. At one year post-resection, she remains in remission on Trametinib. A genetics consult is scheduled to discuss germline BRCA2 testing.
Conclusion: We present a unique case of malignant transformation of a desmoplastic infantile ganglioglioma with a BRCA2 mutation more than a decade after initial diagnosis.

Poster # 292

EARLY PRESENTATION OF GLIOBLASTOMA MULTIFORME IN A TEENAGER WITH LYNCH SYNDROME

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Background: Glioblastoma (GBM) account for only 3% of all childhood brain tumors. While generally associated with a poor outcome, gross total resection, MGMT promotor methylation, and IDH1 mutant status are favorable prognostic features. Recently, molecular profiling is yielding novel treatment options, including cell cycle inhibitors in tumors with microsatellite instability. While most pediatric GBM are unassociated with heritable cancer predisposition syndromes, pediatric GBM has been associated with Neurofibromatosis 1, Li-Fraumeni and Turcot syndromes.
Objectives: To describe GBM in a teenager with a paternal family history of Lynch syndrome (LS).
Design/Method: Review of patient medical records and radiographic imaging; tumor and peripheral blood molecular characterization; and comprehensive literature review.
Results: A 17-year-old young man presented with four months of progressive headache, vomiting, dizziness, and left-sided numbness. Family history was significant for Lynch Syndrome with germline MSH2 mutation in multiple paternal family members, although the patient's father was healthy and untested. Magnetic resonance imaging showed a large, localized vascular right parietal-temporal lobe tumor with significant mass effect. He underwent near-total resection. Pathology confirmed IDH1-mutant GBM. Panel-based next generation sequencing revealed a MSH2 mutation and microsatellite instability without other DNA repair pathway abnormalities. Germline testing showed MSH2 mutation, confirming the Lynch syndrome diagnosis. Genetic counseling for family members was arranged. He was treated with conformal radiation therapy and concurrent temozolomide, followed by lomustine and temozolomide maintenance chemotherapy, reserving pembrolizumab for recurrence
Conclusion: Glioblastomas are rare pediatric tumors that most frequently occur sporadically. Lynch syndrome, a hereditary disorder of DNA mismatch repair, is associated with a markedly increased risk of adult-onset colorectal and endometrial cancers. 1-3% of patients with LS develop GBM occurring at a mean age of 50 years. Hence, genetic testing for Lynch syndrome is often not offered until well into adulthood. To the authors' knowledge, this is the first reported pediatric patient diagnosed with GBM in setting of monoallelic DNA repair defect. This case highlights the importance of 1) considering germline assessment in young patients with positive family history and 2) formulating a surveillance program in those who test positive regardless of young age, and those with positive family history who elect not to be tested. Finally, while GBM are generally associated with a very poor prognosis, tumors characterized by microsatellite instability have responded to PD-1 inhibitors like pembrolizulab, suggesting PD-1 inhibitors could be a valuable therapeutic option to treat this challenging malignancy.

Poster # 293

PINEAL GERM CELL TUMOR PRESENTING WITH INTRACRANIAL BLEEDING AFTER ENDOSCOPIC THIRD VENTRICULOSTOMY

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Background: There are limited literature review reporting bleeding events related to cerebral spinal fluid diversion in primary intracranial germ cell tumors (GCTs) with predominant choriocarcinoma subtype. The exact mechanism of this complication is unknown. This phenomenon is well known in children harboring posterior fossa tumors and is typically due to the changes in cerebrospinal fluid dynamics with resultant changes in the blood flow within the tumor that already harbors fragile vasculature.
Objectives: We hereby report a patient diagnosed with pineal GCT and markedly elevated BHCG who had a intracranial hemorrhage shortly following an endoscopic third ventriculostomy (ETV) procedure to relieve obstructive hydrocephalus.
Design/Method: PubMed search was done with search for terminology including "Pineal GCTs", "ETV", "bleeding". Relevant papers were selected for literature review.
Results: 19 year old male with history of repaired atrial septal defect presented with prolonged worsening headaches. CT scan and MRI of the brain revealed a pineal mass with secondary obstructive hydrocephalus. The serum beta-human chorionic gonadotropin (beta- HCG) was 1140 IU/L while serum Alpha-fetoprotein was within the normal limit. Patient underwent an ETV to treat the hydrocephalus. Six days after surgery, patient presented with new onset seizures, blurred vision, and worsening mental status. On exam, he was initially awake with notable restricted downward gaze and twitching of extremities. Brain imaging was remarkable for intraventricular hemorrhage that led to ETV stoma occlusion; therefore, a ventriculoperitoneal shunt was placed. Chemotherapy was initiated one month after initial diagnosis followed by craniospinal radiation. Currently, his neurological status is at his baseline but with persistent blurry vision.
Conclusion: Pineal GCTs with predominant choriocarcinoma are vascular tumors. Due to the vascularity of this type of tumor, cerebrospinal fluid diversion and the resultant shift in cerebrospinal fluid dynamics and the downstream effects of altered blood flow lend this type of tumor to be at risk for hemorrhage within the perioperative period. Prompt diagnosis and early initiation of therapy is imperative to minimize the morbidity associated with intratumoral hemorrhage.

Poster # 294

CORTICAL-LEPTOMENINGEAL MEDULLOBLASTOMA MIMICKING LEPTOMENINGEAL DISEASE WITH MOLECULAR PROFILE

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Background: We present a unique case of diffuse cortical-leptomeningeal medulloblastoma (MB) mimicking leptomeningeal disease, without a focal mass lesion at diagnosis and provide a rarely reported characterization of the correlative molecular profile of this entity. An 11-year-old male with autism presented with seizures, ataxia and headaches for one month. Magnetic resonance imaging at diagnosis showed apparent leptomeningeal/subarachnoid tumor involving the cerebellar hemisphere and vermian folia. Peri-operatively, non-focal diffuse cerebellar folia

involvement precluded resection, thus a biopsy was performed.
Objectives: To describe a rarely reported instance of leptomeningeal medulloblastoma without a focal mass with correlative molecular profile.
Design/Method: A chart review and patient interview was preformed for this single case study.
Results: Histopathology and molecular signature evaluation yielded a diagnosis of MB, Non-WNT/Non-SHH subtype (WHO grade IV), negative for MYCN amplification. Retention of normal INI1 wild type expression ruled out atypical teratoid/rhabdoid tumor. The patient received 3600 cGy(RBE) craniospinal radiotherapy and posterior fossa boost to 5400 cGy(RBE) with proton beam radiation and chemotherapy as per ACNS0332 for high-risk MB. He was found to have recurrent disease 7 months after completing his initial therapy and currently is receiving salvage therapy with irinotecan, temozolomide and intrathecal cytarabine with hydrocortisone. The patient remains clinically stable.
Conclusion: The unique anatomic compartment distribution of this tumor may reflect either a MB arising from the external granular cell layer with early spread into the subarachnoid space (rather than growing inward to form an intra-axial mass), or a primary leptomeningeal MB with secondary invasion of the underlying cerebellar parenchyma along the perivascular Virchow-Robin spaces with subsequent invasion into the molecular layer parenchyma. In either instance, the anatomical involvement is confined to the cerebellar molecular layer and the subarachnoid space, mimicking “pure” primary leptomeningeal MB on neuroimaging.We present this case to raise awareness of its unique neuroimaging presentation and to provide correlative molecular signature data. Prospective analysis of rare neuroimaging presentations of MB, with correlation of molecular profile and clinical outcome, will contribute to our understanding of uncommon MB phenotypes, their risk category assignment, and the potential need for altered therapeutic approach.

Poster # 295

MEDULLOBLASTOMA IN A CHILD WITH CONSTITUTIONAL CHROMOSOME 2P DUPLICATION INVOLVING MYCN LOCUS

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Background: Constitutional chromosome 2p duplication is a rare genetic abnormality associated with a variety of features, including cardiac defects, dysmorphism, developmental and growth delay. Chromosome 2p is the locus for MYCN gene, a member of MYC family proto-oncogenes. Somatic amplification of the MYCN gene has been documented in pediatric solid tumors such as neuroblastoma, medulloblastoma, Wilms tumor, and rhabdomyosarcoma. Germline mutations in cancer genes such as MYCN increases the risk of malignancies associated with somatic mutation of those genes.
Objectives: To present the first case of medulloblastoma in a child with chromosome 2 p duplication.
Design/Method: we describe the unique case of a female child with duplication of a large region of chromosome 2p24.3-2p16.3 involving MYCN gene, with multiple congenital anomalies who developed a never reported anaplastic medulloblastoma..
Results: an 8-year-old girl with dysmorphic features, cardiac anomaly, severe developmental

and growth delay who was diagnosed with chromosome 2p duplication after birth, presented to the emergency department with dehydration, morning vomiting and unsteady gait. An MRI of the brain showed a large cerebellar mass. She underwent a gross total resection of an anaplastic medulloblastoma. She did not have any metastasis. She was treated with radiation therapy, and standard maintenance chemotherapy in combination with isotretinoin. She had a whole Genome Microarray Assay on peripheral blood which revealed the gain of 1303 oligonucleotide probes in the region of 2p24.3-2p16.3. Genes reported in the region of 2p24.2 included MYCN. She remained in remission until she was 14 years of age when she died of complications of a small bowel obstruction.
Conclusion: Although somatic amplification of MYCN gene has been associated with several pediatric solid tumors in children such as neuroblastoma, medulloblastoma, Wilms tumor, rhabdomyosarcoma, and retinoblastoma, and cases of neuroblastoma and Wilms tumor have been reported in children with constitutional 2p duplication, to our knowledge this is the first case of constitutional duplication of chromosome 2p-associated medulloblastoma in the literature. Based on this case and other cases in the literature, it is evident that patients with 2p duplication- resulting in MYCN amplification, should undergo surveillance imaging for potential pediatric cancer development.

Poster # 296

POSTERIOR FOSSA DIFFUSE MIDLINE GLIOMA H3-K27M MUTANT IN 2 CHILDREN: CASE REPORTS AND REVIEW

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Background: Diffuse midline glioma H3-K27M mutant WHO IV tumors are highly malignant, rare pediatric central nervous system (CNS) tumors characterized by pathogenic histone protein mutation. They occur most often within midline structures, usually the pons, and have a dismal outcome despite aggressive multi-modal therapy. As Magnetic Resonance imaging (MRI) is non-pathognomonic, and histologic appearance is variable, accurate diagnosis requires molecular confirmation, especially in non-pontine tumor locations.
Objectives: To report two children diagnosed with posterior fossa hemispheric diffuse midline glioma H3-K27M-mutant with diagnosis made by panel-based next generation sequencing (NGS)
Design/Method: Review of patient medical records, radiographic imaging, pathology, and published literature.
Results: Case 1: A 12 year-old male presented with 2 weeks of increasing gait ataxia, mild right-sided facial weakness and new seizure. Computed tomography (CT) showed an iso-dense right cerebellar hemispheric mass. MRI further delineated the large, non-enhancing right cerebello-pontine angle mass with right cerebellum and brachium pontis extension, and multiple metastatic foci. Histology from stereotactic needle biopsy showed a highly cellular, infiltrative neoplasm composed of sheets of tumor cells, scattered large bizarre cells, and frequent mitoses, all embedded in loose, coarsely fibrillar stroma, consistent with intermediate or high-grade glioma. NGS showed H3-K27M and 4 additional pathogenic alterations. Case 2: A 9 year-old male

presented with rare paroxysmal emesis and headache, then acute obtundation and seizure. Emergent brain CT showed a large hemorrhagic fourth ventricular tumor and obstructive hydrocephalus. Following tumor resection and ventriculo-peritoneal shunting, post-operative brain and spine MRI's showed gross total tumor resection and no leptomeningeal metastases, respectively. Histology showed a very cellular, high-grade neoplasm composed of sheets of monomorphic small round blue cells containing round, nuclei, stippled chromatin and scant cytoplasm, and frequent mitotic figures, consistent with WHO IV medulloblastoma. However, NGS showed H3-K27M and additional pathogenic glioma alterations including a frameshift mutation in the NF1 tumor suppressor gene, an activating hotspot mutation in the FGFR1 oncogene that localizes within the kinase domain, and a missense mutation in the ATRX tumor suppressor gene, but no characteristic medulloblastoma alterations.
Conclusion: These two case reports enrich the existing literature regarding H3 K27M-mutant malignancies in uncommon, non-midline locations. Although rare, this entity should be considered even in non-midline locations and non-classic histology appearance due to the grim prognosis associated with this diagnosis. These cases provide additional support for the utility of NGS in establishing accurate diagnosis, planning appropriate adjuvant therapy, and providing useful prognosis in children with CNS tumors.

Poster # 297

RADIATION-SPARING TREATMENT OF DISSEMINATED ANAPLASTIC EPENDYMOMA IN INFANTS USING CHEMOTHERAPY

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Background: Ependymomas represent approximately 10% of pediatric brain tumors. Adverse prognostic features include incomplete resection, dissemination, anaplastic posterior fossa primary with balanced genome, and anaplastic supratentorial primary with RELA fusion. Aggressive surgical resection and localized radiation constitute standard treatment. Chemotherapy is considered investigational. However, 1/3 are diagnosed in children less than 3 years of age, when normal brain myelination and development occur at an extraordinary pace, increasing susceptibility to radiation-induced toxicity. Though data are sparse, high dose chemotherapy with autologous stem cell transplantation (HDC-SCT) shows promise in infants where adverse radiation-related late effects would be devastating.
Objectives: To describe successful chemotherapy treatment of an infant with disseminated anaplastic ependymoma, and resolution of spinal metastasis and primary tumor partial response in another infant after induction chemotherapy.
Design/Method: Retrospective review of patient medical records, radiographic imaging, tissue pathology; comprehensive literature review.
Results: Case 1: A ten-month old male developed head tilt, emesis and developmental regression over 1 week. Magnetic resonance imaging [MRI] showed a complex cerebellar mass and prominent spinal cord leptomeningeal disease. He underwent primary tumor gross total resection [GTR] and ventriculo-peritoneal [VP] shunt placement. Pathology showed anaplastic ependymoma. He was treated following ACNS0334B with 3 induction chemotherapy courses then 3 consolidation high-dose chemotherapy stem cell rescue [HDC-SCR] courses. He remains

alive without disease 4 years later and meeting developmental milestones. Case 2: A nine-month old female developed emesis, developmental regression, lethargy, and head tilt over 2 weeks. MRI showed a large solid, enhancing right frontal lobe non-resectable mass, extensive intraventricular and spine leptomeningeal seeding, and obstructive hydrocephalus. She underwent biopsy and VP shunt placement. Pathology showed anaplastic ependymoma with RELA fusion. Evaluation after ACNS0334B induction chemotherapy showed spinal disease resolution and primary tumor partial response. GTR then tandem HRC-SCR are underway.
Conclusion: The efficacy of chemotherapy to treat ependymoma remains controversial. However, limited reports of successful ependymoma treatment in young children and infants with chemotherapy alone exist in literature review. We report 4 year long-term disease-free survival in an infant with disseminated anaplastic ependymoma treated with surgery and chemotherapy alone, and significant clinical and radiographic response after biopsy and induction chemotherapy in a second infant. This expands the current limited experience in radiation-sparing treatment of disseminated anaplastic ependymoma in infants, even those with multiple adverse prognostic features. Radiation-sparing aggressive chemotherapy in very young children with ependymoma is feasible and efficacious without unacceptable radiation-associated adverse intellectual, cognitive and developmental consequences.

Poster # 298

INTRASPINAL GANGLIOGLIOMAS IN CHILD WITH NEUROFIBROMATOSIS TYPE1: CASE REPORT AND LITERATURE REVIEW

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Background: Gangliogliomas are very uncommon primary spinal cord tumors (SCT), accounting for only 1% of all intramedullary SCT. They are infrequently amenable to complete surgical resection, and thus pose significant management challenges, despite a relatively indolent clinical course. Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited disorder associated with predisposition to childhood neoplasms. The NF1 gene encodes neurofibromin, a protein with GTPase-activating activity that is central in RAS pathway regulation. Loss-of-function mutations in the NF1 tumor-suppressor gene result in the absence of functional neurofibromin, with subsequent constitutive RAS signaling, leading to increased cell proliferation and tumorigenesis. The most common NF1-associated central nervous system tumors are low-grade optic pathway gliomas. Literature review documents only 3 children with NF1 diagnosed with primary spinal medullary ganglioglioma.
Objectives: To report a child with multiple meta-synchronous, un-resectable spinal gangliogliomas in a girl with NF1 and review existing literature.
Design/Method: Medical record, radiographic imaging, pathology and literature were reviewed.
Results: A healthy 4-year-old girl with a confirmed constitutional NF1 mutation (c. 654+1G>A; g.91514G>A) presented with several weeks of increasing constipation, urinary retention and a urinary tract infection. Following antibiotic treatment, she subsequently developed progressive back pain, stool retention, and abnormal gait with trunk flexion and short stride. Spine magnetic resonance imaging (MRI) demonstrated 3 discrete, infiltrative intramedullary masses within the

cervical and thoracic spinal cord. The largest at T10-T12 caused significant cord compression accounting for her clinical symptoms. She was treated with dexamethasone pulse and biopsy was performed. Pathology demonstrated grade I Ganglioglioma and immunohistochemistry stains for BRAF and H3K27M protein mutations were negative. She began monthly Carboplatin and Vincristine chemotherapy. After 3 courses, MRI showed stable disease, her neurological symptoms improved but not resolved, and pain control was satisfactory on gabapentin alone without narcotics.
Conclusion: Intra-spinal medullary ganglioglioma are extremely rare in children with NF1. Authors believe this to be the first reported case of meta-synchronous primary medullary gangliogliomas in children with NF1. Favorable overall and progression-free survival and NF1 status are important considerations when determining treatment. Carboplatin/vincristine-based chemotherapy is standard first-line therapy for non-resectable, progressive/symptomatic pediatric low-grade gliomas, given concern for radiation-associated adverse late-effects in young children. Moreover, NF1 status increases the risk of radiation-induced secondary malignancies. Finally, biopsy with panel-based next generation sequencing can provide potential therapeutic targets, including BRAF and MEK inhibitors, thus further delaying or even obviating need for radiation.

Poster # 299

INDUCTION OF NATURAL KILLER T-CELL-MEDIATED NEUROBLASTOMA CYTOTOXICITY WITH A NOVEL FUSION PROTEIN

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Background: Neuroblastoma (NB) is the most common childhood extracranial solid tumor, responsible for 15% of pediatric cancer deaths. Patients with high-risk disease (HRNB) have 5-year overall survival (OS) of <50%. High frequencies of invariant natural killer T cells (iNKTs) in NB tumors are associated with favorable clinical features and improved 5-year OS. iNKTs are innate-like lymphocytes activated by glycolipid antigen (GAg) presented by the MHC-class I-like protein, CD1d. While iNKT antitumor activity is induced by stimulatory GAg (e.g. alpha-Galactosyl Ceramide; alpha-GalCer), clinical efficacy has been limited by iNKT anergy, which can result after a single exposure. However, phenylated GAgs, including C34, were shown to stimulate iNKTs without inducing anergy, even after repeated exposure. We are now developing iNKT-based immunotherapies to optimally target neuroblastoma in a sustained manner.
Objectives: 1. Develop a bi-specific protein compromised of GAg-loaded CD1d molecules fused to single-chain variable fragments (scFv) that recognize GD2, a highly-expressed surface disialoganglioside on neuroblasts. 2. Evaluate the effects of varied anti-GD2 scFv affinities on iNKT-mediated cytotoxicity in vitro.3. Compare the effects of single or repeated exposure to C34 and alpha-GalCer on the activation of iNKT cells in vivo.4. Analyze the tumor microenvironment (TME) and survival of NB-prone mice after treatment with different CD1d-GD2 scFv fusion proteins.
Design/Method: We have previously generated fusion proteins composed of CD1d linked via streptavidin/biotin to anti-GD2 monoclonal antibodies (mAb). To reduce the immunogenicity and increase its activation efficacy, we are now generating a fusion protein between CD1d and anti-GD2 scFv of different affinities without using streavidin/biotin linkage. Using different

GAgs, we will analyze whether C34-loaded fusion proteins improves survival and alters the TME in an immunocompetent preclinical model of HRNB (TH-MYCN+/+ transgenic mice).
Results: Our biotin-streptavidin linked CAbs induced iNKT cell-mediated cytotoxicity of neuroblasts in vitro. Furthermore, administration of these GD2-directed CAbs to immunocompetent mice harboring NB tumors resulted in activation of intratumoral but not peripheral iNKT cells. Additionally, C34 generated significantly more potent iNKT interferon-gamma production than alpha-GalCer or control in vivo, and specific tumor cell cytotoxicity in vitro.
Conclusion: Our study aims to develop a novel reagent to induce sustained activation of iNKTs, direct the activity of these cells against NB, and control tumor growth in TH-MYCN+/+ transgenic mice. We hope to demonstrate a novel immunotherapeutic axis by which to treat HRNB and perhaps other pediatric solid tumors in which iNKT cells play a prominent role.

Poster # 300

TARGETING MYCN-DRIVEN GLUTAMINE METABOLISM TO RESTORE NEUROBLASTOMA SENSITIVITY TO MTORC1 INHIBITION

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Background: Neuroblastoma (NB) is the most common extra-cranial solid tumor of childhood and accounts for 15% of pediatric cancer mortality. MYCN-amplification (MNA) confers a poor prognosis with 50% of MNA patients failing to achieve long-term remission. MYC proto-oncogenes facilitate metabolic reprogramming that promotes chemoresistance. MYCN drives mTOR activity and glutaminolysis to support tumor growth. However, mTORC1 inhibitors have limited efficacy as single agents despite great pre-clinical promise. Our data indicate MNA-NBs rely on glutamine (Gln) as an energy source and upregulate Gln metabolism in response to mTORC1 inhibition. Notably, we show that inhibition of Gln metabolism sensitizes NB cells to the mTORC1 inhibitor, temsirolimus (TEM).
Objectives: 1. Delineate how MYCN drives activation of Gln metabolism2. Delineate how Gln metabolism changes upon acute and chronic exposure to mTORC1 inhibitors in MNA-NB3. Enhance NB cell death with dual inhibition of Gln metabolism and mTORC1
Design/Method: Cell survival was assessed upon Gln starvation in MYCN-ON and -OFF conditions. Expression of enzymes of Gln metabolism were assessed across NB cell lines upon inducible MYCN overexpression/activation, MYCN knockdown, and TEM treatment. Gln metabolic flux was performed in NB cells from 0-24H after MYCN overexpression. Glutaminase (GLS) activity was assessed in MYCN -ON and -OFF conditions. Effects of dual TEM and GLS or TEM and ASCT2 inhibition were determined in MNA cells. NB cells were exposed to increasing doses of TEM to generate resistant cell lines. NB xenografts were treated with TEM. Treatment was suspended and tumors were allowed to regrow to generate a tumor-based TEM-resistance model.
Results: MNA-NB cells rely on Gln metabolism for cell survival. Turning on MYCN or activating its transcription induces the expression of Gln enzymes, in particular GLS1, GLS2, and ASCT2 ($p<0.01$). Conversely, turning off MYCN restores their levels ($p<0.001$). In addition, Gln metabolic flux data upon MYCN overexpression reveals increased TCA cycle Gln

utilization and glutamate:Gln ratios ($p<0.001$). TEM treatment increases intracellular glutamate levels and induces the expression of Gln enzymes in MNA/MYCN -ON cells ($p<0.05$). Cells with chronic supratherapeutic exposure to TEM display IC50 values 4-5 times that of parental lines. Lastly, combined GLS and mTORC1 inhibition profoundly inhibits cell survival across multiple MNA lines to a greater degree than combined ASCT2 and mTORC1 inhibition.
Conclusion: Dual inhibition GLS and mTORC1 is a promising combinatorial strategy in neuroblastoma. Ongoing work in our lab will characterize our current resistance models to develop novel targets to overcome this drug-resistant, highly aggressive disease.

Poster # 301

VALIDATING A HIGH THROUGHPUT DIGITAL SYSTEM FOR IMMUNE GENE PROFILING OF PEDIATRIC NEUROBLASTOMA

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Background: Immune checkpoint inhibitors are a major breakthrough in the treatment of select adult cancers, however response is currently limited in pediatric tumors. High-risk neuroblastoma (especially MYCN-amplified) has a low level of immune cell infiltration, which may prevent a robust response to immune therapies. A number of adult studies have identified biomarkers predictive of response to checkpoint inhibitors, but little is known about which pediatric tumors will be responsive. Further understanding of the immune microenvironment of pediatric tumors like neuroblastoma is needed to successfully employ immune therapies in these patients.
Objectives: The primary goal of this project is to validate a high throughput system for immune gene profiling in neuroblastoma. The secondary goal is to compare the immune-phenotype of different risk groups of neuroblastoma and to identify potential biomarkers of response to immune therapies in future clinical trials.
Design/Method: RNA was isolated from 14 formalin-fixed paraffin embedded (FFPE) neuroblastoma samples collected from patients. Gene expression analysis of 770 genes involved in immune response was performed using the nCounter NanoString PanCancer Immune Profiling Panel. Significantly altered genes from the NanoString analysis were analyzed in the neuroblastoma tumors within the NCI Therapeutically Applicable Research to Generate Effective Treatments (TARGET) matrix, which is a comprehensive database of previously studied genes. NanoStringDiff analysis was used to detect statistically significant differences between risk groups, and between MYCN-amp and non-MYCN-amp tumor samples.
Results: Three tumor samples were high-risk, MYCN-amp neuroblastoma samples and 3 were high-risk, MYCN-non-amp. Five samples were intermediate-risk, and 3 other samples were low-risk. Twelve genes were significantly up-regulated and 39 genes were significantly down-regulated in high-risk (MYCN-amp and non-amp) versus the low-risk neuroblastoma tumor samples as determined by NanoStringDiff analysis. In validation of immune gene profiling of MYCN-amp tumors compared to non-MYCN-amp tumors, 19 genes were significantly down-regulated in our patient samples by NanoStringDiff analysis and within the TARGET database. These genes were all associated with diminished T-cell function within the high-risk MYCN-amp neuroblastoma samples, validating prior findings of an immune depleted microenvironment

of MYCN-amp tumors.
Conclusion: The nCounter NanoString system can reproducibly quantify expression levels of immune signature genes in FFPE tumor samples. NanoString analysis is a powerful tool for delineating tumor immunity and may impact risk stratification. MYCN amplification is associated with a T-cell barren environment and immunity in neuroblastoma as determined by gene assay, and may help direct immunotherapy in clinical care.

Poster # 302

PROTEIN PHOSPHATASE 1 REGULATORY SUBUNIT 1A REGULATES CELL CYCLE PROGRESSION IN EWING SARCOMA

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Background: Ewing sarcoma (ES) is a highly malignant pediatric tumor characterized by the expression of oncogenic fusion transcription factors, mostly EWS/FLI1. Insights into the biology of EWS/FLI1 and its downstream targets in ES initiation and progression could lead to the discovery of novel therapeutic strategies. We recently identified protein phosphatase 1 regulatory subunit 1A (PPP1R1A) as one of the core EWS/FLI1 targets and a potential specific therapeutic target for primary and metastatic ES. Small molecule compound inhibition of PPP1R1A and the associated signaling pathway impaired tumor growth and metastasis in ES xenograft mouse model.
Objectives: In the current study, we seek to identify the underlying mechanisms of PPP1R1A mediated tumorigenesis and metastasis and define additional role of PPP1R1A in ES pathogenesis to facilitate discovery of additional therapeutic targets.
Design/Method: We performed shRNA induced knockdown (iR1A) and CRISPR knockout (R1A-KO) of PPP1R1A in ES cells and assessed cell proliferation by 3T5 growth assay and cell cycle analysis. RNA-seq combined with qRT-PCR and western blotting analyses were utilized to identify and validate PPP1R1A regulated genes at RNA and protein levels respectively.
Results: We found that iR1A and R1A-KO cells proliferated much slower than the control cells. PPP1R1A depleted cells were arrested in G1 to S phase transition which could be rescued by re-expression of 35D, a constitutively active PPP1R1A. We found that Rb, whose phosphorylation releases cell cycle arrest in G1 phase, was hypo-phosphorylated upon PPP1R1A knockdown and hyper-phosphorylated after 35D rescue. Furthermore, depletion of PPP1R1A increased expression levels of cell cycle inhibitors p21 and p27, but not other G1 phase associated proteins. Results from RNA-seq and qRT-PCR analysis showed that PPP1R1A knockdown decreased the level of total mRNA but increased that of poly-adenylated mRNA of a subset of replication-dependent histone genes ($p<0.05$), suggesting a compensation mechanism of the loss of normal pre-mRNA processing of the histone genes in G1-arrested PPP1R1A knockdown cells.
Conclusion: Our findings demonstrate that PPP1R1A promotes cell cycle progression through G1 to S phase by down-regulating cell cycle inhibitors p21 and p27 which leads to Rb hyper-phosphorylation and de-repression of cell cycle. Since PPP1R1A is specifically highly expressed in ES cells, our results indicate that PPP1R1A serves as an ES specific cell cycle modulator. Recently, IGF-1R inhibitors have shown synergistic effect with cell cycle modulators such as

CDK4/6 inhibitors. Thus, combination of PPP1R1A inhibition with IGF-1R inhibitor may be explored for synergistic and specific tumor control in ES.

Poster # 303

INTEGRIN-MEDIATED SIGNALING AS A NOVEL THERAPEUTIC TARGET IN METASTATIC EWING SARCOMA

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Background: Metastatic Ewing sarcoma (ES) has extremely poor survival, necessitating investigations into molecular mechanisms to identify novel targets and develop new therapies. We previously performed a murine in vivo study designed to provide insights into transcriptomic and proteomic signatures for metastatic ES to identify potential therapeutic targets. Comparing profiles of primary tumors to corresponding metastases, we identified aberrant expression of integrin-ß3 (ITGB3) and activation of downstream integrin-linked kinase (ILK) in metastases compared to primary tumors, implicating this pathway as a key regulator in ES metastasis. Our hypothesis is that upregulation of ITGB3 and its downstream signaling events play a key role in ES metastasis and are viable therapeutic targets.
Objectives: To investigate the role of the ITGB3-ILK pathway and its downstream signaling events in ES metastasis and to investigate this pathway as a therapeutic target.
Design/Method: To investigate the role of the ITGB3-ILK pathway, we used siRNA to knockdown ITGB3 and ILK expression in ES cell lines and performed proliferation and invasion/migration assays in vitro. We also inhibited the pathway using small molecule inhibitors targeting ITGB3, ILK and the downstream target activator protein-1 (AP-1), using Cilengitide, Compound 22 and SR11302, respectively. We are using these inhibitors as treatment in vivo and assessing rates of metastasis in our mouse model compared to controls. We generated stable ITGB3 and ILK overexpression (OE) and knockdown (KD) cell lines, which we are using for similar in vitro and in vivo investigations.
Results: Knockdown of ITGB3 and ILK in siRNA ES lines resulted in decreased proliferation, invasion and migration compared to controls. We also found significantly decreased ES proliferation using each of the inhibitors in vitro. Our preliminary studies using Compound 22 in vivo using our mouse model suggest inhibition of primary tumor development and studies are ongoing to assess the effectiveness of inhibiting pulmonary metastasis. Similarly, preliminary in vivo studies of ILK KD lines suggest inhibition, and ITGB3 OE conversely suggests enhancement, of primary tumor development and the studies are ongoing to assess rates of metastasis.
Conclusion: These results support our hypothesis that the ITGB3-ILK pathway and its downstream signaling events play a key role in ES metastasis and may serve as a therapeutic target. Therefore, we continue testing the effects of inhibition of this pathway on metastatic tumor development in our mouse model. We are also testing ITGB3 and ILK expression in human ES primary and metastatic tumor samples from COG to provide a direct patient correlation.

Poster # 304

PERSONALIZED RNA-NANOPARTICLE VACCINES TARGETING OSTEOSARCOMA

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Background: Despite multi-modality approaches for metastatic osteosarcoma (OS), the survival rates and prognosis remain very poor. The use of targeted immunotherapeutics in cancer have shown considerable promise, but there has been a dearth of tumor specific targets for OS.
Objectives: To circumvent the lack of specific targets and overcome antigenic heterogeneity, we have developed a personalized immunotherapeutic that complexes the tumor derived mRNA (whole tumor transcriptome) with a liposomal nanoparticle (NP) to allow systemic delivery of tumor specific antigens to antigen presenting cells (i.e. dendritic cells (DC)) for induction of antigen specific T cell immunity.
Design/Method: Total tumor mRNA was amplified from tumor cell lines or minimal tumor biopsy tissue before complexation with DOTAP nanoliposomes for systemic administration in preclinical murine OS models or canine (pet dogs) patients diagnosed with OS. Preclinical murine models were generated using K7M2 OS cells in BALB/c mice inoculated by tail vein injection to mimic minimal residual metastatic disease from pulmonary OS. Canine patients were screened through a collaboration with the University of Florida veterinary school.
Results: In the metastatic microenvironment of mice inoculated with pulmonary OS, RNA-NPs reprogram the intratumoral milieu with significantly less tumor associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). These tumor loaded mRNA loaded NPs mediate significant anti-tumor efficacy against pulmonary osteosarcoma in the murine K7M2 model with long term survivor benefits (7 of 8 treated mice). We show that the anti-tumor activity of RNA-NPs is dependent on type I interferons released from plasmacytoid DCs, and that long-term survivor outcomes from tumor loaded mRNA-NPs correlates with an increase in intratumoral central memory T cells (not observed in animals vaccinated with GFP RNA-NPs). We have already demonstrated safety of RNA-NPs in acute/chronic murine toxicity studies, and as we prepare to translate this technology into first-in human studies, we have launched a client-owned canine trial. In our first canine subject diagnosed with osteosarcoma, these RNA-NPs were feasible, safe and immunologically active.
Conclusion: RNA-NPs reprogram the intratumoral microenvironment into an immune activated state and mediate long-term survival benefits that strongly correlate with increased intratumoral central memory T cells. From few tumor cells, we have successfully generated personalized tumor-specific RNA-NP vaccines for canine patients within days of an OS tumor biopsy. These vaccines bypass MHC restriction and can be made readily available for all patients/canines providing a renewable antigen resource that can be used to continuously vaccinate patients.

Poster # 305

COMPUTATIONAL ANALYSIS OF THE IMMUNOLOGIC DRIVERS OF PEDIATRIC OSTEOSARCOMA

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Background: Currently, only 1 out of 4 pediatric patients with metastatic osteosarcoma will survive. New treatment options are needed. However, the potential for targeted therapy has been hampered by the heterogeneity of the osteosarcoma genome and immunotherapy options will require a better understanding of the correlations between immune effector cell genomics and clinical outcomes. Our approach stems from evidence that immunotherapies may be of benefit in the treatment of osteosarcoma. We hypothesize that subclinical aberrant immune function is directly involved in the development of metastatic osteosarcoma. Furthermore, we hypothesize that effective treatments aimed at boosting the patient's immune response to osteosarcoma cells will benefit from the combination of targeted therapy using small molecule inhibitors.
Objectives: We will use correlations between clinical outcomes and both tumor-infiltrating lymphocyte (TIL) genotypes and immune cell repertoires in order to help guide future development of immune-based treatment strategies. We will also develop a customized screening panel of small molecule inhibitors that can be applied to tumor samples in order to provide insight into the osteosarcoma-specific aberrant molecular pathways and guide the development of targeted therapies.
Design/Method: The osteosarcoma immune microenvironment will be computationally analyzed utilizing previously sequenced pediatric osteosarcoma genomes from the Pediatric Cancer Genome Project (PCGP): computational network-based methods of detecting both aggregate expression biomarkers as well as infiltrating immune cell signatures will be employed in order to determine the role the immune microenvironment has in clinical outcomes such as survival, occurrence of metastases and recurrence of tumor. We will also perform a computational identification and prioritization of aberrant molecular pathways specific to osteosarcoma, utilizing mutation-calling workflows and molecular pathway data from the curated knowledgebase, Reactome as well as an integrated multi-omics technique for aberrant pathway prioritization.
Results: This work is currently ongoing. We have analyzed 9 normal samples and 3 tumor samples out of 57 tumor/normal pairs. We have recently secured funding for the continuation of this preliminary computational analysis of the osteosarcoma sequencing data and are in the process of completing the whole genome sequencing analysis. Following this, we will further analyze 23 of these samples for which RNA-Seq data is available.
Conclusion: The results of this preliminary study will be used to guide validation experiments into the immune microenvironmental factors that influence pediatric osteosarcoma tumorigenesis as well as disease severity. Our long-term goal is to develop new therapeutic options for pediatric osteosarcoma involving small molecule inhibitors in combination with immunotherapy.

Poster # 306

INNOVATIVE 3D EX VIVO PULMONARY METASTASIS MODEL USING HIGH METASTATIC OSTEOSARCOMA PDX TUMORS

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Background: Osteosarcoma is the most common bone cancer in children and adolescents, and patients with metastatic disease still have extremely poor prognosis. It has been reported that the activation of Wnt/β-catenin pathway is closely associated with osteosarcoma development and metastatic progression.
Objectives: We investigated how the Wnt/β-catenin pathway is activated in lung metastatic sites by employing 3D ex vivo pulmonary metastasis assay (PuMA) model using osteosarcoma PDX tumor (PDX-OS) derived from the relapsed metastatic lung lesion after chemotherapy.
Design/Method: PDX-OS tumurs were dissociated into single cells and transfected with 7xTcf-eGFP//SV40-mCherry (7TGC) lentivirus vector. Thus, we recognized osteosarcoma cells by mCherry and Wnt/β-catenin activation by GFP. Viable 7TGC-labeled tumor cells were injected to NSG mice via tail vein and mice were euthanized within 15 minutes after tumor injection. Transverse sections from each lung lobe were made and we started 3D culture (Day 0). Tumor cells in the lung slices and Wnt/β-catenin activity were observed by a stereo microscope for up to 28 days and fresh culture medium was replaced every other day.
Results: On day 7, tumor cells formed colonies and Wnt/β-catenin signal was markedly activated. On day 7, 10, 14 and 17, lung slices were treated with either vehicle (DMSO) or Tegavivint which is a novel small molecule inhibitor of the Wnt/β-catenin pathway. In the control group, tumor cell colonies continued to grow and demonstrate increased Wnt/β-catenin activity during metastatic colonization and progression. Wnt/β-catenin activity was suppressed in the Tegavivint-treated group and the tumor colonies disappeared by day 14, and recurrence was not detectable up to day 28. On day 28, lung slices in each group were fixed with 10% formalin and processed to Hematoxylin and Eosin (H&E) staining, and no tumor colonies were deteced in Tegavivint-treated group whereas there were a number of colonies in the control group.
Conclusion: Our innovative 3D ex vivo PuMA model demonstrated a critical role for Wnt/β-catenin activation in the establishment and progression of pulmonary metastasis of human osteosarcoma in a real time manner and potent anti-metastatic activity of Tegavivint via blockade of Wnt/β-catenin activation. These findings will open a new insight into elucidating the mechanism of metastasis of tumor cells.

Poster # 307

INTEGRATED ANALYSES IDENTIFY CANDIDATE GENE MEDIATORS OF CHEMOTHERAPY RESISTANCE IN OSTEOSARCOMA

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Background: While adjuvant chemotherapy has proven beneficial for osteosarcoma (OS), outcomes for patients with chemoresistant or metastatic disease remain poor. Extensive clinical research over the past thirty years has identified no effective agents to augment the efficacy of the front-line chemotherapeutic triad of cisplatin, doxorubicin, and methotrexate. Epigenetic processes such as aberrant CpG island methylation bring about gene dysregulation, and

consequently mediate diverse tumor phenotypes including drug resistance. We and others have performed DNA methylation profiling to identify genes relevant to OS carcinogenesis. Because epigenetically mediated drug resistance could be pharmacologically reversible, we developed a strategy to identify targets of CpG island methylation-associated gene silencing potentially related to acquired drug resistance in OS cells.
Objectives: Integrate the analyses of CpG island hypermethylation and differential expression to identify gene targets of epigenetic gene silencing with acquired chemotherapy resistance in OS cell lines.
Design/Method: We have previously reported development of a robust genome-wide methylation profiling strategy to identify genes in which aberrant CpG island hypermethylation is disproportionately prevalent in human osteosarcomas. These gene targets characteristically exhibit transcriptional silencing in OS cell lines. We developed OS cell lines that exhibit high-level resistance to doxorubicin- and cisplatin-mediated cytotoxicity compared to their wild-type congeners. Employing RNA-seq differential mRNA expression analysis, we identified genes exhibiting downregulation associated with resistance to cisplatin or doxorubicin cytotoxicity.
Results: Integrated analysis of the two described data sets yielded a set of genes that exhibit aberrant CpG island methylation in OS and that are transcriptionally downregulated in chemoresistant OS cells. We regard these genes as candidate mediators of chemoresistance in OS. The integrative analysis identified MT1A, HOXA11, ALX4, and TES and other genes as candidate mediators of cisplatin resistance in OS cells. For doxorubicin resistance, genes of interest include RBP1, WT1, SPOCK2, TLX3, MAL2, and others.
Conclusion: The identification and validation of candidate gene mediators of chemoresistance may inform the development of epigenetic-directed therapy to reverse this phenotype in OS. Experiments to validate epigenetic silencing of these target genes in primary OS tumors and to confirm their relevance to chemosensitivity in OS cells are in process. Ultimately, these gene targets may establish a framework for new treatment strategies aimed at reversing chemotherapy resistance, thereby offering potentially effective epigenetic modification strategies for patients with this very high-risk disease.

Poster # 308

LURBINECTEDIN TARGETS THE EWS-WT1 TRANSCRIPTION FACTOR IN DESMOPLASTIC SMALL ROUND CELL TUMOR

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Background: Desmoplastic small round cell tumor (DSRCT) is a rare and aggressive soft tissue malignancy. There is currently no standard therapy and the 5-year survival rate is less than 15%. The disease is defined by the oncogenic EWS-WT1 transcription factor, however, the dependence of the tumor on this target has not been well-established and no EWS-WT1 targeted therapy has translated to the clinic.
Objectives: To develop a molecularly targeted therapy for DSRCT cells using the candidate compound lurbinectedin.
Design/Method: The impact on cell viability of siRNA silencing of EWS-WT1 or lurbinectedin

treatment was established using MTS assay and incucyte cell imaging in BER and JN-DSCRT-1 cells. The effects on EWS-WT1 expression and activity was determined by qPCR, western blot and RNA sequencing. The mechanism of suppression was determined by confocal microscopy, qPCR and western blot analysis.
Results: Silencing of EWS-WT1 leads to the marked suppression of proliferation of both JN-DSRCT-1 and BER cells. This effect is recapitulated by lurbinectedin treatment which impairs cell viability with an GI50 of 0.17 nM which is the lowest reported IC50 of this compound in any cell type. This hypersensitivity is due to the blockade of EWS-WT1 by lurbinectedin. Treatment of DSRCT cells with lurbinectedin causes an immediate redistribution of EWS-WT1 in the nucleus to the nucleolus and subsequent loss of expression of the fusion protein at both the RNA and protein level. The net effect is reversal of the EWS-WT1 gene signature following 12-hour lurbinectedin exposure. The re-distribution of the fusion protein from the nucleus to the nucleolus is similar to what we have reported with EWS-FLI1. However, the loss in expression is unique to EWS-WT1 perhaps accounting for the hypersensitivity of this tumor type to lurbinectedin.
Conclusion: DSRCT is dependent on the EWS-WT1 transcription factor for cell survival. Lurbinectedin directly inhibits EWS-WT1 leading to reversal of its gene signature to cause a marked hypersensitivity of this tumor type to lurbinectedin. These results provide the basis for the clinical translation of lurbinectedin as a target therapy for DSRCT.

Poster # 309

EXOSOMAL BASIGIN (CD147, EMMPRIN) PROMOTES TUMOR PROGRESSION VIA IMMUNOMODULATION

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Background: Fibrosarcoma is a rare childhood soft tissue sarcoma. Treatment regimens vary widely for this tumor, from case reports of spontaneously regressing tumors, to metastatic disease necessitating systemic chemotherapy and surgery. Recently, tumor-infiltrating lymphocytes have been shown to play a pivotal role in infantile fibrosarcoma. Our collaborators were the first to develop an immunocompetent murine model of infantile fibrosarcoma that would allow us to dissect the mechanisms driving spontaneous regression versus progressive disease. The four "progressor" fibrosarcoma cell lines form primary tumors that continue to grow linearly, while the four fibrosarcoma "regressor" cell line tumors grow linearly for 1-2 weeks, then spontaneously regress. Additionally, our lab has previously shown that exosomes, 30-100 nm vesicles secreted into the extracellular space, mediate tumor interactions with the microenvironment, the immune system and play a critical role in metastatic progression.
Objectives: Our objective is to determine whether fibrosarcoma exosome-mediated tumor progression or regression is due to exosome interactions with immune cells.
Design/Method: To determine the role of progressor and regressor derived exosomes in fibrosarcoma biology, we treated mice with regressor-derived exosomes prior to progressor tumor inoculation (and vice versa). Additionally, we examined exosome biodistribution and the

effects of exosome education on hematopoiesis and immune system development. To identify specific exosomal proteins in progressor and regressor exosomes that may mediate the observed functional effects, we performed proteomic analysis of exosomes isolated from progressor and regressor cells.
Results: Tumor cell engraftment and growth was decreased in progressor tumor bearing mice educated with regressor exosomes compared to control. Conversely, treatment of mice with progressor-derived exosomes prior to regressor cell inoculation promoted regressor tumor growth. While progressor exosomes are taken up and affect both innate and adaptive immune cells, regressor exosomes are preferentially uptaken by T cells. In proteomic analysis, basigin (BSG, CD147, EMMPRIN), a cell-surface protein of the immunoglobulin superfamily, is the most common protein specific for progressor, but not regressor exosomes. To determine if exosomal BSG is critical for fibrosarcoma progression, we used an anti-BSG antibody to block progressor exosomal BSG. We found reduced growth of progressor tumors compared to isotype control treated progressor exosome treated tumors ($p<0.0262$). Additionally, our extensive proteomics analysis of tumor and plasma-derived exosomes from >300 pediatric and adult cancer patients and normal controls, revealed that BSG was present in 88% of cancer exosomes but rarely in normal exosomes.
Conclusion: Our findings suggest that exosomal BSG plays important roles in tumor-immune system interactions.

Poster # 310

TOWARDS CREATION OF A ZEBRAFISH ANGIOSARCOMA MODEL TO STUDY TUMOR GROWTH AND METASTASIS

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Background: Angiosarcoma is a rare yet clinically aggressive tumor with a high rate of mortality, especially in the pediatric population. This soft tissue sarcoma is of endothelial cell origin arising in vascular or lymphatic tissues. Angiosarcomas are poorly studied in pediatric and adults. Moreover, angiosarcomas often present with hard to treat metastatic lesions. Recent studies have further classified angiosarcomas by identifying common genetic alterations including in the RAS pathway, TP53 tumor suppressor protein, and various angiogenesis genes. However, a major challenge to the study of angiosarcoma is the lack of cell lines and appropriate in vivo animal models. While originally used in development studies, zebrafish tumor models have provided novel insights on tumorigenesis. Recently we generated tp53 null zebrafish and found that tp53-/- fish spontaneously develop angiosarcomas in addition to other tumors. The angiosarcomas histologically and molecularly resemble the human disease. Moreover, we generated the tumors in syngeneic zebrafish thus enabling transplantation of tumors cells in recipient animals.
Objectives: Utilizing a zebrafish angiosarcoma that develops spontaneously in tp53-/- animals to screen drugs/compounds that inhibit growth and metastasis.
Design/Method: The spontaneous angiosarcomas that arise in tp53-/- syngeneic zebrafish are also GFP+ thus enabling in vivo visualization of tumor growth in recipient syngeneic larval CG1 zebrafish hosts. An in vivo drug screen in 6 well plates with fish bathed in DMSO (control) or

active compound will be used to screen 100 compounds.
Results: We successfully transplanted angiosarcoma tumors generated in an in vivo zebrafish angiosarcoma model. Interestingly we find that the transplanted tumors are extremely invasive and metastatic. Thus, our drug screen will be modified to score for both growth and metastasis in vivo.
Conclusion: In summary, our ongoing study will identify compounds that inhibit growth and metastasis in angiosarcoma. Once hits are identified future studies will focus on molecular mechanisms of action and testing compounds for activity in preclinical murine models.

Poster # 311

NEW METHODS FOR CHROMATIN PROFILING IDENTIFY DISTINCT EPIGENOMES IN DIFFUSE MIDLINE GLIOMAS

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Background: Diffuse Midline Gliomas are an incurable pediatric CNS tumor caused by mutations in genes encoding the replication-dependent histone 3 variant H3.1 or replication-independent histone variant H3.3. These mutations give rise to aberrant chromatin landscapes through inhibition of the Polycomb Repressive Complex-2 subunit Enhancer of Zeste Homologue 2 (EZH2). The contribution of H3 variants to gliomagenesis remains unknown, due in large part to a paucity of methods for profiling protein:DNA interactions genome-wide.
Objectives: To characterize the genome-wide localization of H3 variants in Diffuse Midline Glioma patient-derived cell lines using a novel chromatin-profiling technology, Cleavage Under Targets and Release Using Nuclease (CUT&RUN).
Design/Method: We utilized a novel automated platform for chromatin profiling, AutoCUT&RUN, to profile chromatin landscapes in patient-derived DMG cells lines from patients with either H3.1K27M or H3.3K27M. This method allows for facile probing of genome-wide protein:DNA interactions in a high-throughput manner at low cost and can be used with frozen tissue.
Results: We show that DMG chromatin landscapes are largely determined by H3 variants, and that H3.1K27M-DMGs have substantially lower levels of Polycomb Repressive Complex-2 activity genome-wide than H3.3K27M-DMGs. We also show that the residual PRC2 activity in H3K27M-DMGs is most similar to primitive stem cells, despite these malignancies expressing numerous markers of terminal differentiation. Finally, we demonstrate that H3-mutant DMGs have different responses to epigenome-targeting agents depending on mutant H3-variant.
Conclusion: Our results indicate that mechanisms of H3-variant deposition underlie critical differences in DMG chromatin landscapes, and these differences modulate responses to chromatin-modifying enzyme inhibitors. Importantly, the novel AutoCUT&RUN platform can be easily adapted for use with samples relevant to pediatric oncology and provides a powerful new tool in understanding the role of chromatin biology and epigenetics in pediatric cancer.

Poster # 312

CHIP-SEQ ANALYSIS OF DIFFUSE INTRINSIC PONTINE GLIOMA SHOW INVOLVEMENT OF PRC1 POLYCOMB COMPLEX

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Background: Children diagnose with diffuse intrinsic pontine glioma (DIPG) have one of the lowest overall survival amongst pediatric brain cancer patients. DIPG can be stratified into molecular subtypes based on mutation status in histone encoding genes representing: H3.3K27M, H3.1K27M, and H3 wildtype. Histone mutations drive cellular proliferation by reprogramming the epigenetic landscape including histone modifications. To interrogate the DIPG epigenome, we performed chromatin immunoprecipitation followed by sequencing (ChIP-seq) using patient tumor and control non-malignant specimen. A larger array of epigenetic probes including 4 histone probes were used and a comprehensive epigenetic map across DIPG with respect to histone mutation status was developed.
Objectives: To assess the global histone modification in DIPG tumor tissue using ChIP-seq analysis and to further validate using RNA-seq profiling.
Design/Method: ChIP-seq was performed on DIPG tumors and control healthy pons for histone modifications indicative of active promoter (H3K4me3), repressive promoter (H3K27me3), and enhancer chromatin (H3K4me1 and H3K27ac). We assessed for global differences in histone modifications followed by super enhancer analysis using the ROSE analysis. Already existing RNA-seq data from DIPG upfront biopsy specimens (n=20) were used to validate ChIP-seq results.
Results: Global decrease in H3K27me3 at the transcription start site in DIPG tumors with H3.3K27M mutation compared to DIPG tumor with H3 wildtype. Global increase in H3K27ac of DIPG tumors with H3.3K27M compared to DIPG tumor with H3 wildtype and healthy pons. Super enhancer analysis of top 100 super enhancers showed activation of G protein and NOTCH signalling in H3.3K27M DIPGs, while normal healthy pons showed activation of FGF and PI3K signalling. Additionally, we assessed for unique super enhancers limited to the H3.3K27M DIPG tumors subtracting out super enhancers from healthy pons and H3 wildtype DIPG. Interestingly, PHC2, a component of PRC1 polycomb complex was found to be unique to H3.3K27M DIPGs. Validation by RNA-seq did show up regulation of the NOTCH signalling pathway as well as multiple components of the PRC1 polycomb complex (RING1, PHC2, BMI1, CXB1).
Conclusion: Using primary DIPG tumor tissue for ChIP-Seq analysis is novel. Our study shows that globally, there is increase in H3K27ac and decrease in H3K27me3 indicating a transcriptionally active chromatin in H3.3K27M DIPG tumors. Our super enhancer analysis show activation of NOTCH signaling pathway, a known previously published pathway activated in DIPG. Additionally, we show the possible involvement of PRC1 complex in H3.3K27M DIPG which is a novel finding and a possible new target for DIPG treatment.

Poster # 313

A NOVEL THERAPY FOR GLIOBLASTOMA IN MICE: LAU-0901, A PLATELET-ACTIVATING FACTOR RECEPTOR ANTAGONIST

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Background: Glioblastoma Multiforme (GBM) is a diffuse malignant brain tumor with rapid growth and infiltration, high resistance to available therapies, and poor survival rate. The current standard of care only provides patients with an average survival of 12-14 months. Platelet-Activating Factor (PAF) is a strong mediator of inflammation, and its receptor, PAF-R, is over-activated in the microenvironment of different tumors as part of an enhanced neuroinflammatory response. PAF-R antagonists have been shown to be beneficial in different animal models of experimental cerebral ischemia.
Objectives: The purpose of this study was to determine if PAF-R antagonist, LAU-0901, could hinder GBM progression.
Design/Method: U87MG cells were implanted in the right dorsal CA3 hippocampal region of BALB/c (nu/nu) mice. Intracranial tumor growth was quantified using in vivo bioluminescent imaging on days 10 and 25, and then every 2 weeks. Saline (vehicle, n=6) or LAU-0901 (60mg/kg/day; IP, n= 6) was administered daily from days 10 to 15 post GBM implantation.
Results: Tumor size before treatment on day 10 was identical in both groups. A large GBM mass was present in saline-treated mice and most of these mice died within 6 weeks; only two animals survived for the 10-week survival period. In contrast, tumor size was dramatically reduced by LAU-0901 treatment during the survival period. LAU-0901 treatment diminished tumor size by 80% on day 25 compared to saline-treated group. In addition, body weight increased by 30-45% in LAU-0901-treated mice at weeks 8 and 10.
Conclusion: We have demonstrated that treatment with PAF-R antagonist, LAU-0901, decreased tumor growth, increased body weight, and improved survival in a GBM mouse model. This represents a novel therapy that may potentially translate into a future treatment for patients with GBM.

Poster # 314

USE OF BROMODOMAIN INHIBITORS WITH RADIATION FOR TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA

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Background: Patients with Diffuse Intrinsic Pontine Gliomas (DIPG) have an extremely poor prognosis, with a five year overall survival of 1-2%, and minimal effective therapies. Radiation is a mainstay of upfront therapy, with a goal to alleviate symptoms. Around 80% of DIPGs contain a somatic mutation of histone 3, which causes a change from lysine to methionine (H3K27M) and alters the epigenetic landscape by decreasing trimethylation and increasing acetylation at position 27. This epigenetic change drives oncogenesis of DIPG, and targeted therapies, such as bromodomain inhibitors like JQ1, have been shown in pre-clinical data to inhibit tumor growth and increase overall survival in mouse models. DNA analysis shows that

treatment with JQ1 inhibits production of DNA repair genes, which are upregulated after radiation therapy (RT) and could be vital to tumor cell survival.
Objectives: To determine if combination therapy with RT and bromodomain inhibitors allows for increased inhibition of tumor growth in vitro and improves survival in vivo.
Design/Method: Using an established H3K27M mutant DIPG cell line (SF8628), in vitro assays including RNA sequencing, clonogenic assays, western blotting, and immunofluorescence are being performed to compare the effect of combination therapy (JQ1 and radiation) with monotherapy alone. Cells are treated with 0.5 μM JQ1 for 72 hours and with doses of radiation from 0.1 – 1Gy. Expression of DNA breakage and repair proteins, including gH2X, PARP2, and 53BP1, will be assessed using above modalities. In vivo experiments were performed using SF8628 cells propagated from established xenograft models to 60 nude mice via supratentorial injection. Mice were treated with either JQ1 alone, radiation alone, or JQ1 and RT. RT was administered three times a week for three weeks with 0.8 Gy to the supratentorium, and JQ1 was administered for three weeks once a day via intraperitoneal injection at a dose of 30 mg/kg.
Results: Clonogenic assays demonstrate decreased survival of DIPG cells when treated with combination therapy compared to RT alone. Western blotting and immunofluorescence analysis are currently being performed. In vivo data showed a statistically significant increase in the overall survival of the combination therapy group compared to control and either monotherapy group.
Conclusion: Preliminary data suggest that the combination of bromodomain inhibitors and RT decreases cell survival in vitro and improves overall survival in xenograft models. Further testing is being performed to investigate the downstream effects of combination treatment with the potential goal of using bromodomain inhibitors with RT in the clinical setting.

Poster # 315

RADIATION PRIMING IMPROVES THE ANTI-TUMOR ACTIVITY OF HER2 CAR T CELLS IN GLIOBLASTOMA

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Background: Chimeric Antigen Receptor (CAR) T-cell therapy for glioblastoma (GBM) has been limited due to poor homing, tumor antigen heterogeneity, and complex immunosuppressive tumor microenvironment. One potential strategy to improve tumor control is employing a combinatorial approach with radiation. Combining radiation with checkpoint inhibitor therapy has shown improvement in outcomes through radiation induced upregulation of tumor-associated antigens, adhesion molecules, and chemokine secretion.
Objectives: We hypothesize that priming the tumor with radiation will improve CAR T-cell trafficking to the tumor, increase CAR T-cell recognition of the tumor cells, and increase tumor cell susceptibility to CAR T-cell killing leading to improved responses and durable remissions.
Design/Method: GBM cell lines (LN18, LN229, and patient cell lines) were primed with fractionated radiation (2 gray/day for 5 days). Seventy-two hours after the completion of radiation, tumor cells were treated with second generation HER2-targeted CAR T-cells in vitro. For in vivo studies, orthotopic mouse models were created using human GBM cells. Surface

expression of tumor antigens, immune ligands and T-cell phenotype were analyzed before and after co-cultures using cytometry by time of flight (CyTOF). Established GBM xenografts were treated with fractionated radiation and subsequent intratumoral administration of HER2-targeted CAR T-cells as described above.
Results: Our studies show that irradiated GBM cells exhibit increased susceptibility to HER2 CAR T-cell mediated killing, in comparison to non-radiated tumor cells. This may in part be explained by higher HER2 expression observed on GBM cells following fractionated radiation, both in vitro and in vivo ($p<0.001$). In contrast to the downregulation of HER2 observed on un-radiated GBM cells leading to tumor escape under prolonged immune pressure, CAR T cells demonstrated robust killing of irradiated tumor cells in long term cultures. Further evaluation showed an increase in the percentage of activated CD25+ CAR T cells and expansion of the stem like central memory population (CD95- CCR7+ CD45RA+ CD28+ CD27) after exposure to radiated tumor cells.
Conclusion: Radiation is considered standard of care treatment in GBM, although it only prolongs OS by a few months. CAR T-cell therapy offers a new and exciting approach to brain tumor treatment, however initial studies show limited results. Combining radiation with CAR T cells leads to a synergistic response. This approach is easily translatable and may offer significant benefit. Work is ongoing to study the effect of combined radiation and CAR T-cell therapy and to further define the mechanism that improves the anti-tumor responses of HER2 targeted CAR T cells following radiation.

Poster # 316

UNIQUE PHENOTYPE OF TUMOR-ASSOCIATED DENDRITIC CELLS AFTER CHEMO-IMMUNOTHERAPY USING PTEN-BLOCKADE

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Background: The indoleamine-2,3-dioxygenase (IDO) pathway can be exploited by a variety of tumor types to escape a patient's immune system. IDO activity has been shown to activate regulatory T cells (Tregs) capable of inhibiting effector T cells (CD8+ and CD4+). Destabilization of Tregs by inhibition of PTEN (phosphate and tensin homolog) or by blocking IDO may break IDO-mediated immunosuppression in the tumor microenvironment. Prior work has shown that tumor microenvironments that harbor active immune responses have high numbers of phenotypically unique stimulatory dendritic cells that differentiate from immature myeloid cells and co-express CD103 and Ly6c. Complement component C3 has been previously shown to be mechanistically important for the treatment benefit of IDO-blockade in combination with chemotherapy and radiation in mice with glioblastoma tumors.
Objectives: We hypothesize that intact innate effector mechanisms expressed by stimulatory dendritic cells, such as complement component C3, are critical mediators of immunotherapy drugs (PTEN-blockers and IDO-inhibitors) that act as modulators of antigen-presenting cells.
Design/Method: B16F10 melanoma cells were implanted subcutaneously into thighs of wild-type C57BL/6 mice or C3-deficient C57BL/6 mice. Mice were treated with or without

cyclophosphamide in combination with PTEN-blockade using VO-OHpic. Tumor tissue was freshly frozen and immunohistochemical staining was performed to assess expression of cell surface phenotype markers CD11c, CD103, and Ly6c. The stained samples were analyzed using fluorescent microscopy for co-localization of these markers.
Results: In wild-type mice treated with cyclophosphamide plus PTEN-blockade, cells co-expressing Ly6c and CD103 were more frequent, and these markers both localized to the cell surface. In comparison, untreated wild-type mice had fewer cells co-expressing these markers, and the pattern of staining was different, with cell-surface pattern of CD103 staining but an intracellular pattern of Ly6c staining. After treatment with cyclophosphamide and PTEN-blockade, wild-type mice had tumors with high frequency of stimulatory dendritic cells triple-positive for CD11c, CD103, and Ly6c, whereas tumors from mice deficient in complement C3 had much less frequent examples of these triple-positive dendritic cells, and those observed had a more intracellular pattern of staining for these markers than in wild-type mice.
Conclusion: Treatment of wild-type mice with cyclophosphamide plus PTEN-blockade appears to elicit cells co-expressing Ly6c and CD103, and Ly6c appears to translocate from intracellular stores to cell surface expression after treatment. The ability of this chemo-immunotherapy to elicit Ly6c/CD103 co-expressing stimulatory dendritic cells seems to be at least partially abrogated in mice lacking complement component C3.

Poster # 317

ARMORED GPC3 CAR T CELLS FOR CHILDREN WITH RELAPSED/REFRACTORY LIVER TUMORS

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Background: Hepatoblastoma (HB) and hepatocellular carcinoma (HCC) are the two most common pediatric liver cancers. Available chemotherapies for unresectable or metastatic HB are less effective and associated with significant toxicities. Immunotherapy may help these children. Glypican 3 (GPC3) is an attractive immunotherapeutic target: it is expressed in the majority of HBs and HCCs and not expressed in non-malignant tissues. One effective immunotherapeutic approach is using chimeric antigen receptors (CARs) to redirect T cells to specifically destroy tumor cells, but this immunotherapy has limited efficacy in patients with solid tumors due to limited expansion and persistence of T cells.
Objectives: To examine the effect of the co-expression of IL-15 and 21 on GPC3-CAR T cells' expansion, persistence and antitumor activity and select the construct for further clinical development.
Design/Method: We systematically examined the antitumor properties of T cells co-expressing an optimized GPC3-CAR with IL-15, IL-21 or both (15.GBBz, 21.GBBz and 21.15.GBBz, respectively) in preclinical models of liver cancer.
Results: GPC3-CAR T cells co-expressing IL-15 and/or IL-21 effectively kill GPC3-positive tumor cells and produce effector cytokines in an antigen dependent manner. Constitutive IL-21 expression induces enrichment of less differentiated T cells after initial expansion (Naïve/stem cell memory CD8 T cell subset: 21.15.GBBz 29.2% vs GBBz 13.3%, $p<0.05$) and protects from

apoptosis during repeated killing of tumor cells (21.15.GBBz 40.6% vs GBBz 20.2%, p<0.05). The combined expression of IL-15 and 21 maintains the expression of TCF-1 (CD8 T cell subset, Day 5 during repeated tumor cell killing; TCF+ percentage/MFI: GBBz: 2.1%/4870.3, 15.GBBz: 14.5%/5283.5, 21.GBBz: 5.6%/7126.8 and 21.15.GBBz: 19.6%/9401; p= 0.001/0.008; 0.7/0.013; 0.005/0.22 for 21.15.GBBz, respectively), a transcription factor critical in T cell development and survival. Importantly, the combined expression of both IL-15 and IL-21 induces the highest peak expansion and sustained persistence GPC3-CAR T cells in vivo (Area under the curve: GBBz: 32.4, 15.GBBz: 66.2, 21.GBBz: 21.1 and 21.15.GBBz: 94.7; p <0.0001; =0.17; <0.0001 for 21.15.GBBz, respectively) leading to superior survival HCC xenograft bearing mice (p<0.001, Log-rank).
Conclusion: Our results indicate that the co-expression of IL-21 and IL-15 enhances the antitumor properties of GPC3-CAR T cells. Based on these results, we are now recruiting children in Cohort 1 of a Phase 1 trial to evaluate the safety, expansion, persistence and antitumor activity of GPC3-CAR T cells in children with liver cancers (GAP; NCT02932956). Promising results will justify further clinical evaluation for GPC3+ solid tumors in children and adults.

Poster # 318

ENDOTHELIALIZED MICROSCALE CULTURE SYSTEMS: A NOVEL PLATFORM FOR TUMOR MICROENVIRONMENT STUDIES

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Background: The tumor perivascular niche is a dynamic network of malignant and non-malignant cells with increasing interest as a therapeutic target. Microscale, 3D recapitulations of this niche are important intermediary cultures systems, bridging gaps between 2D cell culture and animal models. Further, they enhance the study of complex biological, chemical, and structural microenvironment interactions.
Objectives: 1. Develop a novel, 96-well plate-based 3D co-culture model for studying spatiotemporal drug effects using medulloblastoma cells suspended in a collagen-based hydrogel covered by an endothelialized monolayer.2. Develop a novel, physiologically relevant, in vitro co-culture model using an endothelialized microfluidic system simulating microvasculature in proximity to tumor cells.
Design/Method: 1. D556 medulloblastoma cells were added to a sterile preparation of a collagen I hydrogel solution. Tumor cell-hydrogel suspension was added to each desired well, spread over the bottom of the well, and cross-linked at 37 degrees for 30 minutes. HUVECs suspension was pipetted into each well, on top of the collagen hydrogel encapsulated tumor cells, and topped with growth media. After 48 hours of culture, cyclophosphamide and cisplatin were added to desired wells, aspirated at specific time-points, and followed by a live/dead assay with confocal microscopy. 2. Microvessel networks were fabricated within a 1% gelatin/agarose solution using a silicon wafer mold, defining branching channels of 100um (width) x 25um (height). These molded channels were applied to a PDMS adapter layer. Inlet and outlet ports were drilled for endothelial cell seeding and culturing with continuous media perfusion. Central wells were drilled for culturing of D556 medulloblastoma cells. The base was constructed via a thin

gelatin/agaraose layer on a glass coverslip, and crosslinking solution bonded the device layers. HUVECs gravity-flowed into the microvessels, and were cultured under continuous media flow for up to 21 days. Confocal microscopy was then utilized to image the devices.
Results: 1. We were able to show diffusion of chemotherapeutics across the HUVECs monolayer and affecting tumor cells within the collagen I hydrogel, modeling spatiotemporal transit of medications within a basic perivascular niche.2. We were able to clearly image the microvessel networks and tumor cells, confirming 3D endothelial cell-cell adhesions and the ability for the model to sustain long-term co-culture conditions.
Conclusion: Development of novel, endothelialized microscale co-culture devices for drug development and tumor microenvironment study is feasible, and confocal imaging within devices can be reliably performed. These first generation devices serve as models for incorporation of additional cell lines and patient-derived samples.

Poster # 401

COMMUNICATION CURRICULUM FOR PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOWS INCORPORATING BEREAVED PARENTS

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Background: Despite acknowledgement of the importance of effective communication in oncology, pediatric hematology/oncology (PHO) fellows consistently identify communication training as a deficiency during fellowship. Most communication training that fellows receive prior to, and during, PHO fellowship is composed of didactic sessions and observations of conversations facilitated by more senior clinicians. In partnership with bereaved parents who lost a child at our institution, we developed a comprehensive, longitudinal communication curriculum to enhance the training of pediatric hematology/oncology fellows.
Objectives: To determine the short- and long-term effect of PHO fellows' participation in a comprehensive, multimodal, and longitudinal communication curriculum, for which trained bereaved parents serve as educators and facilitators.
Design/Method: We developed a four-part, longitudinal communication curriculum incorporating bereaved parents as educators and facilitators. Two sessions included role-playing with bereaved parents acting as parents in difficult news discussions. The curriculum also includes self-lead educational experience including modules, didactics and example video clips. PHO fellows also received a pocket communication guide with conversation "roadmaps" and example phrases. Participants completed pre- and post-session surveys and a follow-up survey 6 months later. The post-session survey included retrospective pre-program assessment items to correct for response shift because of participation in the session. The post-session and follow-up surveys includes multiple open-ended questions to further probe the participant experience. Yearly cohorts were analyzed separately given potential changes to the training based on feedback from prior sessions.
Results: Since the program was developed in 2015, 24 PHO fellows have participated in the orientation communication training session and 18 PHO fellows have participated in the multiple elements of the longitudinal curriculum. Participants showed significant improvement in self-reported comfort with communicating difficult information to patients and families and the

results persisted over time. Statistically significant changes from retro pre- to post- and retro pre- to follow-up surveys were seen across cohorts in multiple areas. Responses to open-ended questions were overwhelmingly positive.
Conclusion: We have developed one of the first comprehensive, longitudinal communication curricula for PHO fellows that engages bereaved parents as educators. This four-part curriculum, which includes two sessions of small group and one-on-one role play with bereaved parents, resulted in significant changes in participant comfort with communication skills, and these results persisted over time. Assessment of the curriculum is ongoing and will include objective measures of fellow skills monitored over time and incorporate feedback from patients and families.

Poster # 402

COMMUNICATION SKILLS TRAINING FOR PEDIATRIC RESIDENTS: LEARNING TO GIVE BAD NEWS

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Background: Communication has been described as the most common "procedure" in medicine and the importance of effective communication is well-established. Physicians' ability to communicate effectively may influence patient treatment choices, compliance, outcomes and patient satisfaction. Despite this, prior studies have demonstrated that physicians, at various levels of training, feel they lack sufficient knowledge of communication techniques and desire more formal training.
Objectives: We developed a standardized patient (SP) based communication training program for pediatric residents. The goal was to demonstrate feasibility of implementation, as well as improved self-assessed skill and comfort level in various aspects of communication in trainees.
Design/Method: The program consists of three two-hour sessions. Prior to meeting, residents are provided with material on communication strategies, and asked to complete a pre-training questionnaire. Participants are then given the opportunity to communicate difficult information, such as a new HIV diagnosis or telling a parent her child has leukemia, with minor alterations in SP response (i.e. anger or denial). Following each interaction, trainees are given feedback by the preceptor, SP and peers. Following course completion, participants complete a complimentary post-training questionnaire. The primary endpoint is change in trainee comfort level and self-assessed skill level pre- and post-training.
Results: To date, 22 pediatric residents have participated in the program. Pre-training questionnaires demonstrated the majority of trainees had a low comfort level discussing a poor prognosis (59%) and telling a patient they are going to die (77%). Half or more self-reported low skill levels in assessing a patient's ability to discuss bad news, communicating a poor prognosis, and discussing DNR (50%, 59%, 64%, respectively). Following course completion, there was a significant increase in self-assessed skill and comfort level in all of the areas described above ($p<0.05$).
Conclusion: In contrast to more time-consuming programs, preliminary data suggests this concise training program is effective and realistic for pediatric residents in their first year of training. Further planned study will evaluate if the program results are sustained by sending

follow-up surveys to residents during subsequent years of training. Finally, to evaluate the feasibility of implementing the course more broadly, we plan to distribute a survey to assess the current status of communications skills training at other institutions, to be completed by pediatric residency program directors. The ultimate goal is to distribute the program to other centers currently lacking formal communication training.

Poster # 403

SPREADING LIKE WILDFIRE: BURNOUT IN ALL THREE YEARS OF PEDIATRIC HEMATOLOGY ONCOLOGY FELLOWSHIP

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Background: Burnout is plaguing doctors at all levels with severe consequences. Despite the high clinical complexity and emotional intensity, burnout among pediatric hematology-oncology (PHO) faculty has been less prevalent than previously described (Roth, PBC, 2011), including pediatrics overall. However, a recent study of pediatric subspecialty fellows described extremely high levels of burnout at 60% (Okorie, Acad Peds, 2016). The prevalence and associated risk factors for burnout among PHO fellows remains unknown.
Objectives: 1. Describe the prevalence and determinants of burnout among PHO fellows 2. Evaluate for associated outcomes of high levels of burnout
Design/Method: A cohort of 115 PHO fellows enrolled in a novel humanism curriculum study were administered the Maslach burnout inventory, the empowerment at work scale, patient-provider orientation scale (PPOS), pediatric hematology oncology self-assessment in humanism tool (PHOSAH), and satisfaction in training scale. Secondary analyses were performed on the data collected using chi square analysis for demographic risk factors, and t-test for the continuous outcome variables.
Results: A total of 45/115 fellows (39.1%) met criteria for high level of burnout. No demographic variables were identified as statistically significant risk factors to predict high levels of burnout, including year of fellowship. The prevalence of high-level burnout among 2nd and 3rd year fellows was not significantly lower than that of 1st year fellows (36% vs 46%,p=0.3), revealing burnout to be an issue across the full fellowship experience. Fellowship program size was not significantly associated with level of burnout, though there was a trend towards large programs contributing a higher proportion of fellows with high levels of burnout (62.2% of fellows with high burnout trained in large programs vs 47.1% of those without high burnout). Those who met criteria for high burnout were associated with poor outcomes on scales assessing empowerment (52.8 vs. 58.7, p=0.0002), patient-centeredness (67.1 vs. 73.7, p=0.002), self-assessment in humanism (5.7 vs 9.2, p<0.0001), and satisfaction with training (21.7 vs. 26.2, p<0.0001).
Conclusion: This cross-sectional study demonstrates that more than one third of current PHO trainees are experiencing high levels of burnout. Interestingly, research years may not be as protective as previously thought and those at larger programs might be at higher risk, though more data is required. High level burnout is associated with decreased satisfaction with training, poor empowerment, and less patient-centered care. These data beg the need for longitudinal

investigation of burnout in PHO fellows, both for their own well-being but also for the possible impact on patient care.

Poster # 404

PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOW EDUCATION IN SEXUAL AND REPRODUCTIVE HEALTH

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Background: Adolescent and young adult cancer patients (AYAs) report a need for improved patient-clinician communication on sexual and reproductive health (SRH) issues. Key clinician-reported barriers to SRH communication with AYAs include discomfort initiating conversations and lack of knowledge on how to talk to AYAs about SRH issues, including how to assess for specific problems and provide appropriate counseling. Currently little is known about pediatric hematology/oncology fellow education on SRH for AYA cancer patients.
Objectives: To determine the current status of pediatric hematology/oncology fellow education on SRH issues relevant to cancer patients.
Design/Method: Surveys were mailed and emailed to pediatric hematology/oncology fellowship program directors in the United States. The survey was designed to separate out individual fellowship program education practices on fertility, sexual health (SH), and safe sex practices (SSP), and included 2 demographic questions. Analyses were aided by SPSS software.
Results: Surveys were sent to 69 pediatric hematology/oncology programs across the United States with a 91% response rate (n=63). Participating fellowship program sizes ranged from 1-24 fellows, with a mean of 7.2 (SD 5.0) fellows per program. Overall, fellowship program directors reported more structured education opportunities for fellows on fertility compared to SH and SSP. A total of 85% (n=52) reported education sessions on the impact of cancer on female fertility, 87% (n=53) on the impact of cancer on male fertility, 77% (n=47) on female fertility preservation options, and 84% (n=51) on male fertility preservation options. Program directors reported fewer structured education opportunities on SH and SSP. Forty-one percent (n=26) had education on contraception during treatment, 32% (n=20) on safe sex practices during cancer treatment, 11% (n=7) on cancer impact on body image, 11% (n=7) on impact of cancer on female sexual function, 14% (n=9) on impact of cancer on male sexual function. Barriers to fellow education included an already saturated fellow curriculum (fertility 29%; SH 40%; SSP 38%), not required or expected part of program (fertility 8%, SH 26%, SSP 25%), and lack of experts to teach (fertility 23%, SH 47%, SSP 25%).
Conclusion: Pediatric hematology/oncology program directors report limited structured fellow education on SH and SSP, with slightly more time dedicated to fertility. Guidelines by the American Academy of Pediatrics and the National Comprehensive Cancer Network highlight SRH conversations as essential to comprehensive AYA care. Given AYA report of suboptimal clinician-patient communication on SRH issues, future research may focus on developing strategies to improve clinician education during fellowship.

Poster # 405

THE "10-MINUTE TEACHER": IMPROVING PEDIATRIC HEMATOLOGY/ONCOLOGY EDUCATION FOR PEDIATRIC TRAINEES

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Background: Medical educational models are evolving to create a more learner-centered focus to optimize learning. Pediatric residents are often taught in a traditional lecture forum and have limited time throughout the day to accomplish a multitude of tasks. Utilizing various adult learning theories as a guide, a new curriculum for pediatric trainees was created to enhance education while minimizing interruptions to workflow.
Objectives: We utilized a novel learner-centered curriculum to increase resident practical knowledge and comfort with treating various pediatric hematology/oncology disorders.
Design/Method: A pediatric hematology/oncology curriculum was created to address the need for additional learner-centered teaching for residents with limited time in the workday. Over the course of ten weeks, weekly sessions were held with residents stationed on the pediatric floor, pediatric Intensive Care Unit and on the pediatric hematology/oncology elective. The sessions took place on the pediatric floor, and were flexible in scheduling time and topic. The sessions each lasted approximately 10-15 minutes, and were case-based with a focus on practical management tips; the curriculum included topics such as thrombocytopenia, iron deficiency anemia, bleeding disorders, lymphadenopathy, acute leukemia, and sickle cell disease complications. The sessions included approximately 5 learners at a time and were interactive to optimize active learning in the small group setting. Pediatric residents were then surveyed anonymously regarding the impact of these teaching sessions.
Results: 24 pediatric residents were exposed to the teaching curriculum. All surveyed residents reported that the sessions increased knowledge of topics discussed. 90% of residents reported an increase in comfort in caring for patients with diagnoses discussed, and they were able to use the information directly to care for patients. The sessions did not interfere with workflow for >90% of residents. All residents reported that flexibility in scheduling sessions and learner input into choosing the topics were beneficial. The small group setting and practical "pearls" of teaching were the top reported features of these sessions.
Conclusion: A novel learner-centered curriculum was created to supplement pediatric resident hematology/oncology education using various strategies directed toward teaching adult and millennial learners. This curriculum increased residents' knowledge and comfort in managing various pediatric hematology/oncology disorders, and was delivered in a time-efficient manner so as not to disrupt clinical duties. The ultimate outcome will translate into improved patient health and care. This curriculum model may be optimized for use in other pediatric divisions as well as other departments to promote continual and ideal learning for medical trainees.

Poster # 406

NEEDS ASSESSMENT OF ADVOCACY TRAINING FOR PEDIATRIC HEMATOLOGY-ONCOLOGY FELLOWS

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Background: Child health in the United States is increasingly impacted by social, community, and environmental factors. As a result, the role of general pediatricians and pediatric subspecialists has expanded to include advocacy on a range of topics affecting child health. Both the Accreditation Council for Graduate Medical Education (ACGME) and the American Society for Pediatric Hematology-Oncology (ASPHO) have recognized the importance of advocacy training for pediatric hematology-oncology trainees. However, current practices and trainee preferences around advocacy training for pediatric hematology-oncology fellows are not well understood.
Objectives: To assess current practices and trainee preferences around advocacy training among pediatric hematology-oncology fellows in the United States.
Design/Method: We conducted a cross sectional electronic survey of current pediatric hematology-oncology fellows in 38 fellowship programs across the United States. Participants were asked about their experiences with prior and current advocacy training, as well as preferences for advocacy training in fellowship.
Results: There were 102/309 (33%) fellow respondents, representing fellows in their first (24%), second (37%), and third (39%) year of training. The majority of respondents (68%) perceived value in prior advocacy training during residency. While 30% of respondents strongly agreed and 55% agreed that advocacy was relevant to their future role as a hematologist-oncologist, most fellows (60%) reported no advocacy training during fellowship, and only 27% reported that their current fellowship advocacy training was valuable. The majority (70%) believed advocacy training should be a part of hematology-oncology fellowship curriculum. When asked about preferred learning strategies, 82% of respondents reported "case-based teaching" and 64% reported "project-based learning" as best for cultivating advocacy skills. 79% of respondents noted they had not previously participated in child advocacy efforts with pediatric hematology-oncology subspecialty organizations, but would like to do so in the future.
Conclusion: Pediatric hematology-oncology fellows report advocacy training is a valuable skill to learn during training and current practices do not meet trainee learning goals. Case and project-based modules are likely to be well received by fellows. These data offer an opportunity for collaboration between ASPHO and training programs.

Poster # 407

LONG-TERM BENEFITS OF A MENTORING PROGRAM FOR YOUNG INVESTIGATORS IN THE CHILDREN'S ONCOLOGY GROUP

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Background: The mentorship of junior faculty is critical to the long-term success of an organization. The Children's Oncology Group (COG) created a mentorship program in 2004 to

help foster relationships between Young Investigators (YIs; those <10 years from their first faculty appointment) and senior members to further YIs' career development and involve them in COG research endeavors. We have previously described the long-term impact of the program on participating mentees, but this is the first examination of the impact and perception of the program on mentors.
Objectives: To evaluate the long-term success of the COG YI mentorship program from the perspective of mentors serving in the program.
Design/Method: An online survey was completed between 8/2018-11/2018 by 136 individuals who served for ≥ one year as a mentor in the COG YI mentorship program. Statistical comparisons were made with the Kruskal-Walis Test.
Results: We achieved a 74.2% response rate and since 28 mentors had multiple pairings, we report on 138 total mentees/mentors pairs. Mentors were 57.4% male, while the mentees were 39.1% male. Overall, mentors rated the mentoring of YIs as highly important (median rating = 90 on a scale of 1-100; 81, 100 25th, 75th quartiles). Most mentors (78.2%) reported that a mentor was instrumental to their own success in COG. Even more (92.1%) reported that a mentor was instrumental to their overall career development. Many of the mentors reported that they enjoyed serving as a mentor in the program (72.3%), and 43.6% felt it positively affected their career. The median success rating (on a scale of 1-100) across the mentor/mentee pairings was 75 (39, 90 25th, 75th quartiles). Scores did not differ by sex of the mentor or the mentee. Mentoring success scores improved with the frequency of mentor/mentee interactions, $p<0.001$. Many mentors reported deriving a direct benefit from mentoring (60.1%). Mentor/mentee pairs that set goals at the beginning of the program reported higher success ratings than those that did not ($P<0.001$). Tangible successes from the mentoring program included: current mentee involvement on a COG committee (45.7%), ongoing communication between the mentor/mentee (53.6%), and publication of a manuscript written by the mentor/mentee pair (38.4%).
Conclusion: Mentors indicate that mentorship is important to success in pediatric oncology. Long-term mentoring success improves when mentors and mentees set goals and meet frequently.

Poster # 408

PRACTICING MEDICINE IN THE GRAY: A FRAMEWORK FOR TEACHING EVIDENCE BASED PRACTICE UNDER UNCERTAINTY

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Background: Evidence based practice has been described as the optimal combination of physician experience, sound research, and patient preference. However, physicians in practice often find themselves balancing what may be optimal with what is feasible. What appears on the surface as a black and white decision becomes gray, as physicians deal with uncertainty. This is no less true in the field of Pediatric Hematology and Oncology (PHO), where physicians consistently face situations in which evidence is conflicting, scare or complex. While this is commonplace in practice, there lacks formal curricula to teach trainees the skills needed to navigate uncertain situations.
Objectives: To develop a PHO curriculum for teaching decision making under uncertain

conditions.
Design/Method: Based on a comprehensive scoping review and thematic analysis (currently under review for publication,) we developed an educational model illustrating how a learner might approach a medical decision under uncertain conditions. We adapted this model to the context of PHO fellowship training, by soliciting usability feedback from fellows and faculty during their decision-making process. We then developed a curriculum based from the model. The curriculum is being piloted with a cohort of fellows and faculty within the PHO division at Children's Hospital of Richmond at VCU.
Results: The resulting curriculum includes four sessions incorporated in a journal club setting. The first is a small group discussion of the uncertainty framework with background literature provided. The second and third sessions are each centered on a clinical scenario with inherent uncertainty and a fellow assigned to examine supporting literature and facilitate discussion. The fourth session involves an individual reflective writing exercise on an actual clinical scenario with small group discussion. Feedback from our fellows and faculty will be gathered using a behaviorally anchored survey instrument following implementation of the pilot program.
Conclusion: Learning how to face uncertainty in clinical practice is a crucial aspect of PHO training that necessitates the development of a formal curriculum based on a sound framework. We plan to collect baseline and post-implementation data on perceptions, tolerance for ambiguity, and cognitive task analysis in actual patient decisions to assess the efficacy of our own curriculum. In addition, we identified the lack of a valid instrument to assess learners' abilities to make decisions under uncertain conditions. Future work will include the development and validation of such an instrument. Based on outcomes from our pilot, we anticipate disseminating the curriculum and instrument to other pediatric fellowship training programs.

Poster # 409

QUANTIFYING THE DELAY IN INDUSTRY-SPONSORED PEDIATRIC ONCOLOGY DRUG DEVELOPMENT: US REGULATORY REVIEW

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Background: Industry-sponsored pediatric oncology studies typically occur following investigations in adults. The Food and Drug Administration (FDA) Reauthorization Act (FDARA) of 2017 amended the United States (US) pediatric requirements to extend the promise of precision medicine to pediatric patients with cancer by requiring earlier investigations. The Act mandates that sponsors planning to submit a marketing application for certain new molecularly targeted drugs and biologics after August 18, 2020 are no longer exempt from investigating in pediatrics if they are seeking an adult orphan oncology indication for their product. To accelerate oncology therapy development in pediatrics and ensure sponsors meet the US regulatory requirements, it is important to understand the current obstacles that delay pediatric oncology drug development and consider potential solutions.
Objectives: To quantify the delay in pediatric development of orphan-designated oncology drug and biologic products eventually approved in the United States for pediatric use between 2017-2018, highlight the potential road blocks, and describe possible options to promote accelerated

pediatric oncology drug development.
Design/Method: Products approved for pediatric oncology indications were identified on the FDA website. Respective study starts, defined as when the first participant was enrolled, for adult and pediatric interventional industry-sponsored studies were collected using clinicaltrials.gov.
Results: Twelve products had received at least one pediatric oncology US approval between 2017-2018. Of the twelve oncology products, six had industry-sponsored pediatric studies initiated following the adult studies, with an average delay of 3 years, 4 months (39.833 months). Five of the twelve products approved in 2017-2018 had included both pediatrics and adults in their preliminary studies.
Conclusion: Pediatric oncology drug development experiences a general delay in study start in comparison to adult studies. The reasons for this delay are multifactorial and range from feasibility to regional regulatory requirements to study in pediatrics. Sponsors should consider innovative methods to incorporate pediatrics earlier into the overall drug development plan to ensure this population receives potentially beneficial therapies without delay. Full implementation of the amended Pediatric Research Equity Act provisions of FDARA in 2020, which mandates early evaluation of appropriate new drugs based on relevance of molecular mechanism of action to cancers in children, is also expected to decrease this delay.

Poster # 410

IMPROVING CINV IN PEDIATRIC ONCOLOGY: A ROLE FOR PHARMACOGENETICS?

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Background: Despite high rates of cure in pediatric oncology, substantial numbers of patients experience treatment-related toxicities. Pharmacogenetic analysis aims to define how genetic variation influences interpatient variability in drug response and toxicity. Despite technological advances, few genetic variants have amassed a sufficient level of evidence to influence drug selection or dosage adjustments.
Objectives: This study is investigating the development of chemotherapy induced nausea and vomiting (CINV). The widespread use of 5-HT3 receptor antagonists such as ondansetron has dramatically decreased the proportion of patients that experience CINV, but up to 30% of patients still do not obtain satisfactory symptom control. In this study, genes associated with ondansetron metabolism were analyzed and patients monitored for development of CINV to determine a possible relationship between genetic profiles and symptoms.
Design/Method: DNA was extracted from blood using Qiagen Qiasymphony. The polymorphism rs45460698 on the 5-HT3RB gene was genotyped by a custom Taqman assay. Polymorphisms ABCB1 3435C>T (rs1045642) and G2677A/T (rs2032582) were genotyped using commercially available pre-designed Taqman assays. All Taqman assays were purchased from ThermoFisher Scientific and analyzed on the Applied Biosystems Quantstudio 3 analyzed using ABI Quantstudio Design and Analysis software. Presence of a deletion in 5-HT3RB has been associated with INCREASED nausea. Presence of either ABCB1 TT variant has been

associated with LESS nausea. 5-HT3RB and ABCB1 genotypes were combined to create 8 phenotype groups. Patients' electronic medical records were manually reviewed to determine the presence and severity of CINV. CINV was defined as use of granisetron as antiemetic instead of ondansetron OR use of ondansetron plus 3 other antiemetic medications around the clock.
Results: Ninety three patients were included. In the group expected to have highest nausea (deletion of 5-HT3RB plus absence of either TT variant), 7 patients (41%) experienced ondansetron failure compared to 14 (18%) in all other groups combined. This difference was statistically significant (Chi-Square test, p=0.0425). Patients in this group were 2.24 times more likely to meet the definition for ondansetron failure compared with other groups (95% confidence interval of (1.07, 4.68)).
Conclusion: Pharmacogenetics has the potential to tailor medications to each patient with the goal of reducing symptom burden. We have identified a genetic profile associated with increased risk of ondansetron failure.

Poster # 411

GENETIC PROFILING OF ADME MARKERS IN MULTIPLE SAMPLE TYPES USING DNA OLIGONUCLEOTIDE ARRAYS

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Background: Pediatric cancer patients pose unique challenges in that twenty percent do not respond to standard therapy and 22% of all hospital admissions are due to adverse drug reactions (ADRs). Genetic variation in drug absorption, distribution, metabolism, and excretion (ADME) genes has been tied to drug efficacy and safety in adults for many years, but the study and implementation of pharmacogenomics in children has lagged. However, there is growing appreciation for the potential value of pediatric personalized medicine, particularly for children undergoing treatment plans involving multiple therapeutics and requiring pain management, such as the pediatric oncology patient population.
Objectives: PharmacoScan™ Solution enables comprehensive, accurate genotyping on a DNA microarray of ~4,600 markers in over 1,000 genes involved in drug-metabolizing enzymes and transporters. The array plate format allows either 24 or 96 samples to be processed at a time. A novel incorporation of multiplex PCR into the Axiom™ workflow solves the genotyping challenges of key variants that are part of highly homologous, multi-gene families such as CYP2D6, a gene involved in the metabolism of over 25% of prescribed drugs. As personalized medicine research becomes increasingly important, we set out to expand the application of this platform by characterizing genotyping performance across different DNA sample types and extraction methodologies.
Design/Method: To this end, the characterization and verification of genotyping performance of saliva and buccal cell sample types was carried out. The study verified the use of both magnetic, bead-based high-throughput DNA isolation and manual, precipitation-based DNA extraction methods.
Results: Both extraction methods provided high-quality genomic DNA (gDNA) that is compatible with PharmacoScan Assay. This study demonstrated similar genotyping performance

between DNA from oral samples versus whole blood.
Conclusion: PharmacoScan™ Assay offers a streamlined workflow consistent with the needs of pharmacogenetic profiling studies. The expansion of this platform to support less invasive sample types, such as saliva and buccal cells, will better support the use of this assay for pharmacogenomic research in the pediatric population. For Research Use Only. Not for use in diagnostic procedures.This work was produced by Thermo Fisher Scientific.

Poster # 412

TACKLING TRANSFUSION-RELATED IRON OVERLOAD (TRIO) IN CHILDHOOD CANCER SURVIVORS

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Background: Transfusion-related iron overload (TRIO) is a potential cause of morbidity and mortality in survivors of childhood cancer who received multiple packed red blood cell transfusions (PRBCTx) during treatment. Excess iron causes tissue damage through chronic formation of free radicals, which can cause significant organ damage resulting in liver, cardiac, and endocrine dysfunction, as well as death. While long-term follow-up guidelines by the Children's Oncology Group recommend obtaining a baseline serum ferritin for patients who underwent hematopoietic stem cell transplant (HSCT), there are no recommendations for routine screening in patients treated with chemotherapy alone.
Objectives: To determine the prevalence of iron overload and frequency of screening for TRIO among pediatric cancer and BMT survivors at our institution. To reduce risk for long-term complications from TRIO in this population by developing an institutional clinical practice guideline for screening and management.
Design/Method: We retrospectively reviewed medical records over a 10-year period (2007-2017) to identify patients with a history of hematologic or oncologic diagnosis requiring treatment with chemotherapy and/or HSCT who received ≥10 PRBCTx. Exclusion criteria included death. Records were reviewed to determine whether these patients had a screening ferritin performed within a year after receiving ≥10 PRBCTx, and whether a T2* MRI was performed if the serum ferritin was >1000 ug/L.
Results: We identified 114 patients at risk for TRIO, 44 of whom had a history of HSCT and 70 of whom were treated with chemotherapy alone. The average number of PRBCTx received during treatment was 26 and 19 for the HSCT and chemotherapy alone groups, respectively. While 91% (40/44) of the at-risk HSCT patients had a screening ferritin performed, only 31% (22/70) of the at-risk chemotherapy alone patients had screening ferritin performed. Of those screened, the serum ferritin was found to be >1000 ug/L in 40% (16/40) of HCST patients and 45% (10/22) of chemotherapy alone patients. T2* MRI was performed in 31% (8/26) of patients with serum ferritin >1000ug/L and 100% of these patients demonstrated radiographic evidence of iron overload.
Conclusion: Patients treated with chemotherapy alone were not screened as frequently for TRIO as patients with a history of HSCT, though the prevalence of iron overload was similar between

the two groups. Based on these data, we developed a clinical practice guideline for screening and management of TRIO for all childhood cancer survivors.

Poster # 413

TRANSFUSIONAL IRON OVERLOAD IN PEDIATRIC ONCOLOGY AND TRANSPLANT PATIENTS

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Background: Patients with malignant disorders receive multiple red blood cell (RBC) transfusions, leading to long-term exposure to toxic iron accumulation from lack of excretion of excess iron. The impact of exposure to toxic iron is augmented in oncology patients when transfusions are during periods of bone marrow suppression and oxidative stress from oncological treatment, increasing the risk of long-term complications including endocrinopathies or cardiac failure. Considering these complications are reversible or preventable, it is essential to diagnose and treat iron overload in these patients.
Objectives: Assess the impact of iron overload in oncology/BMT patients in whom clinical MRI evaluation was completed
Design/Method: An IRB approved retrospective chart review identified all oncology/BMT patients using billing diagnosis data for inpatient and clinic visits between 2007 and 2017. Oncology/BMT patients who had an MRI for clinical evaluation of iron overload were identified and retrospective chart reviews were completed. Descriptive analysis of the data was completed using Jmp.
Results: During the study period, 90 patients were evaluated with MRI for hemosiderosis at a median 3 years after oncologic diagnosis. The median liver iron concentration (LIC) in the diagnostic MRI was 8.11 mg/g (1-33.5 mg/g). Of the 80% of subjects noted to have clinically significant iron overload with LIC > 4 mg/g, 67% underwent treatment with chelation or phlebotomy and 50% had a follow up MRI. Clinically significant cardiac iron (T2* < 30 ms) was demonstrated in 20% of patients with 5% having more severe cardiac iron levels (T2*< 20 ms). Pituitary iron overload or volume loss was noted in 35% of the 20 patients that were evaluated.
Conclusion: Although iron overload is increasingly recognized in oncology patients, it is frequently overlooked or managed with sub-optimal therapy or follow-up. In this cohort, many patients had moderate or severe iron overload at diagnosis with a small portion notable for cardiac or pituitary iron loading, which can lead to significant clinical sequelae. For patients seen by the iron overload program, treatment decisions were based on LIC, age at the time of iron overload, presence of elevated transferrin saturation indicating circulating toxic iron, and presence of pancreatic, pituitary or cardiac iron. Those noted to have exposure to labile plasma iron were treated with chelation while younger patients with mild iron overload were not treated considering this iron would likely be utilized for growth. Evaluation and management guidelines based on knowledge regarding iron homeostasis and clinical implications are needed for optimal long-term care.

Poster # 414

DO INFORMED CONSENT FORMS ADEQUATELY INFORM PATIENTS OF TRANSFUSION-ASSOCIATED INFECTIOUS RISKS?

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Background: Informed Consent (IC), a medical ethics cornerstone, dictates patients must be informed of treatment benefits and risks. Although transfusion risks of HIV and Hepatitis are largely mitigated, the risk of emerging pathogens, parasitic, and bacterial contamination persist. According to the FDA, Babesia and bacterial contamination represent the greatest infectious risks from blood transfusion today. At least 1:2,300 transfused platelet units contain bacteria, resulting in 1 symptomatic bacteremia per 10,000 transfusions and a fatality every 51,440 transfusions. The FDA estimates over 200 sepsis cases and 20 deaths/year.
Objectives: The question is raised whether patients are adequately informed.
Design/Method: An internet search engine was queried on April 1, 2018 with the phrases 'blood product informed consent' or 'transfusion informed consent', limited to PDF documents, pages hosted in the US, and excluded if they combined consent (i.e., surgical consent with a subsection on transfusion). Because several informed consent forms (ICFs) referred to a 'Patient Information Sheet', an additional query for this phrase was run. Infectious risks discussed were extracted from each eligible document.
Results: Twenty-two (22) ICFs met review criteria. No ICF addressed risk differences across component type (i.e., platelets/plasma/RBC). Mean time since last ICF revision was 5y (range: 3m to 14y). Despite being the greatest transfusion-transmitted infection risk (~1:2,300), less than half (9) of ICFs list bacteria; only 2 contained any risk magnitude information (RMI). In comparison, HIV infection (~1:1,000,000) was presented in all ICFs, with RMI found in 10. Mention of Hepatitis was present in 1/3 (HepB) to 2/3 (HepC) with RMI ranges similar to HIV. Parasitic risks were mentioned in 3 and emerging pathogens in 1, without data on RMI. Some ICFs mentioned routine bacterial testing and culture, but none mentioned the pathogen-reduction or enhanced bacterial detection methods recommended by FDA Draft Guidances to reduce infection risk.
Conclusion: Blood product IC varied greatly for transfusion-transmitted pathogen risks. None of the surveyed forms accurately represented the current FDA position on bacterial contamination and Babesia risks. ICFs that do not properly inform patients of current blood transfusion hazards or risk-reduction options may raise questions regarding medical ethics and potential for legal risk to providers. Transfusion medicine authorities (i.e. AABB and FDA) should offer specific, updated guidance on risk information for Informed Consent Forms.

Poster # 415

THE INITIAL COMMUNICATION OF A PEDIATRIC ONCOLOGY DIAGNOSIS BY NON-ONCOLOGIST PEDIATRIC PROVIDERS

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Background: Receiving a cancer diagnosis is a life-changing experience for patients and families. The importance of the initial discussion with an oncologist is well documented, but little is known about the communication of the initial diagnosis, often by a non-oncologist physician, and its impacts on transition to oncologic care.
Objectives: This study sought to understand the initial diagnosis experience from the patient, caregiver, and physician perspective.
Design/Method: Semi-structured interviews were conducted at a large academic medical center with recently (within the last 3 months) diagnosed pediatric/adolescent oncology patients, caregivers, their primary pediatricians or other non-oncologists involved in diagnosis, and their oncology team. Interviews were transcribed, independently coded by two readers, and compared for agreement.
Results: Those involved in the initial cancer diagnosis of 30 patients were interviewed, encompassing 34 family caregivers, 12 patients, 12 primary pediatricians, 14 other diagnosing physicians, and 16 oncologists. Interview content analysis generated several themes.Patient-Caregiver:-Urgency: Families often inferred a sense of urgency (regarding seeking referrals, tests, etc.) from physicians even when purpose of tests or diagnosis was unclear-Language: 'Malignancy' and 'mass' were terms often used by physicians during discussions, but these were often not understood as 'cancer' by families-Preference: Generally families preferred to know if cancer was high on a differential; however some appreciated waiting to hear "cancer" until there was greater certainty of diagnosis -Transition to oncology: Information related to physician thought processes, next steps, and expectations as relayed by diagnosing physicians reassured families as care transitioned to oncologyPediatrician/Diagnosing Physician: -Communication influences: Factors including definitiveness of diagnosis, anticipated family reaction, and experience delivering cancer diagnoses impacted language used by physicians-Patient understanding: Physicians acknowledged that terms like "tumor" and "mass" can be unclear to families and mask concern for cancerOncologist:-Impact on consultation: Oncologists reported more productive conversations with families who had been well-prepared by diagnosing physicians; families coming with more ambiguity were more likely to be upsetTriad:-Concordance: Responses were relatively concordant across the 3 groups regarding qualities of the initial diagnosis conversation, with some discordance between families and diagnosing physicians regarding whether the word "cancer" was used in discussion
Conclusion: There was wide variation in family experiences leading up to diagnosis, and physicians expressed a multitude of factors influencing how a diagnosis was communicated. Understanding these influences in conjunction with families' needs may allow physicians to better tailor messaging when delivering diagnoses, in turn improving patient transition to oncologic care.

Poster # 416

UTILIZING TECHNOLOGY TO OPTIMIZE COMPREHENSIVE CARE FOR CHILDREN WITH NEWLY DIAGNOSED CANCER

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Background: Children with cancer have complex psychosocial issues that require a collaborative approach from a multidisciplinary team. Achieving optimal comprehensive care is

frequently limited by competing demands and intensive treatment. An ongoing quality improvement (QI) initiative aimed to achieve and sustain a comprehensive care model for a pediatric patient with newly diagnosed cancer was piloted at the University of Florida in 2018. We identified key drivers and barriers to the successful implementation of such care and designed an order panel within the electronic medical record (EMR) to utilize technology in achieving our goal.
Objectives: The overall goal of this QI project was to utilize the electronic medical record (EMR) order panel function to improve the overall delivery of comprehensive and psychosocial care services for newly diagnosed pediatric oncology patients.
Design/Method: A standard Plan-Do-Study-Act (PDSA) QI model was utilized. Specific goals were identified based on the Psychosocial Standards of Care Project for Childhood Cancer (PSCPCC). These included: (1) Baseline PT and OT evaluations for 85% of patients within 15 days of diagnosis; (2) Dental screening for 80% of patients within 30 days of diagnosis; (3) Nutrition consult to 80% of patients who are underweight (defined as BMI < 18.5) OR obese (defined as BMI > 30) within 15 days of diagnosis; (4) Palliative care consultation to 80% of patients with high risk diagnoses or relapsed and/or metastatic disease within 15 days of diagnosis; (5) Neuropsychology screening for 85% of patients within 30 days of diagnosis; and (6) Psychiatry evaluation for 80% of patients with prior history of anxiety and/or depression within 15 days of diagnosis. Key drivers included patients, caregivers, and multidisciplinary providers.
Results: Initial rates for PT and OT evaluation were 28.5% and 36.5%, increasing to 76.5% and 55% respectively. Dental screenings were done in 8.5% of patients at baseline, increasing to 63%. Nutrition consults had been placed for no patients at baseline, improving to 12.5%. Neuropsychology screenings were documented for no patients at baseline, improving to 55%. Palliative care consults improved from 0% to 100% of patients meeting criteria. There were no patients who qualified for psychiatry referral. These data reflect the first cycle of our quality initiative.
Conclusion: Improved delivery of psychosocial care for a newly diagnosed pediatric patient with cancer can be achieved and maintained through a standardized process in the EMR. The order panel increased providers' awareness of psychosocial services and abilities to provide comprehensive care while minimizing process burden.

Poster # 417

IMPROVED COORDINATION OF CARE FOR PICU PATIENTS WITH NEWLY DIAGNOSED ANTERIOR MEDIASTINAL MASSES

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Background: Anterior mediastinal (AM) masses comprise a heterogeneous group of tumors of the lung, mediastinum and pleura. Since these masses differ in type, clinical evolution and size, children may present with a spectrum of cardiorespiratory symptoms. This makes them medical emergencies that require prompt intervention, including rapid diagnosis and initiation of treatment. There were 32 Children's Mercy Hospital (CMH) PICU patients diagnosed with AM

masses from 2010-2017. The time from presentation to initiation of treatment was longer when patients required surgical biopsy (mean 153 hours) compared to those who did not (mean 58 hours).
Objectives: This project's main objective is to reduce time from admission to obtaining a diagnostic surgical specimen to less than 24 hours for all patients admitted to the PICU with newly diagnosed AM masses with a secondary objective of reducing time to initiation of chemotherapy.
Design/Method: Using Plan-Do-Study-Act quality improvement methodology, a bedside huddle (intervention #1) was implemented that requires the presence of an oncologist, intensivist, anesthesiologist, interventional radiologist, and ENT surgeon to determine the safest approach to obtain a diagnostic specimen from patients. The huddle occurs at the time of admission, or prior to 0800 if the patient presents overnight. All of the above-mentioned departments within CMH were notified/educated and agreed upon the process. In addition, a new organizational standard protocol that guides this multidisciplinary, team-based diagnostic approach is now available on the hospital's intranet (intervention #2). It can also be found within the mediastinal mass power plan that was created within our electronic medical record (intervention #3).
Results: Baseline data was collected on all patients who presented to the PICU with an AM mass from 2010-2017. The mean time for obtaining surgical diagnostic procedures in the historical group of 22 patients was 34 hours. Seven patients have been treated since implementation of these interventions in January 2018; the mean time from presentation to surgical diagnostic procedure for these patients was 16.8 hours (50.5% decrease, p=0.02). The mean time to initiate therapeutic chemotherapy has also been decreased from 155 hours to 83 hours since implementation of interventions (46% decrease, p=0.03).
Conclusion: We demonstrated that with improved communication and coordination between services, time from admission to obtaining a diagnostic surgical biopsy specimen can be safely reduced to less than 24 hours. This subsequently leads to a quicker diagnosis and thus quicker initiation of therapy, which overall lessens the risk of cardiovascular compromise due to tumor growth.

Poster # 418

FAMILY-CENTERED ROUNDING IN PEDIATRIC ONCOLOGY AND I-PASS ROUNDING IMPLEMENTATION

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Background: Family-centered rounding conducted in a patient's room with physicians, nursing and family at bedside has been recommended since 2003 by the American Academy of Pediatrics. Most published information on family-centered rounds stems from pediatric hospital medicine. There is minimal knowledge about prevalence of family centered rounding nationally in pediatric oncology.Use of a standardized handoff tool such as I-PASS in resident signout has been associated with reduction in medical errors and preventable adverse events. Adaptation of the I-PASS mnemonic to a communication tool for rounding has also been reported to decrease adverse events. To the author's knowledge, to date there has been no prior attempt to implement I-PASS rounding on a pediatric oncology unit.

Objectives: Report prevalence of family-centered rounding in pediatric oncology care. Describe the implementation of I-PASS rounding on a pediatric oncology unit.
Design/Method: A survey regarding pediatric hematology-oncology education was distributed to pediatric residency programs via REDCap with section on family-centered rounding. Using quality improvement methodology, I-PASS rounding was implemented on the pediatric oncology service with Smart AIM to improve nursing and family attendance on rounds to over 80% during first 6 months without significant increase in rounds duration, the key balancing measure.
Results: The survey was distributed to 201 pediatric residency programs with 82 respondents (40.7%) answering the family centered rounding questions. 74/82 respondents (90.2%) reported that their general pediatrics team routinely practiced family centered rounds. 61/82 respondents (74.3%) that stated their hematology-oncology team routinely practiced family centered rounds.I-PASS rounding was implemented on the pediatric inpatient unit with the first 3 PDSA cycles focused on optimizing family and nursing presence on rounds as well as building a multidisciplinary huddle to update other care team members. Over the first 6 months, nursing attendance on rounds increased from 11% to 90.7% and family attendance increased from 0% to 84.5%. Rounds duration increased from 16.15 minutes to 17.8 minutes per patient.
Conclusion: Although family-centered rounding is not as prevalent in pediatric oncology care as it is in general pediatrics, the majority of responding programs reported it being routinely practiced at their institution.Initial implementation of I-PASS rounding was highly successful at our institution. We were able to readily include nurses and families on rounds meeting our Smart AIM without significant increase in duration of rounds. Future PDSA cycles will focus on using the I-PASS mnemonic to improve communication in rounds and assess effects on adverse event rate.

Poster # 419

CHEMOTHERAPY ADMINISTRATION ON DAYS: SHIFTING THE PARADIGM

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Background: Historically, the majority of inpatient chemotherapy at Phoenix Children’s Hospital was started during night shift. Administering chemotherapy at night is less safe due to the decreased level of multidisciplinary staffing including the presence of fewer doctors and pharmacists to verify the correct drug, dose and timing for each administration of medication. To avoid chemotherapy administration errors and improve patient safety, we undertook an in-depth analysis of our processes surrounding the initiation of inpatient chemotherapy to find areas for intervention to hang chemotherapy earlier.
Objectives: To evaluate our current practices around inpatient chemotherapy administration, including clinic appointment times and processes surrounding admitting children for scheduled chemotherapy.To identify areas for improvement in our admission and hydration processes and enact changes in order to start chemotherapy as early as possibleTo analyze the efficacy of interventions intended to lead to earlier chemotherapy hang times.

Design/Method: A committee of stakeholders was created including inpatient medical director, inpatient nurses, outpatient nurses, chemotherapy pharmacists, information technology specialists and inpatient nurse practitioners. Process maps detailing the step by step process of admitting children from clinic to the inpatient floor for scheduled chemotherapy were created. We followed continuous Plan/Do/Study/Act cycles to identify areas for improvement in order to hang chemotherapy earlier. Interventions have included education of both inpatient and outpatient staff about making it a priority to hang chemotherapy earlier, providing IV hydration to patients while they await blood counts and bed assignments in clinic, streamlining the admission process, and updating pharmacy earlier with admission decisions. We then analyzed chemotherapy hang times pre- and post-interventions to evaluate efficacy.
Results: In October and November 2016, the baseline percentage of inpatient chemotherapy that started on day shift (7am to 7pm) was 42%. The average start time for the first dose of scheduled chemotherapy was 8:10pm. Two years later, with the enactment of interventions aimed at hanging chemotherapy earlier, 78.5% of scheduled inpatient chemotherapy was started on day shift and the average start time for chemotherapy was 5:56pm, more than two hours earlier.
Conclusion: We have successfully enacted several interventions to shift chemotherapy hang times earlier in the day in an effort to provide safer patient care. Through ongoing analysis and interventions, we hope to continue finding new ways to improve our inpatient chemotherapy administration processes.

Poster # 420

IMPROVING THE TIMELINESS OF CHEMOTHERAPY ADMINISTRATION PRIOR TO HEMATOPOIETIC STEM CELL TRANSPLANT

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Background: Patients who are planned for hematopoietic stem cell transplantation (HSCT) are often admitted to the bone marrow transplant (BMT) unit the day they are due to begin their conditioning regimen. Timely initiation of high dose chemotherapy during regular work hours is important for patient safety, as during the night shift there are fewer physicians available for urgent or unexpected matters, and typically no attending physician is present on the unit. Other vital members such as chemotherapy certified pharmacists are also not available overnight to help address any unforeseen chemotherapy questions or concerns. Also, when chemotherapy is administered during the night shift, patients' sleep is disrupted by frequent nursing assessments. A review of data at our institution from October 2017 to August 2018 showed that approximately one-third of our chemotherapy is started during the night shift (which begins at 19:00), and the average time from admission to start of chemotherapy is approximately seven hours. There are currently no well-defined benchmarks for timeliness of chemotherapy initiation.
Objectives: The aim of this quality improvement initiative was to decrease the percentage of patients admitted for same-day chemotherapy who start their infusion in the BMT unit after 19:00 from 30% to <10% by March 1, 2019.
Design/Method: We identified barriers to timely initiation of chemotherapy through process mapping and analysis of failures. The primary barriers were 1) late admissions (after 12pm); and 2) time from admission to preparation of chemotherapy. We addressed mechanisms to mitigate

these barriers through Plan-Do-Study-Act (PDSA) testing. Interventions included: 1) providing families specific admission times and their rationales; and 2) process for notifying pharmacy of admissions immediately upon arrival. Finally, we used standardized control charts to measure the impact of the interventions on change.
Results: From September 2018 to November 2018, the percent of late starts decreased from 30% to 8%, late admissions decreased from 32% to 17%, and average time from admission to start of chemotherapy decreased from seven to six hours.
Conclusion: The interim results of this initiative show that our two process changes have made substantial headway at achieving our aims by March 1. Ongoing data collection and analysis are underway to evaluate the sustainability of the interventions over time.

Poster # 421

IMPROVEMENT OF ORAL CHEMOTHERAPY DOSE DOCUMENTATION AFTER AN ELECTRONIC MEDICAL RECORD TRANSITION

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Background: Home-administered oral chemotherapy plays a significant role in the treatment of acute lymphoblastic leukemia (ALL) therapy. In our oncology clinic, providers document oral chemotherapy doses in the progress note and the medication is prescribed through the treatment plan in the electronic medical record (EMR). The treatment plan then populates the medication list as well as the After Visit Summary (AVS) the patient and family receive. Following a transition to a new EMR, we identified discrepancies in dose documentation. We are employing quality improvement methods to increase the accuracy of oral chemotherapy dose documentation with the global aim of improving communication among providers and with families.
Objectives: Our smart aim is to increase the documentation of the current correct dose of oral chemotherapy (methotrexate and mercaptopurine) in the progress note, medication list, treatment plan, and AVS for 95% of clinic visits for ALL patients in maintenance by June 30, 2019.
Design/Method: Baseline data were collected from time of EMR transition until first intervention. Patients in ALL maintenance therapy were identified using a report of treatment plans. Using manual chart review, we collected data assessing for matching oral chemotherapy doses in the progress note, medication list, treatment plan, and AVS. Baseline data were presented to providers, followed by Plan-Do-Study-Act (PDSA) cycles focused on group and one-on-one process discussions. Key drivers were identified to find optimal processes to target. Weekly chart review and a P chart were utilized to monitor for changes attributable to interventions.
Results: At baseline, 50 patients were found to be in the maintenance phase of therapy. There was consistency of oral chemotherapy documentation across the EMR in only 28.2% of visits. The dose was not documented in the progress note in 24.8% of visits and 53.6% of treatment plans. The medication list was inaccurate in 32.2% of visits, and the AVS was incorrect in 34.5% of visits.
Conclusion: Data collection and PDSA cycles remain ongoing. Current interventions have focused on education of clinic providers. While this is not sustainable, systematic changes have been difficult to achieve during EMR transition. We have identified several new trends,

including documentation inconsistencies when medications are held for side effects and incorrect overriding of automated EMR features. These have become new targets for improvement. Results of this ongoing work will inform our goal of improvement in communication and the potential for increased adherence to oral chemotherapy.

Poster # 422

IMPROVING DISCHARGE EDUCATION THROUGH A MULTI-TEAM MODEL IN THE PEDIATRIC ONCOLOGY UNIT

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Background: Children with cancer are particularly vulnerable to adverse events associated with transitions in care, such as hospital discharges. To minimize disease and treatment-related complications that can lead to rapid death, consensus recommendations from a Children's Oncology Group expert panel support a patient/family centered approach, in conjunction with a team-based support network, for discharge planning. Existing literature focuses on patient and provider satisfaction, and the varying methods to relay the wealth of information from provider to patient, as well as parental insight into ways to reduce errors. However, there is no data that specifically addresses parental comprehension of critical discharge instructions.
Objectives: We hypothesized that a discharge process with a multidisciplinary team would lead to safer discharge to home for our newly diagnosed pediatric oncology population. Our research aims to examine whether a quality improvement bundle with an interdisciplinary team, including pediatricians, pediatric oncologists, nurses, pharmacists, and social workers, in conjunction with take-home material, can improve parental comprehension and retention of anticipatory guidance.
Design/Method: We developed a nine question parental survey to gauge comprehension of key discharge instructions. Prior to and after our intervention, we collect surveys at the first post-hospitalization clinic visit. Our intervention includes the following multidisciplinary components: residents providing comprehensive education, nursing reviewing thermometer/fever guidelines and line care, social work providing on-call information, pharmacy reviewing medications, and the attending confirming parental understanding. We also developed English and Spanish written instructions to aid in discharge teaching, as well as a checklist for healthcare providers. Comparing pre- and post-intervention data, we will refine our strategies to improve scores on our survey instrument.
Results: In our pre-intervention data set (n=7), we found that all families had a deficiency of knowledge in at least one key area. 43% could not identify our emergency number, 43% did not know the fever threshold, 71% did not know what to do in the event of fever, and 29% were noted to have deficiencies in all key areas that also included PJP prophylaxis and anti-emetic management.
Conclusion: We have identified that our current discharge process does not result in optimal parental comprehension and/or retention of critical healthcare information. As such, we have initiated a comprehensive program to ensure consistency and improve parental knowledge of home-care instructions for children with new diagnoses of cancer. Post-intervention data collection is ongoing for at least fifteen subjects.

Poster # 423

IMPROVING INPATIENT THROUGHPUT AND UNIT EFFICIENCY VIA PROVIDER DISCHARGE ORDERING PROCESS

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Background: In pediatric hematology oncology and transplant units, there is frequently a shortage of inpatient beds, resulting in a delay of admissions from the ED and in planned admissions from the outpatient clinic for patients requiring chemotherapy or admission for acute illness.
Objectives: This Quality Improvement (QI) project aimed to improve throughput and efficiency by increasing the percentage of discharges before noon for Pediatric Hematology, Oncology, and Bone Marrow Transplant (BMT) patients on the inpatient hospital unit (LCH11) by improving the provider discharge ordering process. The outcome goal was to increase the percentage of discharges by noon without altering patient care standards. As a process measure, this QI project also attempted to increase the percentage of discharge orders written by 10am.
Design/Method: A multidisciplinary QI team convened using the Model for Improvement as the QI framework. An aim statement, key driver diagram, pareto chart, and process flow map were completed. Change ideas tested through multiple PDSA cycles included standardizing rounding times, modifying the rounding process, and anticipating discharges with pre-discharge planning meetings. Weekly annotated run charts and control charts were used to evaluate improvement.
Results: P control charts were used to analyze the percentage of the target population who were able to be discharged by noon and the percentage of provider discharge orders written by 10am. Baseline data revealed a mean percentage of patients discharged before noon of 40% with lower control limit (LCL) of 2% and upper control limit (UCL) of 80%. After implementing change ideas, the mean rose to 49% with LCL at 17% and UCL at 81%. Goal was 45%. At baseline, the percentage of discharge orders written by 10am's mean was 23%, LCL 0% and UCL 53%. After implementing change ideas, the mean rose to 29% with LCL at 0% and UCL at 57%. Goal for this process measure was 25%. This means 33 patients in the last 5 months were able to go home earlier than in the past.
Conclusion: By meeting goals, patients were less likely to have a delay in admissions for essential treatments. Utilizing QI tools, we were able to align perspectives and identify important change ideas crucial to improving our provider discharge ordering process and throughput. This project illustrates that use of QI tools and methodology can improve efficiency and the delivery of care to our vulnerable patients.

Poster # 424

SAFER PRESCRIBING OF LIQUID LORAZEPAM AND OXYCODONE IN A PEDIATRIC ONCOLOGY POPULATION

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Background: Children with cancer are often prescribed many medications for symptom management at home. Two commonly used medications, lorazepam and oxycodone, have potentially serious adverse effects if given incorrectly. These medications pose a unique risk for medication errors in pediatric patients because prescribed doses of liquid formulations may be very difficult to prepare using standard oral syringes.
Objectives: To increase the proportion of liquid lorazepam and oxycodone prescriptions for pediatric oncology and stem cell transplant patients written as a dose that can be measured and administered with standard syringes to 85% within five months.
Design/Method: A quality improvement (QI) project led by pediatric hematology-oncology fellows to improve the safety of liquid lorazepam and oxycodone for pediatric cancer patients began in February 2018. Following key stakeholder meetings, a multidisciplinary group developed a set of safe, standardized, weight band dosing guidelines along with recommended syringe sizes. Guidelines were posted at workstations in inpatient and outpatient settings in March 2018. Plan-do-study-act cycles were used to implement guidelines and increase prescriber compliance. These included: education sessions for prescribers, creation and posting of easy to use guidelines in poster and pocket-size cards, and incentives for prescriber adherence to guidelines. Prescription data was reviewed at two week intervals and used to provide feedback and modify interventions. Data was analyzed using statistical process control charts.
Results: Prior to the intervention, an average of 62% of lorazepam prescriptions and 84% of oxycodone prescriptions were written at doses that could be measured and administered with standard syringes. Following QI project implementation, prescriptions written at the recommended guidelines doses increased to 85% for lorazepam and 93% for oxycodone. Providers also began specifying syringe size on the prescription itself. The total number of liquid oxycodone and lorazepam prescriptions did not change as a result of the improvement initiative. After removal of incentives, the average number of prescriptions that were written at doses that could be easily administered with standard syringes had fallen to 75% for lorazepam and 85% for oxycodone over the subsequent 3 months.
Conclusion: A QI process providing standardized prescribing guidelines for two high risk medications can improve the proportion of prescriptions written at appropriate and safe doses that can be measured by families at home using standard syringes. However, following removal of incentives, prescribing practices trended towards baseline. Further improvements should be implemented to ensure sustainability of the positive changes.

Poster # 425

REDUCING WAITING TIME AT A PEDIATRIC NEURO-ONCOLOGY CLINIC BY OPTIMIZING PROCESS FLOW: A QI PROJECT

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Background: Efficiency is an important aspect of healthcare quality and wait time is often an important predictor of patients' satisfaction with hospital services. Long wait times may cause distress among patients and may be perceived as a substandard delivery of health care. Highly complex pediatric patients with cancer frequently need multiple appointments within a day and scheduling these appointments may be challenging, even in a well-coordinated hospital system. Using formal improvement methods can help define and implement effective solutions.
Objectives: To decrease the percent of patients who have to wait >30 minutes before room placement in the neuro-oncology (NO) clinic from 22% to 5% over the course of 9 months.
Design/Method: Wait time was defined as the time from when the patient reported to the clinic (or from the time of scheduled appointment for those who came early) to the time when the patient was placed into an exam room. Baseline data was collected over 4 weeks on all patients scheduled to see NO providers (n=556). Random sampling technique was used to collect waiting time data during the duration of the project. The process flow was studied and summarized in Failure Mode and Effect Analysis map. A pareto chart was used to identify the most common reasons for delayed room placement. A Key Driver Diagram was constructed and iterative Plan–Do-Study-Act (PDSA) cycles were used to test interventions. Run and shewart charts were used for data analysis.
Results: The study was performed over the course of 9 months. Analysis of baseline data (pareto chart) showed that provider and room availability were the two most common reasons for delayed room placement (38.4% and 30% respectively). Several PDSA improvement cycles focused on optimizing patient distribution and workload among clinic providers have been completed. The median percent of the patients who have to wait >30 minutes decreased from 22% to 10%. The median average waiting time has decreased from 22 to 11 minutes.
Conclusion: The percent of patients waiting more than 30 minutes in the waiting room was significantly reduced by implementing changes in the process flow. Several other key drivers for timely delivery of care to fully achieve 5% goal have been identified. The strategy for continued improvement has been developed and several additional interventions are underway. This project also helped us to appreciate the complexity of the whole system (hospital) and highlighted the need for interdepartmental cooperation in order to improve patient flow throughout the hospital.

Poster # 426

HEALTH LITERACY IN PARENTS OF CHILDREN WITH CANCER: COMPARISON OF HISPANICS AND NON-HISPANIC WHITES

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Background: Health literacy (HL) is the ability to process health-related information to function effectively in the healthcare environment. Thirty-six percent of U.S. adults have limited HL and Hispanics have the lowest among all racial/ethnic groups. Individuals with limited HL have higher healthcare utilization and poorer health status. Parents of children with cancer must process complex information about the disease to effectively navigate the healthcare system. Research on HL in the pediatric cancer setting is lacking.
Objectives: We assessed HL in adolescents with cancer and in Hispanic and non-Hispanic

White (NHW) parents of children with cancer. Additionally, we assessed acculturation levels in Hispanic parents and the correlation of different measures of HL among each other.
Design/Method: Sixty-one parents of children (0-17 y) with cancer and ten adolescent patients (13-17 y) at Rady Children's Hospital-San Diego were enrolled. To assess HL in parents, we used the English or Spanish form of the 1)Short-form of the Test of Functional Health Literacy Assessment(s-TOFHLA), 2)Newest Vital Sign (NVS), 3)Parental Health Literacy Activities Test(PHLAT), 4)Rapid Estimate of Adult Literacy in Medicine(REALM) or Short Assessment of Health Literacy for Spanish Adults(SAHLSA-50), and 5)Brief Health Literacy Screen (BHLS). In adolescents, we used s-TOFHLA, NVS, REALM-TeenS and BHLS. To measure acculturation, we used the Hispanic Acculturation Questionnaire(SASH). Two-sample t-tests, univariate/multivariate linear regression, and Pearson-correlation analyses were used for statistical analysis.
Results: Hispanic parents had significantly lower HL, as measured by the NVS, than NHWs ($p<0.001$). In parents, lower HL levels (measured by the NVS and S-TOFHLA) were positively correlated with older age ($p<0.001$), lower education level ($p<0.001$), informal employment ($p<0.006$), and Spanish language ($p<0.001$). Additionally, S-TOFHLA was significantly correlated with NVS ($p<0.001$), PHLAT ($p<0.001$), and REALM ($p<0.021$). In adolescents, HL (measured by NVS and S-TOFHLA) was not significantly associated with age, gender, or cancer type and lower S-TOFHLA was not significantly correlated with NVS.
Conclusion: We show significant differences in HL levels between Hispanic and NHW parents of children with cancer. NVS was correlated with s-TOFLHA and could serve as a rapid assessment of HL in the clinical setting for parents. Cancer treatment is complex, involving intensive treatments, clinical trials, and requiring advanced parental knowledge about the disease. By identifying parents and patients with limited HL, we can help them navigate cancer therapy. Future research should test culture and language-appropriate interventions, including the systematic use of teach-back, pictorial instruction, and patient navigation, to improve HL and, ultimately, cancer care in underserved children.

Poster # 427

BARRIERS AND FACILITATORS OF CLINICAL TRIAL ENROLLMENT IN A NETWORK OF PEDIATRIC ONCOLOGY CLINICS

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Background: The percentage of participants enrolling in pediatric oncology clinical trials far outnumbers that seen in medical oncology clinical trials, however a similar disparity of enrollment among racial and ethnic minority participants exists. The demographics of the St. Jude affiliate program provides an opportunity to explore if diverse racial and ethnic communities impact clinical trial enrollment. The St. Jude affiliate network spans eight institutions in the Southeastern and Midwestern regions of the United States and allows children access to St. Jude clinical trial participation close to home. The affiliates together contribute one-third of primary therapeutic enrollments on St. Jude clinical trials.
Objectives: We sought to identify specific barriers and facilitators to pediatric oncology clinical trial enrollment by exploring the perspectives of key stakeholders and to determine if the

enrollment percentage varied based on racial and ethnic demographics of each affiliate area.
Design/Method: A validated qualitative survey of medical directors was utilized to identify themes related to the process of clinical trial recruitment and retention. The transcribed results were coded by two reviewers and categorized as barriers or facilitators to clinical trial enrollment.
Results: Each affiliate medical director related that clinical trial participation is an important goal for current and future pediatric oncology patients, however several barriers were identified. The major barriers identified were transportation, complex trial design and language discordance. Transportation factors included lack of or limited transportation to the medical facility, and the problem of missing time away from employment for parents. Complex trial design was described as a barrier for the reason that multiple randomizations were often difficult to understand, study endpoints were at times unclear, or timelines were undefined. Language discordance required the additional step of obtaining a translated informed consent. Facilitators of enrollment were identified as the participant and parents having a general awareness of scientific investigation, and the importance of building a trusting relationship by involving key family members with the clinical team. There was no correlation between the racial and ethnic population of an affiliate area and the percentage of clinical trial enrollment.
Conclusion: Affiliate medical directors identified approaches to strengthen clinical trial enrollment that included access to translation services, assistance with transportation needs, pragmatic clinical trial design, education regarding clinical research and a team approach to build trust with participants and their families. The demographics of affiliate areas did not impact enrollment.

Poster # 428

CLINICAL TRIAL PARTICIPATION DIFFERS BY PARENTAL PRIMARY LANGUAGE IN PEDIATRIC LEUKEMIA PATIENTS

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Background: Disparities in enrollment on oncology clinical trials for minority populations are a concern. Currently, research exists on disparities in outcomes and clinical trial participation by race and ethnicity, but there is little research on disparities by language differences.
Objectives: The objective of this study is to examine clinical trial participation for newly diagnosed pediatric patients with leukemia based on the primary language of their parents or legal guardian.
Design/Method: We retrospectively reviewed medical records of patients less than 18 years of age with newly diagnosed leukemia who initiated treatment at Children's Healthcare of Atlanta between January 1, 2011 and December 31, 2015. Records were reviewed for parental primary language, race, ethnicity, and trial participation. Fisher's Exact Test was used to compare clinical trial participation by demographics. Unadjusted logistic regression was conducted to determine the effect that parental primary language had on clinical trial participation.
Results: Among 404 patients newly diagnosed with acute myeloid leukemia or acute lymphoblastic leukemia, we identified 294 patients after excluding patients that were 18 years or older (n=16), diagnosed when no clinical trial was open (n=69), or that were ineligible for a

clinical trial (n=25). In the sample, 68% (n=199) of the patients were White, 27% (n=80) were African American, and 5% (n=14) were other racial groups. Additionally, 22% (n=64) were Hispanic ethnicity. The majority of parents' primary language was English (82%, n=240), with 16% (n=47) Spanish and 2% (n=7) non-English, non-Spanish. Overall, 84% (n=248) of patients enrolled on a clinical trial. Eighty-five percent (n=204) of patients whose parents' primary language was English and 87% (n=41) of patients whose parents' primary language was Spanish enrolled on a clinical trial. In contrast, 57% (n=3) of patients' whose parents' primary language was non-English, non-Spanish did not enroll on a clinical trial. There was no difference in clinical trial participation by race (p=0.85), or ethnicity (p=0.74). Patients whose parents' primary language was Spanish were 1.21 (CI: 0.48-3.05, p=0.69) times more likely to participate in a clinical trial than those whose parents' primary language was English. Patients with non-English, non-Spanish speaking (primary language) parents were significantly less likely to participate in a clinical trial (OR 0.13, CI: 0.03-0.62, p=0.01) than patients with parents whose primary language was English.
Conclusion: Disparities in therapeutic clinical trial enrollment exist when parental primary language is not English or Spanish. Future directions will examine this disparity in multivariate models, and evaluate if these disparities influences treatment outcomes.

Poster # 429

BEHAVIORAL ADHERENCE PATTERNS ACROSS MINORITY AND NON-MINORITY PEDIATRIC PATIENTS WITH CANCER

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Background: Pediatric acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are highly curable diseases, with 95% of patients achieving remission within 28 days of starting induction therapy. Unfortunately, ~20% of patients relapse. It is well documented that medication adherence impacts disease morbidity and mortality. In fact, low levels of 6-mercaptopurine (6MP) metabolites in the blood, indicative of low medication adherence, have been linked to disease relapse.
Objectives: The purpose of this study was to describe the longitudinal patterns of oral 6MP adherence for minority and non-minority patients using behavioral adherence measures in a multisite cohort of pediatric patients diagnosed with ALL or LBL.
Design/Method: The sample included 139 patients across six centers aged 7-19 years and diagnosed with ALL or LBL. Patients identified as non-Hispanic/Caucasian (n = 75; 54%), Hispanic/any race (n = 48; 34.5%), or non-Hispanic/non-Caucasian (n = 16; 11.5%). Medication adherence to 6MP was examined using electronic monitoring (i.e., Medication Event Monitoring System; MEMS). This provided daily, objective information about timing of medication doses over a 15-month period.
Results: For the entire cohort, unconditional growth curve modeling indicated mean behavioral adherence rates of 84.4% at baseline, which declined to 75.2% over 15 months of follow-up. There were no differences in medication adherence for non-minority (n=76; 55%) versus minority (n=63; 45%) patients. Adherence rates for minority patients ranged between 79-85%

across the 15-month study compared to 79-88% for non-minority patients. Three trajectories of 6MP behavioral adherence were identified for the entire cohort: 1) optimally adherent (67.1% of sample): averaging 95% behavioral adherence; 2) moderately adherent (20% of sample): averaging adherence rates of 67% across 15 months; and, 3) chronically nonadherent (12.9% of sample): averaging 60% adherence at baseline and decreasing to ~40% at 15 months. It is notable that there was a higher percentage of Caucasian patients in the chronically nonadherent (58.8%) and moderately (53.8%) adherent groups compared to minority patients.
Conclusion: Our findings indicated no significant differences in rates of behavioral adherence between minority and non-minority patients across 15 months of maintenance treatment. Our results provided increased support for implementing preventative adherence promotion interventions across pediatric cancer populations regardless of race or ethnicity. Therapeutic interventions should be delivered to those patients who demonstrated problematic patterns of 6MP adherence that will ultimately place them at an increased risk for disease relapse.

Poster # 430

FLU FIGHTERS: INCREASING THE NUMBER OF FLU VACCINES IN PEDIATRIC HEMATOLOGY ONCOLOGY PATIENTS

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Background: We developed the “Flu Fighters” project to increase the number of pediatric hematology oncology patients who receive the seasonal influenza vaccine. Increasing the number of flu vaccines administered should reduce the number of patients who contract the flu, thus reducing the number of patients who face more severe complications from the flu. Preventing unnecessary flu complications potentially decreases hospitalizations and other high-cost, acute-care medical interventions.
Objectives: The outcome goal of this project was to administer the flu vaccine to at least 95% of patients with a diagnosis of leukemia or neuro-oncology (i.e. brain tumors) on active chemotherapy who were older than six months of age with no medical contraindications.
Design/Method: An interdisciplinary team reconvened to drive this quality improvement project, leveraging lessons learned from previous flu seasons. This QI project utilized the Model for Improvement as the framework, with annotated run charts to monitor the impact of changes tested. Change ideas were tested with multiple PDSA cycles. The team designed a decision support tool (flu form) for staff use when offering vaccination to outpatient pediatric hematology oncology patients. Pre-visit planning was initiated to target patients needing a flu vaccine.
Results: A p control chart was used to analyze the percentage of the target population receiving flu vaccines weekly. The goal was to vaccinate 95% of the target population with the flu shot by December 31, 2018. At baseline, the upper control limit (UCL) was 3%. The mean (or average) was 1% and the lower control limit (LCL) was 0%. After testing change ideas, improvement was demonstrated (special cause variation) increasing the UCL to 100%, mean to 95%, and LCL to 88%. We met goal by week 9, which was 7 weeks earlier than anticipated based on the previous year’s outcomes. We exceeded the target reaching 97%, also an improvement over previous years.

Conclusion: By meeting goal earlier than past flu season, this QI project ensured our most vulnerable patients were less likely to be impacted by severe flu complications. Through refining use of our decision support tool and implementing pre-visit planning, we increased the efficiency of achieving goal. This QI project illustrates that use of decision support tools and pre-visit planning along with an engaged veteran QI team can positively impact the delivery of care to vulnerable populations potentially decreasing hospitalizations and high cost interventions.

Poster # 431

VACCINATION STATUS IN PEDIATRIC CANCER SURVIVORS: IMMUNE STATUS AND KNOWLEDGE REGARDING COMPLIANCE

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Background: Recommendations for assessments of immune status and vaccination administration in childhood cancer survivors are not clear. Little data exists regarding rates of vaccination after chemotherapy, and patient/caregiver knowledge of vaccination recommendations post-chemotherapy.
Objectives: 1. Evaluate vaccination rates in a cohort of childhood cancer survivors2. Determine immunity to vaccine-preventable diseases after chemotherapy in childhood cancer survivors3. Explore knowledge and barriers to compliance to vaccination after chemotherapy in childhood cancer survivors
Design/Method: A single institution study of childhood cancer survivors treated from 1996-2018. Part 1: retrospective chart review assessing patient's vaccination status, Part 2: assessment of titers to five vaccine preventable diseases, Part 3: survey of patients/caregivers regarding knowledge/beliefs about vaccination after completion of chemotherapy
Results: A total of 120 patient charts were reviewed, of which 51% (61/120) were female. Median age at cancer diagnosis was 2 years (birth–17 years), median time since chemotherapy completion was 99 months (10-240 months). Vaccination records were available for 82% (98/120) of patients, from which 57% (56/98) of patients were up-to-date with vaccinations before chemotherapy, with 83% (81/98) of patients receiving vaccinations after chemotherapy. Median age at diagnosis was significantly less (2 vs 4 years) in patients who received vaccinations after chemotherapy compared to those who did not ($p<0.02$). Median time since chemotherapy completion was higher in those who received vaccinations after chemotherapy compared to those who did not (107 vs 60 months, $p<0.02$). Median time to receiving vaccinations post-chemotherapy was 14 months (0-192 months). Immunoglobulin titers were assessed in 27 patients, and 74% (20/27) of patients were not immune to one or more conditions tested. A lack of immunity to various pneumococcal strains was the most common deficiency noted. There was no difference in the median age at diagnosis or time since chemotherapy completion in immune versus non-immune patients.Surveys were completed by 33 patients/caregivers. One-third (11/33) of respondents were unaware that vaccinations could resume after chemotherapy completion. One-third (11/33) of respondents also felt concerned about the safety of vaccinations in their child after chemotherapy, although 88% (29/33) agreed that they would give vaccinations if recommended by their pediatrician/pediatric oncologist.
Conclusion: A majority of childhood cancer survivors resume vaccinations after chemotherapy

completion, although immunity to certain conditions remains low. Considerably variability exists in the time to receiving vaccinations after chemotherapy completion. Patients/caregivers remain uncertain if vaccinations can be given post-chemotherapy, but are willing to do so if recommended by their pediatrician/pediatric oncologist.

Poster # 432

VACCINATION STATUS IN PEDIATRIC CANCER SURVIVORS: SURVEY OF PEDIATRIC ONCOLOGY PROVIDER'S PRACTICES

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Background: Vaccination after chemotherapy is important for health maintenance in childhood cancer survivors. There are few evidence-based guidelines for vaccinations in childhood cancer survivors after chemotherapy completion, and little is known regarding pediatric oncologist's practices in this important aspect of survivorship care.
Objectives: 1. Characterize current beliefs, resources utilized and practices of pediatric oncologists for recommending giving vaccinations after a child has completed chemotherapy.
Design/Method: An anonymous electronic cross-sectional survey of pediatric oncologists conducted from August to November 2018.
Results: A total of 317 pediatric oncology providers completed the survey. A majority (97%) of respondents were pediatric oncologists, with the largest proportion 204/317 (64%) having been in clinical practice for >10 years. Over 71% (226/317) of practitioners routinely recommended giving vaccinations after chemotherapy. From this group, 67% (151/226) were using one or more published guidelines to direct their practice, with the Children's Oncology Group's Long Term Follow-up Guidelines being the most frequently used resource. Assessment of vaccine specific titers prior to resumption of vaccinations was routinely performed by 24% (55/226) of providers. Inactivated and live vaccines were most often restarted post chemotherapy at 6-12 months (69%, 157/226) and >12 months (50%, 112/226), respectively. Among providers not routinely recommending giving vaccinations post-chemotherapy (91/317), the most commonly cited reason was a deferral to the patient's primary care provider (PCP) regarding vaccination decisions (56/91), although many providers commented on a willingness to help guide the patient's PCP. Providers who were in practice >10 years were two times more likely to recommend giving vaccinations after chemotherapy compared to providers practicing <10 years as determined by chi-square analysis (OR=2.08, [1.26,3.44], p=0.004).Forty percent (127/317) of providers felt comfortable with current published guidelines regarding vaccinations for childhood cancer survivors, and 79% (250/317) of providers felt that more evidence-based guidelines would be helpful to guide patient care.
Conclusion: Pediatric oncology providers are recommending giving vaccinations to childhood cancer survivors, most commonly starting vaccinations around 6 months after chemotherapy completion. Most providers are using one or more published guidelines to direct their recommendations, although a majority feel that more evidence-based guidelines would be helpful.

Poster # 433

IMPROVING NEUROPSYCHIATRIC AND ENDOCRINE SCREENING IN SURVIVORS OF CHILDHOOD CANCER

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Background: Treatment advances have led to an ever-increasing number of childhood cancer survivors (CCSs) resulting in a higher risk for late effects which include neuropsychiatric and endocrine disorders. Baseline analyses of neuropsychiatric and endocrine screening practices in our clinic revealed poor compliance with the Children's Oncology Group Long-Term Follow-Up (LTFU) Guidelines (version 4.0). Though our brain tumor patients received excellent neuropsychiatric screening (96%), only 36% of our leukemia patients and 12.5% of our bone marrow transplant (BMT) patients underwent appropriate neuropsychiatric testing. Primary endocrine tests with poor compliance were LH/FSH/gonadal dysfunction screening in leukemia patients (0%) and bone mineral density screening in all patients (27%).
Objectives: To improve compliance with recommended neuropsychiatric testing to 80% and endocrine screening to 70% in CCSs over a period of 12 months (July 2018-June 2019).
Design/Method: Several Plan-Do-Study-Act (PDSA) ramps were completed in parallel over the first 6 months of this project. Potential barriers contributing to gaps were identified, key drivers assessed through provider surveys and key stakeholder discussions, and effective interventions were discussed. Interventions included educating all providers, physical reminders in the clinic and patient folders, frequent discussions with endocrine and neuropsychology groups to facilitate provider/resource availability, engaging our nursing staff, and navigating insurance coverage.
Results: A chart review of 60 (27 male, 33 female) CCSs was performed July-December 2018. Median age at diagnosis was 6.7 years (range 0.11-20.1 years) with a median follow-up time of 6.2 years (range 2.4-12.3 years). Diagnoses included brain tumors (n=13, 21.7%), leukemia (n=26, 43.3%), BMT (n=7, 11.7%), and solid tumors (n=14, 23.3%). Appropriate neuropsychiatric testing was performed in 88.6% of all patients (100% brain tumors, 87.5% leukemia, 75% BMT). Screening for LH/FSH/gonadal dysfunction was performed in 69% of patients (leukemia patients: 44%, improved form 0%), and for bone mineral density in 74% of patients (improved from 27%). Of those with screening completed, 95.0% (19/20) had actionable neuropsychiatric findings and 27.8% (15/54) had treatable endocrine disturbances.
Conclusion: Our quality improvement efforts have resulted in a significant improvement in screening for neuropsychiatric and endocrine late effects in CCSs. With increased screening, many actionable neuropsychiatric and endocrine disturbances were identified, leading to better comprehensive care for CCSs. Further interventions will include creation of a LTFU electronic order set to help navigate our recent transition to a new electronic health record system, additional provider surveys and reminders, and ongoing discussions with our multidisciplinary stakeholders.

Poster # 434

SURVIVORSHIP CARE PLANS AND ADHERENCE TO RECOMMENDED HEALTH BEHAVIORS IN CHILDHOOD CANCER SURVIVORS

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Background: Survivorship care plan (SCPs) are promoted as a strategy to improve care in childhood cancer survivors – a group that faces an elevated risk of medical and psychological late effects due to previous cancer therapies. In addition to an individualized treatment summary and schedule of off-therapy surveillance tests, the SCP includes recommendations regarding desirable physical activity and dietary behavior.
Objectives: To determine the impact of providing SCPs on 1) sedentary time, 2) moderate-to-vigorous physical activity, and 3) meeting the CDC recommendation of ≥5 servings of fruits and vegetables.
Design/Method: Childhood cancer survivors diagnosed with cancer at <18 years at a regional cancer center, alive and off therapy ≥1 year with no previous survivorship clinic attendance, were all given a SCP as part of a clinical trial randomizing patients to follow-up with their primary care provider or a specialty survivorship clinic. Patients (or parents of minors) completed questions regarding physical activity and diet, at baseline and 12-months post-randomization. Outcomes were analyzed using the paired t-test and McNemar's test.
Results: Overall, 96 participants (47% female) enrolled at a median of 17.1 (IQR=11.5-21.0) years of age and 5.7 (IQR=4.2-8.3) years post-diagnosis of cancer (31% leukemia, 18% lymphoma, 9% brain tumor, 29% solid tumor, 13% other). Compared to baseline responses, there was a statistically significant decrease in total weekly sedentary time (240 minutes pre- vs. 180 minutes post-SCP, t-value=-2.11, p=0.04). There were no significant differences in total weekly moderate-to-vigorous physical activity (270 minutes pre- vs. 225 minutes post-SCP, t-value=-0.36, p=0.72) or frequency of survivors meeting daily recommended servings of fruits/vegetables (30% pre- vs. 34% post-SCP, McNemar's test statistic=0.04, p=0.84). Randomization to primary care provider (N=47) or specialty survivorship clinic (N=49) was not associated with differences in health behaviors.
Conclusion: Providing SCPs was associated with a reduction in sedentary time in childhood cancer survivors. We found that many survivors did not adhere to recommendations for exercise/diet, despite being provided with a SCP. Additional interventions are needed to supplement the SCP to improve health behaviors in this high-risk population.

Poster # 435

KNOWLEDGE AND ADHERENCE TO COG SURVIVORSHIP GUIDELINES IN SURVIVORS OF CHILDHOOD CANCER IN MANITOBA

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Background: Survivors of childhood cancer are a unique population who are at risk for a wide variety of late onset adverse effects related to their therapy. With the highest incidence of diagnosis occurring before the age of 5 years, many survivors have little knowledge about their

disease, treatment, and need for long term follow-up. In the past decade this population has received increasing recognition, with many pediatric oncology centers instituting specific long term follow-up clinics in accordance with the Children's Oncology Group (COG) long-term follow-up guidelines. With the variety of clinic designs, and limitations on duration of follow-up, many survivors remain at risk for incomplete follow-up.
Objectives: This study aimed to determine if the institution of the AfterCare program at CancerCare Manitoba has increased survivor knowledge, and improved adherence to the COG follow-up guidelines. The Aftercare program included clearly defined inclusion criteria, discharge criteria, and guidelines on how to discharge a patient to a primary care physician.
Design/Method: Questionnaires, based on those used in the Childhood Cancer Survivor Study were distributed to 50 survivors involved in the AfterCare program, and 50 survivors followed prior to the programs initiation. The questionnaire responses were graded as a yes/no answer, or as follows: accurate with detail, accurate without detail, generic response with no further detail, incorrect, or unknown.
Results: Information was collected from the patient completed questionnaires and medical chart reviews; 42 responses were received (control group n=18, experimental n=24). Survivors followed in the AfterCare program, had better overall knowledge about their treatment and requirements for ongoing screening for adverse effects. Survivors also received more in person and more frequent risk reduction counseling, more guideline-driven screening for adverse effects, placed a higher importance in ongoing screening, and rated their overall health higher than those followed prior to the initiation of the AfterCare program. However, survivors followed in the AfterCare program had less trust in their primary care physician, reported higher levels of anxiety in regards to health issues related to their treatment, and in regard to future fertility. Mental health was an under met need in both groups.
Conclusion: Going forward it will be important to educate those taking over care of this population to increase survivors' trust in primary care providers. It will also be important to address anxiety in survivors, to provide appropriate mental health support, and to support knowledge transfer from parents of young survivors to the survivors themselves.

Poster # 436

RISK FACTORS FOR OBESITY IN LONGTERM SURVIVORS OF CHILDHOOD CANCER: A SINGLE CENTRE STUDY FROM INDIA

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Background: With improvement in survival of childhood cancers, late effects have become an important area of concern. Obesity is one such complication where early detection and intervention can prevent heart disease, stroke and diabetes mellitus.
Objectives: To analyze the prevalence of obesity and its risk factors among childhood cancer survivors.
Design/Method: The hospital database was mined to identify childhood cancer survivors who were ≤18 years at diagnosis, had completed treatment prior to August 2016 and were in complete remission. Out of 514 patients contacted, 400 consented for evaluation. Demographic, disease and treatment characteristics were abstracted from e-medical records. Thorough history, physical

examination and anthropometry were recorded along with and basic laboratory parameters. Obesity was defined by body mass index as per Centre for Disease Control and WHO criteria using Asia-Pacific guidelines for South Asians. Bone mineral density was studied among a subset high adiposity was defined as levels of body fat percent greater than the 85th percentile of McCarthy's reference data for each age-sex group. The risk factors studied included demographics and treatment exposure. Institutional Ethics committee approval was obtained.
Results: The median age of the study population was 17 years, 314 were males, 85% of the patients belonged to Kuppuswamy middle class and median time from treatment completion was 6 years. Primary diagnosis included hematological malignancies (301) and solid tumors (99). Treatment exposures included chemotherapy (400), radiotherapy (118), surgery (106) and stem cell transplant(9). Prevalence of obesity was 30.7%(123/400). High adiposity as observed by BMD was observed among (33/65) 51% of survivors tested. These are much higher than those reported in published Indian studies (2.6-9%). Most obese patients were survivors of acute lymphoblastic leukemia (ALL, 64/180; 35.5%), Ewing sarcoma (8/26; 30.7%), Non-hodgkin lymphoma (13/43; 30.2%) and Hodgkin lymphoma (16/58; 27.5%). Of the 64 patients with ALL who received cranial radiotherapy, 28 were obese (43.7%; p=0.04). ALL (OR=1.5; 95%CI: 0.98-2.3) and exposure to cranial RT among ALL survivors (OR=1.72; 95%CI: 0.9-3.2) were found to be significant risk factors for development of obesity. Metabolic syndrome was observed among 30%(36/123) of obese patients.
Conclusion: High prevalence of obesity and metabolic syndrome was observed among childhood cancer survivors at a median of 6 years from treatment completion. ALL and exposure to cranial radiotherapy were found to be significant risk factors for obesity. Promotion of healthy lifestyle with emphasis on nutrition, weight monitoring and physical exercise need to be prioritized to prevent/delay onset of cardio-metabolic complications in them.

Poster # 437

GO WITH THE FLOW: A FEASIBILITY STUDY TO ASSESS A YOGA PROGRAM FOR AYA SURVIVORS AND SIBLINGS

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Background: Pediatric adolescent and young adult (AYA) cancer survivors experience anxiety, fatigue, and deconditioning as on-going effects following their cancer treatment. A needs-assessment survey identified a gap in programming for the AYA survivor population within our institution. We sought to establish an off-site yoga program for AYA survivors and siblings.
Objectives: The primary objective was to assess feasibility of an off-site yoga program for AYA cancer survivors and siblings.
Design/Method: Our pediatric oncology program collaborated with a local yoga studio on an IRB-approved research project to offer a three-month weekly yoga class for AYA survivors and their siblings (ages 10-20 years). As an incentive to participate, a personal yoga-mat was provided for the enrollee at the first class attended and the participant to attend the most sessions received an I-pad mini. Families were notified of the class by mailed flyers, telephone calls, and providers during routine clinic visits. Additionally, the class was advertised on social media and by posted-flyers in exam rooms. Prior to initiation of the program, the yoga studio was provided

with an educational lecture about pediatric cancer survivorship and late-effects.
Results: A total of 111 families were identified to be potentially eligible for the study. Flyers were mailed to the most recent addresses of potential participants; three mailings were returned. All potential families were telephoned as well. Of these, 24 expressed interest and requested more information to be provided; two enrolled. Thirty families were approached during clinic visits and seven enrolled at this time. A total of nine patients enrolled and no siblings enrolled. Five were female and the average age of enrolled participants was 15 years (age range 10-20 years old). The cancer diagnoses included leukemia, lymphoma, brain cancer, and bone tumors. Four of the nine enrolled participants did not attend any classes. Of the five participants who attended, most participants (80%) attended six or more of the twelve sessions. Participants were contacted after six weeks and at twelve weeks to identify barriers to attendance. Participants reported transportation and time conflicts as the biggest challenges. Of the patients who attended the class, the overall experience was a positive one.
Conclusion: Although there is an expressed interest for program development for the AYA survivor population, feasibility remains a challenge. A future possibility may be to offer on-site yoga classes which run concurrently during clinic hours. This may address the reported challenges of transportation and time-conflicts.

Poster # 438

CARING FOR CHILDHOOD CANCER PATIENTS AND SURVIVORS: A SURVEY OF PEDIATRIC PRIMARY CARE PROVIDERS

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Background: Pediatric primary care providers (PCPs) provide episodic acute medical care for on-therapy childhood cancer patients and health maintenance care for childhood cancer survivors. However, the level of comfort expressed by PCPs in providing healthcare to these populations are lacking.
Objectives: To assess PCP comfort level in caring for on-therapy childhood cancer patients and childhood cancer survivors, and confidence in their knowledge regarding immunizations for childhood cancer survivors.
Design/Method: Cross-sectional survey of practicing pediatric PCPs in Alabama using a 23-item mailed questionnaire. PCPs provided demographic characteristics and rated their comfort level (across a 7-point Likert scale) in providing acute medical care for on-therapy childhood cancer patients and health maintenance for childhood cancer survivors. Ratings of confidence level regarding knowledge of immunizations for childhood cancer survivors were also collected. Multivariable logistic regression identified factors associated with PCP comfort (rating >5) in providing care.
Results: Response rate was 64.4% (259/402 eligible PCPs). A large proportion of PCPs reported providing episodic acute medical care to on-therapy childhood cancer patients (70%) and health maintenance care to childhood cancer survivors (91%) in their practice within the past year. Mean PCP comfort level was higher when collaborating with a pediatric oncologist in providing acute medical care for on-therapy patients and health maintenance care for childhood cancer survivors (mean rating: 6.0±1.5 and 6.4±1.3, respectively), as compared to independently

providing such care (mean rating: 4.6±1.8 and 5.0±1.7, respectively, p<0.0001). The proportion of PCPs comfortable providing care in collaboration with a pediatric oncologist was significantly higher than providing care independently: For on-therapy patients (75.6% vs 35.6%; p<0.0001); for survivors (84.9% vs. 47.8%, p<0.0001). In multivariable analysis, factors associated with PCP comfort in providing care in conjunction with a pediatric oncologist included: on-therapy patients: rural location (vs urban, Odds Ratio [OR]: 5.0, 95% Confidence Interval (CI): 1.9-13.1, p=0.03) and caring for >6 on-therapy patients in the past year (vs none, OR: 3.8, 95%CI: 1.9-7.5, p=0.0001); survivors: practice location <50 miles from pediatric oncology specialty care (vs >50 miles, OR: 2.8, 95%CI: 1.3-6.1, p=0.009). Only 30% of PCPs were confident in their knowledge about immunizations for childhood cancer survivors (mean confidence level: 4.5±1.7).
Conclusion: PCPs are significantly more comfortable in providing acute medical care for on-therapy childhood cancer patients or health maintenance care for childhood cancer survivors when collaborating with pediatric oncologists. Shared care models between PCPs and oncologists to define medical homes for these patients should be further explored.

Poster # 439

NEXT-GENERATION SEQUENCING AS A NONINVASIVE TEST TO IDENTIFY PATHOGENS IN PEDIATRIC PATIENTS

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Background: Conventional diagnostic techniques in microbiology are limited by the time needed to grow certain organisms in culture, poor sensitivity and need for invasive procedures when an infection is confined to a particular anatomic location, often precluding our ability to implement appropriate antimicrobial therapy. Next-generation sequencing (NGS) detects sequences of circulating cell-free DNA in plasma to identify pathogenic organisms in a noninvasive manner.
Objectives: To describe our pediatric experience with a commercially-available plasma NGS test for detection of clinically relevant infectious pathogens and its impact on patient care.
Design/Method: A retrospective data analysis on all pediatric patients for whom plasma NGS testing for infectious pathogens was sent for clinical purposes at Lurie Children's Hospital from December 2016 through August 2018 was performed. Results of NGS testing were available for clinical use in real-time. We reviewed the indication for NGS testing, other infectious testing utilized, and any relevant changes in the patient's care.
Results: One-hundred plasma NGS tests were sent on 79 pediatric patients with a median age of 11 years. Sixty patients (76%) were immunocompromised and 19 (24%) patients had an apparently normal immune system. Hematology, oncology and hematopoietic stem cell transplant patients accounted for 35 (44%) of the patients. NGS testing identified the same pathogen as standard microbiological testing in 38% of cases. NGS testing was also diagnostic in 17% of cases that were highly suspicious for an infectious process, yet no pathogen was otherwise identified, including a patient with refractory acute myeloid leukemia whose meningitis was diagnosed as Rothia mucilaginosa based on NGS testing. NGS testing identified only organisms deemed non-pathogenic in 15% and was negative in 30%. There were 54 invasive procedures performed to identify causative pathogens in 42 (53%) of these patients.

NGS resulted in a clinically relevant diagnosis more frequently than invasive sampling. Among the 24 procedures that identified a pathogen, NGS testing identified the same pathogen in 83%. Of the 30 procedures that were non-diagnostic, NGS testing showed a relevant pathogen in 40%, including a patient with Evan's syndrome with progressive pneumonia despite antibiotics whose NGS testing revealed Aspergillus fumigatus.
Conclusion: Plasma NGS for infectious pathogens provided clinically relevant diagnostic information in more than half of patients in whom testing was sent, including many for whom standard testing methods were non-diagnostic. The test also demonstrated potential for avoiding invasive procedures in some patients. Further evaluation of the performance characteristics of NGS testing in the clinical setting is warranted.

Poster # 440

TIME TO ANTIBIOTIC FOR FEBRILE NEUTROPENIC ONCOLOGY PATIENTS AT REGIONAL EMERGENCY DEPARTMENTS

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Background: Timely administration of antibiotics (<60min) may be associated with improved outcomes in patients with febrile neutropenia (FN). Many pediatric oncology/comprehensive cancer centers and affiliated emergency departments (referral ED) track time to antibiotic (TTA) as a quality metric. However, TTA at non-cancer center-affiliated EDs (regional ED) has not been examined previously.
Objectives: Estimate TTA in children with FN presenting at regional ED (primary outcome), and examine its association with adverse outcomes (need for >1 fluid bolus, >1 antibiotic, admission to intensive care unit, need for invasive ventilation/inotropic support within 24h of presentation), both when compared to children with FN presenting at UAB referral ED.
Design/Method: We abstracted data for pediatric oncology patients (age <21y) who were admitted for FN (temperature >100.3°F and absolute neutrophil count <500/mm3 secondary to chemotherapy) between 8/2012 and 8/2017 to UAB, either from a regional or referral ED. TTA was compared between the two cohorts (regional vs referral ED) after adjusting for demographic/disease characteristics. Delay in antibiotic administration was defined as >60min between time of triage and first dose of antibiotic. Factors associated with delay in antibiotic administration and adverse outcomes were estimated using logistic regression.
Results: 389 FN admissions occurred in 205 eligible patients (referral ED: 285 [73.3%], regional ED: 104 [26.7%]). Demographic/disease characteristics did not differ by presenting ED. The median TTA was significantly higher among children presenting at a regional ED vs. referral ED (117.5 minutes [interquartile range, IQR: 70, 170.5] vs. 46 minutes [IQR: 32.5, 67.5], p<0.0001). After adjusting for age at FN episode, gender, race, malignancy type, and year of FN episode, presentation at regional ED was associated with significantly greater odds of delay in antibiotic administration (OR=9.5, 95%CI 5.5-16.6, p<0.0001). In an analysis adjusted for delay in antibiotic administration in addition to previously mentioned variables, neither delay in antibiotic administration (OR=1.1, 95%CI 0.6-2.0, p=0.7) nor presenting ED (OR=0.8, 95%CI 0.4-1.6, p=0.6) were associated with an adverse outcome.
Conclusion: Febrile neutropenic pediatric oncology patients presenting to regional EDs have

significantly longer TTA when compared to those presenting to a referral ED at an academic children's hospital. A lack of association between TTA and adverse outcomes suggests the need for further examination of using a 60min cut-off to define delay in antibiotic administration.

Poster # 441

NOVEL PROTEOMIC BIOMARKERS FOR RISK STRATIFICATION OF CLINICAL OUTCOMES DURING FEBRILE NEUTROPENIA

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Background: Febrile neutropenia (FN) is a leading cause of hospitalization, morbidity and mortality among patients receiving chemotherapy.
Objectives: We hypothesize that select serum proteins may generate a distinctive proteomic profile early in the course of FN that could be utilized to develop sensitive FN risk-stratified predictive models that are associated with clinical outcomes.
Design/Method: or this study, we defined high-risk FN (HR-FN) clinical outcomes as those requiring either prolonged hospitalization (>7 days) or developing clinical sepsis (including bacteremia, needing ionotropic support or management in ICU). Low-risk FN (LR-FN) patients had none of above clinical outcomes. Plasma samples were isolated from peripheral blood at the time of FN presentation (n=40). For analysis, plasma samples were pooled into 5 groups of cases (HR-FN) and controls (LR-FN), matched by underlying disease and age. Proteins were prepared by polyacrylamide gel electrophoresis followed by visualization with Coomassie staining. Peptides were prepared and isolated by elution after in-gel trypsin digestion from 24 gel bands, and identified by label-free intensity based (iBAQ) mass spectrometry. The significance of group wise differences in protein abundance was assessed by Wilcoxon Mann Whitney test after adjustment for multiple testing (Benjamini-Hochberg). Principal component analysis (PCA) and unsupervised hierarchical clustering were used to visualize the results.
Results: We enrolled 25 patients, who experienced 40 FN events (range 1-3 events/patient). The median age was 11 years (range 3-19). The principal diagnosis was typical of a pediatric oncology unit, including acute leukemia (52%), CNS (22%) and bone tumors (17%). The median length of hospitalization was 4 (LR-FN) and 11 days (HR-FN) respectively. We identified 294 serum peptides after initial filtering for noise and reproducibility. Unsupervised clustering and PCA of these signals demonstrated distinct separation between LR-FN and HR-FN groups. Of these, thirty-one proteins differed significantly in abundance (FDR-adjusted p-value < 0.05). These included both clinically utilized C-reactive protein and novel markers such as beta-2-microglobulin, fibrinogen-like protein 1, intercellular adhesion molecule 1, amyloid A protein and tenascin, which were elevated in HR-FN. Whereas, protein S100-A9 was higher in the LR-FN group. Six peptides showed excellent testing characteristics by receiver operator characteristics (ROC).
Conclusion: Serum protein analysis during an FN event demonstrates a unique proteomic profile that is associated with HR clinical outcomes. These proteomic differences may represent novel biomarkers which could be useful in upfront FN risk stratification. Further development of such novel signatures may lead to timely therapeutic interventions to reduce FN-associated morbidity and mortality.

Poster # 442

OUTCOME AND DISPOSITION OF ONCOLOGY PATIENTS WITH NON-NEUTROPENIC FEVER AND POSITIVE BLOOD CULTURE

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Background: Oncology patients presenting with non-neutropenic fever are commonly treated as outpatients if well-appearing at presentation. In the subset of patients who develop positive blood cultures, some are evaluated as outpatients prior to admission whereas others are directly admitted to the inpatient unit for further care based on physician preference. In these patients, timely re-culture and antibiotic therapy is essential, yet it is unknown which management style is most efficient.
Objectives: To evaluate outcomes of non-neutropenic patients with positive blood culture first re-evaluated in clinic versus those directly admitted to an inpatient unit and develop recommendations based on data.
Design/Method: We conducted a 5-year retrospective chart review (2012-2016) identifying febrile oncology patients who later developed a positive blood culture in the outpatient setting. Mann-Whitney U test was used to compare time to antibiotics between patients first seen outpatient and those directly admitted.
Results: Of 845 non-neutropenic fever encounters managed as outpatients, there were 48 episodes (43 patients) whose initial blood cultures became positive while the child was outpatient. The median age was 3.78 years (range 0.73 - 23.63). Thirty-five (81.4%) positive cultures were from central catheters. Median time to detection were 12.78 hours (range 7.53 – 188.3). Forty-one patients (85.4%) received Ceftriaxone at onset of fever. After positive blood cultures, 77.1% (n= 37) were seen outpatient before admission, 14.6% (n=7) were directly admitted, 6.3% (n=3) received outpatient antibiotics, and 2.1% (n=1) observed outpatient without antibiotics. Median time from notification of positive culture to patient's return for antibiotics was significantly less in patients first evaluated outpatient (73 minutes, range 20 - 245) compared to those directly admitted (145 minutes, range 74 - 277), p-value 0.0214. Vital signs upon return were available for 38 episodes. Hypotension was initially documented in 3 (7.9%) patients, with one requiring vasopressor support and ICU admission. Tachycardia and tachypnea were presented in 16 (42.1%) and 2 (5%) patients, respectively. No patient required oxygen within 6 hours. No patient died within 2 weeks of the febrile episodes.
Conclusion: The majority of oncology patients with non-neutropenic fever and positive blood cultures were stable upon return. However, given significantly less time to antibiotics at our institution, we recommend that patients are evaluated outpatient prior to admission. Since most patients do well, the practice of direct admission could potentially be explored in the future if there are changes that would allow faster antibiotic administration, preferably with tools to screen for septic patients.

Poster # 443

CLINICAL VALUE OF RESPIRATORY VIRAL PANEL IN PEDIATRIC PATIENTS WITH CANCER AND FEBRILE NEUTROPENIA

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Background: Polymerase chain reaction (PCR) respiratory viral panel (RVP) testing is often used in evaluation of pediatric patients with cancer and febrile neutropenia, but the clinical implications of RVP results and their correlation with adverse outcomes such as PICU admission or hospital length of stay (LOS) have not been well characterized.
Objectives: To describe the epidemiology of RVP testing in pediatric patients with cancer and febrile neutropenia and compare rates of PICU admission or hypotension and LOS between patients with and without positive RVPs.
Design/Method: A retrospective cohort of children ages 0-21 with cancer admitted to Children's Healthcare of Atlanta for febrile neutropenia from January 2013 to June 2016 was identified. Patient age, cancer diagnosis, maximum temperature, lowest blood pressure, RVP and bacteremia, LOS, and PICU admission were abstracted. Significance was assessed using Wilcoxon rank sums, Chi-square, or Fisher's exact tests as appropriate. All outcomes were modeled using generalized estimating equations with patient as a repeated measure. All outcomes except for bacteremia were adjusted for age, sex, bacteremia, and diagnosis.
Results: The 318 patients identified had 696 total febrile neutropenia admissions. RVPs were sent in 37.6% and blood cultures were sent in 99.4% of admissions. Patients who had RVPs sent were younger (median 5.7 vs. 8.5 years, $p<0.001$) and had higher maximum temperatures (39.3° vs. 39.0°, $p=0.001$). In patients with RVPs sent, RVPs were more likely to be positive in males (57.1% vs. 43.0%, $p=0.019$) and in patients with acute lymphoblastic leukemia (ALL), even when controlled for age ($p=0.009$). There were no significant differences in maximum fever or lowest blood pressure based on RVP positivity. There was an increased likelihood of PICU admission if an RVP was sent (OR=2.24, $p=0.004$), but not with positive RVP ($p=0.55$). Bacteremia was associated with longer LOS (mean 12.86 vs. 4.8 days). RVP was not significantly associated with increased LOS, and having positive RVP and bacteremia did not increase LOS.
Conclusion: This study suggests that RVP positivity during febrile neutropenia does not impact LOS, degree of hypotension, or PICU admission, raising the question of the utility of sending this sometimes costly testing. Patients with ALL were more likely to have positive RVPs likely due to their relative lymphopenia during treatment. Research is ongoing to expand the sample size to evaluate correlations with individual viruses, including influenza. Future research should more deeply assess if RVP positivity influences physician comfort in discharging patients with febrile neutropenia.

Poster # 444

DIAGNOSTIC YIELD OF DAILY BLOOD CULTURES IN PATIENTS WITH PERSISTENT FEVER AND NEUTROPENIA

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Background: Current Infectious Disease Society of America (IDSA) guidelines suggest daily blood cultures on the first three days of fever in stable patients receiving chemotherapy with fever and neutropenia. The risks of blood cultures include unnecessary treatment of contaminants, introducing infection, and patient discomfort, though must be balanced against the need to identify bloodstream infections (BSIs) in immunosuppressed patients.
Objectives: To determine the diagnostic yield of daily blood cultures and to identify potential risk factors for bacteremia in patients hospitalized for fever and neutropenia.
Design/Method: This is a retrospective cohort study of patients with fever and neutropenia admitted to the pediatric oncology service at UMass/University Medical Center from 1/1/2011 to 12/31/2015. Chart review identified patients receiving chemotherapy admitted for fever (>38°C) and absolute neutrophil count (ANC) < 500. Individual episodes ended when the subject was afebrile for 72 hours or had ANC >500. BSI was defined as a known pathogen, or commensal organism isolated on two separate cultures. Isolates that met neither criteria were considered contaminants. The primary outcome was identification of a BSI identified after the initial blood culture.
Results: 38 patients met inclusion criteria, with 98 episodes of febrile neutropenia, resulting in 251 blood cultures; 22 cultures were positive, growing 23 total organisms. Of these, 16 cultures (17 organisms) were true BSIs, and 6 were contaminants. Overall, 14 BSIs were identified on initial blood culture, one on day 2 (Klebsiella oxytoca), and one on day 4 (Candida albicans, in a patient who developed rash and thrush). Of the contaminants, 4 were from initial blood culture, and 2 from cultures obtained after day 3 of fever. Our data showed no association between the malignancy type, ANC, height of fever, age, or history of central line infection and diagnosis of BSI. However, stage of therapy was a potentially significant risk factor in patients with leukemia, with an increased association between induction and consolidation therapy and BSI compared to maintenance or intensification.
Conclusion: Of the 98 episodes of febrile neutropenia, 2 BSIs were identified after the initial blood culture, one within 3 days of fever, and one in a patient with clinical changes. This study supports the current IDSA guidelines that suggest discontinuing daily blood cultures after day 3, unless clinical changes arise. Our study also suggests that stage of therapy may be an important predictive factor for new BSIs.

Poster # 445

PEGFILGRASTIM ADMINISTRATION TIMING AND ITS EFFECT ON FEBRILE NEUTROPENIA IN PEDIATRIC PATIENTS

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Background: Pegfilgrastim is administered at the completion of myelosuppressive chemotherapy to shorten the time that patients are neutropenic. The recommendation of waiting at least 24 hours after the completion of chemotherapy before giving pegfilgrastim stems from the possibility of stimulating and thereby exposing myeloid progenitor stem cells to the toxic environment of chemotherapy, thus prolonging neutropenia and increasing risk of febrile

neutropenia and severe infections. Several adult studies reveal a higher risk of febrile neutropenia among patients who received pegfilgrastim within 24 hours of chemotherapy compared to those who received growth factor on days 2-4 after chemotherapy, while other studies show no increased risk or are inconclusive. Currently, there are no data in pediatric malignancies that evaluate the effect of timing pegfilgrastim administration on the rates of febrile neutropenia.
Objectives: To determine if there was a difference in the prevalence of febrile neutropenia when pegfilgrastim was administered within 24 hours or greater than 24 hours after completion of chemotherapy.
Design/Method: This was an IRB-approved retrospective study conducted at Arkansas Children's Hospital. Medical records of all pediatric patients from 2010 through 2017 who received pegfilgrastim after chemotherapy for malignancy were analyzed. Eligible patients were those who had at least one dose of pegfilgrastim after chemotherapy as part of first-line treatment for any malignancy other than leukemias, with available data on the timing of pegfilgrastim administration in relation to chemotherapy administration. A total of 1,463 doses of pegfilgrastim given to 238 patients were included in the analysis.
Results: Data were obtained from medical records on 238 patients with a median age of 10 years (range 1 month-22 years). Of the 1,463 pegfilgrastim doses, 1,246 doses were given less than 24 hours and 217 were given more than 24 hours after the completion of chemotherapy. There was no statistical difference between the groups for age, cancer types, or number of chemotherapy courses. The frequency of febrile neutropenia for all cycles was 24.6% (306 events) for less than 24 hours and 24.9% (54 events) for more than 24 hours administration of pegfilgrastim. On multivariate analysis, febrile neutropenia occurrence did not differ significantly between administration times of pegfilgrastim.
Conclusion: There was no statistically significant difference in the frequency of febrile neutropenia among pediatric patients when pegfilgrastim was given less than or more than 24 hours after the completion of chemotherapy.

Poster # 446

EVALUATING EFFICACY OF AN EMPIRIC ANTIBIOTIC REGIMEN IN PEDIATRIC PATIENTS WITH FEBRILE NEUTROPENIA

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Background: Neutropenic fever in a pediatric oncology patient necessitates emergent initiation of efficacious broad spectrum antibiotic(s). The current International Pediatric Fever and Neutropenia Guideline Panel recommendation is for monotherapy with a 4th generation cephalosporin, antipseudomonal β-lactam, or carbapenem, plus a second Gram-negative agent or glycopeptide if specific indications exist. Our institution has utilized cefepime +/- vancomycin in this context for over two decades.
Objectives: We therefore sough to evaluate the degree of antibacterial coverage offered by this antibiotic combination at our institution and, if necessary, to determine whether a more efficacious combination is necessary.

Design/Method: We reviewed all blood culture isolates obtained from pediatric oncology patients at the Children's Hospital of Michigan, a large urban, academic, tertiary pediatric hospital over a 12-year period (01/01/2006-12/31/2017). Antibiotic susceptibilities for all unique isolates were recorded based upon minimum inhibitory concentration (MIC) breakpoints, reported in microgram (µg) per milliliter (mL), and subsequent interpretive categories as provided in the Clinical and Laboratory Standards Institute (CLSI)'s M100 (Performance Standards for Antimicrobial Susceptibility Testing, 28th edition), or M45 (Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria, 3rd Edition). Percentage susceptibility was calculated by dividing the number of isolates of a species susceptible to an antibiotic by the total number of isolates of that species against which that antibiotic was tested. Antibiograms were generated based on this data, and intraspecies antibiotic susceptibility comparisons made.
Results: 188 Gram negative and 509 Gram positive unique isolates were obtained, for a total of 697 (155 Gram positive and 343 total isolates, if coagulase negative Staphylococcal (CONS) species are excluded). Cefepime and meropenem both covered 95.7% of tested Gram negatives. Stenotrophomonas (Xanthomonas) maltophilia was the most resistant Gram negative organism, sensitive only to ciprofloxacin and trimethoprim/sulfamethoxazole; no antibiotic covered all Gram negatives. No antibiotic offered significantly improved coverage compared to cefepime. 96.0% of total tested Gram positives were vancomycin-susceptible (including all CONS); resistant organisms included Enterococcus faecium and Enterococcus faecalis, which both displayed 100% daptomycin susceptibility. Linezolid did not offer significantly improved coverage compared to vancomycin (98.1% vs. 96.0%, $p=0.055$), while daptomycin did (100% vs. 96.0%, $p<0.0001$). Including and excluding CONS, 46.3% and 72.5% of total Gram positive isolates were sensitive to cefepime.
Conclusion: In our population, cefepime +/- vancomycin remains an efficacious first-line empiric therapy for febrile neutropenia, with several notable minor exceptions. Unit-specific surveillance of antibiotic resistance is warranted to ensure ongoing appropriate empiric antibiotic coverage.

Poster # 447

IMPROVING THE REFERRAL PROCESS OF HEMATOLOGY/ONCOLOGY PATIENTS FROM HOME TO THE EMERGENCY DEPARTMENT

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Background: Hematology/Oncology/Transplant (HOT) patients frequently present to the emergency department (ED) from their home setting for a variety of acute reasons, including fever and neutropenia and vaso-occlusive episodes. These patients are a unique population with specific needs that are often emergent and require prompt evaluation and treatment. The process of notification and communication between HOT providers (attendings, fellows, and nurse practitioners) and ED providers at our institution was not standardized and utilized both electronic medical record (EMR) and telephone communication. This process was inefficient; HOT providers often spent a long time on hold and as a result, there were patients for whom advance notice was not provided to the ED.

Objectives: To institute a standardized method to refer established HOT patients to the ED using a Quality-Improvement based format (Plan-Do-Study-Act cycles)
Design/Method: Data were collected from HOT providers over a one month period to determine efficacy of current telephone-based method, with a goal to decrease time spent by HOT providers to triage patients by 20%. During our initial PDSA cycle, a list of key information which was essential for both types of providers was developed, including diagnosis, chief complaint, presence of a central line, initial workup, and HOT contact person with contact information. We then formatted a tool based entirely in the EMR which allows HOT providers to input referred HOT patients directly into the ED incoming patient list. PDSA cycles were coordinated with the manager of patient care operations in the ED, senior application analyst for Epic and the quality and safety manager for the HOT division.
Results: HOT providers spent a median time of 16 minutes (range: 1 - 30 minutes) on the phone to inform the ED of a patient's impending arrival. For 7% of patients, there was no verbal discussion between the HOT and ED providers. Over the first month after implementation, there were a total of 55 HOT patients referred to the ED and 93% (51/55) were referred to the ED using the EMR based tool. Providers reported < 1 minute spent on data input when using the tool.
Conclusion: The EMR-based referral tool provides autonomy for the HOT providers to contact the ED and immediate confirmation that the patient has been added, allows ED providers to quickly and accurately identify information to begin critical interventions, and prevents miscommunication. Further analysis will include impact on time to interventions, and subsequent cycles will include expansion of access to HOT nurses.

Poster # 448

RED BADGE: IMPROVING TIME TO ADMINISTRATION OF ANTIBIOTICS IN IMMUNOCOMPROMISED PATIENTS

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Background: Oncology patients are an immunocompromised population with significant potential for infectious morbidity and mortality secondary to chemotherapy-induced neutropenia and presence of central venous access. Prompt administration of antibiotics within 60 minutes to febrile patients may reduce infectious complications. Cohesive efforts between the Emergency Department, Oncology Department, nursing staff and security at Children's National Health System (CNHS) led to development of a protocol to mitigate perceived barriers: parental knowledge of risk, language barriers, registration, delay in orders and delay in administration.
Objectives: To determine if implementation of our "Red Badge" Protocol decreases time to antibiotic administration in the ED for febrile oncology patients and to further develop process for quality improvement
Design/Method: The "Red Badge" Protocol was implemented April 2016. Patients were included if treated for an oncologic diagnosis at CNHS and presented to our ED with fever between May 2016-November 2018. A LEAN process was used to identify targets for improvement resulting in the following process: 1) education of parents to call the on-call

Oncology provider for fever, who notifies the ED, 2) pre-registration of patient in the electronic medical record (EMR) and ordering of antibiotics and blood cultures prior to arrival, and 3) patient identification using a "Red Badge" to expedite triage. Patient charts are retrospectively reviewed and relevant data extracted to identify barriers to prompt antibiotic administration.
Results: Of total patient encounters (n=611), 307 (57%) were male; the median age was 6 years (IQR 3-11). 32% identified as Caucasian, 21% African American, 19% Latino, 5% Asian and 23% identified as "other" or no specification. The median time to antibiotics improved from a median 57 minutes (IQR 43-66) prior to "Red Badge" Protocol implementation to 34 minutes (IQR 16-49) for the 6 months post implementation. The average percentage of patients receiving antibiotics within 60 minutes from triage improved from 60% to 84%. Evaluated documented reasons for delay included "delay in care" (n=33), "no prearrival" (n=30), "difficult port access" (n=9), "no emla" (n=4) "did not adhere to red badge" (n=6), and "parent refusal" (n=2). Ongoing evaluation of data is used to modify process to improve time and compliance.
Conclusion: Our study indicates that implementation of a multidisciplinary, hospital-wide protocol improves the time to administration of antibiotics in the ED for febrile oncology patients. This protocol improves the identification and minimizes barriers to care for this high-risk population. Future directions involve continued strategies to overcome the barriers to timely administration of antibiotics.

Poster # 449

INTERVENTIONS TO OPTIMIZE ADMINISTRATION OF ANTIBIOTICS IN FEBRILE IMMUNOCOMPROMISED CHILDREN

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Background: Febrile immunocompromised pediatric patients are at high-risk of adverse outcomes if not promptly treated. Increased time to antibiotics (TTA) in these patients has been associated with prolonged hospital stays, more intensive care needs, and death. Reducing TTA for these patients has thus become a target of quality improvement for many organizations; current guidelines indicate empiric antibiotics should be initiated within 60 minutes from presentation.
Objectives: To reduce the time between initial assessment and antibiotic administration in febrile immunocompromised patients at our institution in each of 2 cycles over 6 months.
Design/Method: We collected data using chart review over a period of six months from March 2018 - August 2018. For each patient we identified the following: TTA in minutes, location of assessment (clinic versus emergency room), underlying diagnosis (Sickle Cell Disease and Acute Leukemia), ANC<1000 when febrile, and if pre-hospital communication was completed. Root cause analysis identified the following as institutional changes to be made in order to reach our objective of decreasing TTA in our patient population: 1. Advanced notification prior to the patient's arrival to the ED, accomplished by counseling parents during regular clinic visits to call staff prior to going to the Emergency Room. 2. Pre-registration when possible. 3. Prompt triage. 4. Prioritized diagnosis in ED on patient identification board - i.e. "Cancer Fever" so that these patients were recognized as requiring prompt care by all team members. 5. Ensured antibiotics

were available in the automated medication dispensing system (PYXIS)at all times, including broad-spectrum antibiotics (i.e. Cefepime or Zosyn) that were not previously stocked in the PYXIS and which added unnecessary time to have the medication order received, filled, and delivered by the pharmacy.
Results: Baseline data collected showed that mean TTA at our institution for high-risk Hematology/Oncology patients was 343 minutes (n=8). Data collected for cycle one demonstrated an improvement from baseline of 70% with mean TTA of 103 minutes (n=8). Data collected for cycle two demonstrated an improvement from the previous cycle by 52% with mean TTA of 49 minutes (n=7).
Conclusion: The TTA in febrile immunocompromised pediatric patients at our institution was effectively reduced via our QI protocol. Advanced ED notification, pre-registration, prompt triage, ED diagnosis prioritization, and ensuring that indicated antibiotics are readily available are key interventions in this initiative. The success at our institution suggests that the initiatives in this protocol might reduce TTA across settings.

Poster # 450

THE USE OF BLOOD CULTURE ALGORITHM TO IMPROVE CULTURE COLLECTION IN PEDIATRIC ONCOLOGY PATIENTS

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Background: Active engagement in quality improvement (QI) is an ACGME requirement, yet a national review found most had "limited participation" in QI. Twenty trainees in our pediatric hematology/oncology fellowship identified blood culture utilization as their QI priority, and used Lean Sigma to investigate a hospital-wide blood culture algorithm to improve the proportion of appropriately drawn blood cultures.
Objectives: We investigated how appropriately the algorithm was utilized on inpatient pediatric oncology patients prior to and after several interventions aimed at disseminating the algorithm to members of the care team. Our primary endpoint was to quantify the cultures drawn "inappropriately", with a goal of reduction to ≤10%.
Design/Method: All cultures drawn between July 2015-February 2018 were retrieved from the electronic health record. Fellows conducted a retrospective chart review of >750 blood culture episodes and scored these for "appropriate" or "inappropriate" per the algorithm. Fellows discussed inappropriate culture episodes with the team on-service, to provide direct feedback when the algorithm failed.
Results: Prior to algorithm application, 28.2 cultures/100 patient days were drawn on average on pediatric oncology inpatients. Following introduction of the algorithm, on average 24.1 cultures/100 patient days were drawn; this change represents a 14% decrease in rate of cultures drawn. The proportion of inappropriate culture episodes decreased from 55.53% to 11.11%. 75% of fellows provided direct feedback to inpatient teams on appropriate blood culture practices. The time from first fever to antibiotic administration did not change after application of the algorithm.
Conclusion: Conclusions: Correct application of a decision algorithm can reduce total cultures

drawn on an inpatient pediatric oncology unit. Fellow-led education of the multi-disciplinary care team decreases the rate of inappropriate cultures and provides active engagement in QI. Algorithm application did not adversely affect the time from first fever to antibiotic administration.

Poster # 451

OUTPATIENT STEP-DOWN MANAGEMENT OF LOW-RISK PEDIATRIC PATIENTS WITH FEVER AND NEUTROPENIA

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Background: Fever in the setting of chemotherapy-induced neutropenia represents a significant complication in the treatment of pediatric oncology patients, accounting for 17,000 hospitalizations and 27% of all pediatric cancer-related costs annually. At Memorial Sloan Kettering Cancer Center, approximately 365 pediatric fever and neutropenia (FN) admissions occur yearly and represent 21% of all pediatric cancer admissions. Traditionally, these patients have been managed solely on our inpatient unit until absolute neutrophil count (ANC) recovery to >=500/mm3. Previous studies have demonstrated that FN patients who meet low risk criteria can be safely discharged with subsequent outpatient management prior to ANC recovery, resulting in lower healthcare costs and improved quality of life (QOL) among patients and families.
Objectives: The aim of this quality improvement initiative is to decrease inpatient hospital census, decrease healthcare costs for pediatric FN, and improve patient and caregiver QOL.
Design/Method: We developed an algorithm for outpatient step-down management of low-risk pediatric patients with FN based on the International Pediatric Fever and Neutropenia Guideline. All patients with FN received initial inpatient treatment with intravenous antibiotics for a minimum of 48 hours. Patients who met low-risk eligibility and outpatient management criteria were discharged home on oral antibiotics until ANC increased to >=100/mm3. Patients were followed in the ambulatory clinic until ANC recovery to >=500/mm3. Readmission was required for recurrence of FN or for any clinical worsening prior to ANC recovery >=500/mm3.
Results: During the first Plan-Do-Study-Act (PDSA) cycle from September – December 2018, 58 (72.5%) of 80 pediatric admissions for FN met low-risk eligibility, and 27 (46.5%) of these patients met outpatient management criteria. Twenty (74%) of these 27 patients were discharged early according to our algorithm. In this group, median time from admission to ANC recovery >=500/mm3 was 5.6 days and median length of hospital stay was 2.5 days, saving an average of 3.1 hospital days per patient or a total of 50 inpatient hospital days. Seven eligible patients (26%) were not discharged early based on provider or family preference. Two patients who were discharged early (10%) required readmission (one for fever recurrence; one for cellulitis). There were no deaths or serious invasive infections among early discharged patients.
Conclusion: Step-down management of FN in appropriately selected low-risk pediatric oncology patients is safe and efficacious. Further PDSA cycles are required to ensure continued safety, improved QOL, and to perform cost analysis. In the future, we will incorporate upfront outpatient management of FN in appropriate low-risk patients.

Poster # 452

DECREASED CENTRAL LINE-ASSOCIATED BLOOD STREAM INFECTIONS IN ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS

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Background: Children with newly diagnosed acute lymphoblastic leukemia (ALL) require central venous access to facilitate their care. These lines are associated with a risk of central line-associated blood stream infections (CLABSIs) which can lead to increased morbidity, mortality and health care costs. Literature suggests that peripherally inserted central catheters (PICCs) have lower rates of CLABSIs compared to other central lines, especially in patients with severe neutropenia (SN) defined as an absolute neutrophil count (ANC) <500/microliter of blood. In January 2017, our hospital implemented a new protocol whereby all new ALL patients with SN received a PICC line and a mediport when ANC >/=500 (moderate-to-no neutropenia or MN) to decrease CLABSI rates. Following one month of therapy and recovery of ANC>/=500, PICCs were replaced with mediports.
Objectives: To compare the incidence of CLABSIs in the first month of therapy before and after initiating this protocol.
Design/Method: We prospectively gathered data on new ALL patients for 18 months (January 2017–July 2018) following implementation of the protocol (POST) and retrospectively for the two years prior (PRE). We used Fisher's exact test to compare the CLABSI rates between the groups.
Results: 46 and 36 new ALL patients aged 0-21 years old were treated PRE and POST, with 19 and 12 of these presenting with SN. In the PRE group, the overall CLABSI rate was 13%: 7% in those with MN and 21% in those with SN. In the PRE group, 37% of those with SN received a mediport with a CLABSI rate of 29% and 63% of SN patients received a PICC with a CLABSI rate of 17%. In the POST group, all SN patients (N=12) received a PICC with 0% rate of CLABSIs. Overall, the rate of CLABSIs in the MN group was unchanged (7.4% PRE vs 8.3% POST, p>0.99). Following implementation of this protocol, the overall incidence of CLABSIs fell from 13% to 5.6% (p=0.46) and CLABSIs in the SN group dropped from 21% to 0% (p=0.14).
Conclusion: Though none of the observed differences achieved statistical significance due to a small sample size, these preliminary findings suggest that PICCs in new ALL patients with SN may result in a lower incidence of CLABSIs in the first month of therapy. If these results are validated with more prospective data, we would recommend other centers adopting this policy to decrease the risk of CLABSIs in this population.

Poster # 453

IMPACT OF PERIPHERAL BLOOD CULTURE RESULTS IN MANAGEMENT OF CHILDREN WITH CANCER

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Background: The majority of pediatric oncology patients require central venous access for therapy which carries a risk for morbidity and mortality from line related complications in an immunocompromised host, specifically bacteremia and sepsis. Therefore, children with cancer and central venous catheters who develop a fever warrant prompt evaluation and antibiotic administration. Evidence regarding the utility of peripheral blood cultures, in addition to central blood cultures, as a part of this evaluation is lacking.
Objectives: To retrospectively evaluate and describe the impact of peripheral blood culture results for the first set of paired blood cultures taken from children with cancer who have a central venous line.
Design/Method: A retrospective evaluation of children with cancer and a positive paired blood culture (central and peripheral) was performed at Riley Hospital for Children at Indiana University Health between July 1, 2013 to June 30, 2017. The database was created using a clinical research database to extract pediatric oncology patients with positive blood culture results from an electronic infection control medical record. Then, laboratory data and medical management factors associated with positive blood culture results were extracted via electronic medical record review. Descriptive analyses of culture results and clinical data were performed and comparisons made via Fischer's exact test.
Results: There were a total of 190 paired blood cultures with at least one positive culture result from children with cancer. Of these, 106 (55.8%) were positive in both the central and peripheral culture, 57 (30%) were positive in the central culture only and 27 (14.2%) were positive in the peripheral culture only. The most common organisms isolated from positive peripheral cultures only were coagulase negative Staphylococcus species (18.5%), Streptococcus mitis (14.8%), and Capnocytophaga sputigena (11.1%). The need for intensive care unit (ICU) admission within 48 hours after the blood cultures differed by type of positivity; 28.4% for both central and peripheral, 9.3% for central only, and 0% for peripheral only (p-value <0.001). Central line removal also depended on type of positivity: 21.7% for both central and peripheral, 17.5% for central only, and 3.7% for peripheral only (p-value=0.08).
Conclusion: In this population, peripheral blood cultures provided important medical information that lead to differences in clinical decisions. Further evaluation of the impact on actual long-term medical decision making is warranted.

Poster # 454

PROCALCITONIN: A POTENTIAL ROLE IN DIFFERENTIATING INFECTION AND MALIGNANCY

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Background: Serum inflammatory markers such as C-reactive protein (CRP, normal <8.2mg/L), erythrocyte sedimentation rate (ESR, normal <23 mm/hr) and procalcitonin (PCT, normal < 0.25 ng/ml) are often used during work up of infectious and malignant processes. PCT may be less specific for malignancy, as data suggests it tends to rise predominantly with bacterial infections.

Objectives: We present three cases of pediatric cancers, each initially thought to be infectious in origin. These cases suggest that normal or minimally elevated PCT along with highly elevated CRP and/or ESR may point clinicians toward a diagnosis of neoplasm.
Design/Method: Three pediatric cases admitted to the hospital with suspected infection who were eventually diagnosed with a neoplastic process.
Results: Case 1A 7-year-old girl presented with 6 weeks of right hip pain. Lab work revealed CRP of 24.3 mg/L and PCT of 0.06 ng/ml. MRI was concerning for osteomyelitis but did not improve with antibiotics. Labs on readmission showed a CRP of 25.7 mg/L, ESR 60 mm/hr, and PCT 0.22 ng/ml. Surgical biopsy and pathology confirmed Pre-B Cell ALL. Case 2A 3-year-old boy presented to the ED with 3-4 weeks of hip pain. Admission labs included an ESR of 77 mm/hg, CRP of 207.5 mg/L and PCT of 0.36 ng/ml. MRI was concerning for septic joint and osteomyelitis, but he did not improve on antibiotics. On readmission, ESR was 110 mm/hr, CRP 239.9 mg/L and PCT 1.42 ng/ml. CT showed a calcified adrenal mass and spinal enhancement. Biopsy of the mass and bone marrow revealed neuroblastoma.Case 3A 16-year-old boy presented with lymphadenopathy, nausea, vomiting, and fever, already on oral antibiotics for suspected infectious lymphadenitis. On admission, labs revealed a leukocytosis of 31,550 with 84% granulocytes and a normocytic anemia. ESR was >120mm/hr, CRP was 195.4 mg/L, and PCT was 0.05 ng/ml. Biopsies of a sternal lesion and an axillary lymph node were consistent with nodular sclerosing Hodgkin lymphoma.
Conclusion: We describe three pediatric oncology cases with elevated ESR and CRP, and low or normal PCT levels. The low PCT supports previous studies, which have demonstrated lower PCT levels in malignancies. PCT has been shown to rise in bacterial infection. The potential use of PCT to help differentiate malignancy from infection especially in bony lesions suspected to be osteomyelitis and adenopathy may be worth a larger study.

Poster # 455

COMPARISON OF BLOOD STREAM INFECTIONS IN PAEDIATRIC HEM-ONCOLOGY AND GENERAL PAEDIATRIC PATIENTS

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Background: Periodic review of blood stream infections is required to optimise antibiotic strategies in children on cancer chemotherapy, as infections are a major cause of morbidity and mortality in children. It is important to compare the infection profile of this group with that of general paediatrics, as the latter represent the spectrum of infections in the community, from where the immuno-compromised also acquire most of their infections.
Objectives: This study was done compare the bacteriological profile of blood stream infections in children on cancer chemotherapy with immuno-competent children.
Design/Method: Blood cultures from Pediatric Hem-Oncology and general paediatrics (GP) patients from June 2016 to May 2017 were analyzed for spectrum of infection and antibiotic susceptibility
Results: 2117 blood cultures were performed, 1000 from PHO and 1117 GP. 54 (5.4%) and 42 (4%) of the blood cultures were positive in PHO and GP respectively. Gram-negative to gram-positive ratio in PHO was 54:46 and in GP was 57:43. In PHO Klebsiella, NFGNB,

Pseudomonas and E.coli contributed to 80% of the gram-negative isolates. In GP, NFGNB and S.typhi comprised 76% of the gram-negative isolates. 77% of gram-positive isolates in PHO were CONS and 64% in GP were S.pneumoniae. All isolates of E.coli in both groups were ESBL. In PHO, 67% Klebsiella and 54% NFGNB were ESBL compared to 100% and 49% in GP. CRO was seen in 46% NFGNB in PHO compared to 27% NFGNB and in 17% E.coli. NFGNB in PHO showed poor antibiotic sensitivity with amikacin having the highest sensitivity of 61.5%. All the other gram-negative isolates in PHO except one pan-resistant Pseudomonas, were sensitive to amikacin. Two of nine S.aureas were MRSA, and 2 of 4 Enterococci were VRE, distributed equally between the groups.
Conclusion: High rates of antibiotic resistance were seen in both hem-oncology patients and in general paediatric patients. This calls for judicious use of antibiotics both in the immunocompromised and immunocompetent children as well as periodic auditing.

Poster # 456

CLOSTRIDIUM DIFFICILE INFECTION IN PEDIATRIC CANCER: AN INSIGHT FROM KIDS' INPATIENT DATABASE

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Background: Patients with cancer are predisposed to Clostridium Difficile Infection (CDI) due to their immune compromised state, medications that disrupt the gut microbiota, and frequent health care exposures. Despite this association, the national rate and clinical outcome of CDI among pediatric cancer patients is unknown.
Objectives: Define CDI incidence and health outcomes nationally among pediatric oncology patients in the United States (U.S.).
Design/Method: We performed a retrospective cohort analysis of the Health Cost and Utilization Project (HCUP) - Kids' Inpatient 2000-2012 Database (KID) for patient ≤ 20 years. Patients were included if they had a medical diagnosis of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), lymphomas (Hodgkin and non-Hodgkin), brain tumor, neuroblastoma, bone tumors (Ewing's Sarcoma and Osteosarcoma) and hepatoblastoma. Encounters for chemotherapy were excluded. Patients with a principal diagnosis of CDI (ICD-9-CM code 008.45) were identified. We performed descriptive statistics to characterize the cohort in terms of personal demographic factors (age, race, sex, insurance type), and hospital characteristics (size, region, teaching status, and urban or rural location). Data weights were applied to sampled patients to provide national estimates. The in-hospital mortality rate, total charges, and hospital length of stay (LOS) were compared between cancer patients with and without CDI using bivariable analyses.
Results: A total of 353,448 admissions were included for analysis. The cohort comprised of 7,019 patients with a CDI, for an overall incidence 20 per 1,000 admissions. CDI incidence increased over the study period, peaking in 2012 (29 per 1,000 admissions). The median age was 7 years, most patients were male (53.5%), and whites (56%) were more commonly affected than other races. CDI were most often reported in large hospitals (62.7%), urban teaching settings (93.3%), and the south and west regions (62.6%) of the U.S. Patients frequently were covered by private insurance (50.3%). AML was the most common diagnosis associated with CDI (4.5%).

Compared to patient without CDI, patients with CDI had significantly higher mortality rates (3.4% vs. 1.3%, $p < 0.0001$), longer median LOS (11 days vs. 4 days, $p < 0.0001$) and higher median total charges per hospitalization ($65,000 vs $19,600). The total CDI-associated net charge was $730,912,107.
Conclusion: CDI incidence increased nationally among pediatric oncology patients admitted to U.S. hospitals from 2000-2012 and is significantly associated with increased mortality and hospital LOS. Attention should be directed towards efforts to minimize risk of these serious infections.

Poster # 457

HELPING OUR PEERS ENDURE STRESS (HOPES) – NEW DATA FOR A CISM-BASED PEER SUPPORT TEAM

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Background: Repeated exposure to suffering and trauma likely increases the rate of burnout among clinical staff in Pediatric Hematology / Oncology (PHO). While the Institute of Medicine has recommended that some response be provided to address the needs of healthcare workers exposed to dying children, the responses that have been developed have been highly variable, largely under-studied and report varying degrees of success.
Objectives: The HOPES team (Helping Our Peers Endure Stress) is an all-volunteer, multidisciplinary team within the division of PHO that provides peer support utilizing the Critical Incident Stress Management (CISM) model. We hypothesize that the availability of the HOPES team will increase resilience and decrease burnout through improved awareness and destigmatization of burnout, and the provision of peer-support services. We report baseline burnout, resilience, compassion satisfaction and secondary trauma in PHO staff, and describe the acceptance and utilization of the HOPES team.
Design/Method: All staff members with direct patient interaction within the division of PHO were sent an anonymous link to complete the ProQOLv5 and Brief Resilience Scale, validated assessments of resilience, compassion fatigue, burnout and satisfaction. Survey participants were also asked the number of times they had experienced particular critical incidents, as well as their perceived level of distress after dealing with traumatic events.
Results: Ninety two (61%) of the 150 pre-needs assessment surveys were completed. Overall, physicians were found to have statistically significant higher rates of burnout versus nursing staff. An inverse relationship was found between years in medicine, as well as years in PHO, and burnout scores. We also found that as years in both medicine and PHO increased, resilience increased. Survey responders aged 50-80 years were had higher compassion satisfaction that those 20-35 years. Rates of secondary trauma were higher in those experiencing >3 critical incidents in the past 12 months versus those experiencing 1-2. In its first 9 months, the HOPES team has run 28 interventions: 17 1:1 sessions, 10 debriefings and 1 defusing. Staff response to the HOPES interventions has been overwhelmingly positive.
Conclusion: Staff members working in PHO repeatedly witness suffering and trauma, making them vulnerable to secondary trauma and burnout. Those who have spent more time in their careers are more resilient, which may serve as a protective measure against burnout. The HOPES

team demonstrates the feasibility of utilizing an all-volunteer, CISM-based, peer support team within PHO to address critical incident stress, with the potential to impact burnout and compassion fatigue.

Poster # 458

AN EVALUATION OF PSYCHOSOCIAL NEEDS AMONG HEALTHCARE PROVIDERS IN VIETNAM

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Background: Approximately 84% of childhood cancers occur in low- and middle-income countries (LMICs) with ~300,000 cases diagnosed globally every year. Vietnam has enjoyed rapid economic development yet its access to mental health services lacks this same growth. In Vietnam, physician/nurse to patient ratios are much higher with lower resources compared to the United States. Concurrently, compassion fatigue and burnout are a growing concern in pediatric hematology-oncology providers affecting patient care.
Objectives: Our global aim was to evaluate the positive and negative effects of providing patient care in southern Vietnamese pediatric hematology-oncology physicians and nurses, to identify which medical profession is more susceptible to these effects, and to provide an individualized intervention. Smart aim: 50% of participants will experience an increase in compassion satisfaction and resilience and a decrease in burnout scale and secondary traumatic stress after 6 months with a monthly longitudinal intervention.
Design/Method: Compassion satisfaction, burnout and secondary traumatic stress was measured using the Professional Quality of Life (PROQOL) survey. Resilience was measured using the CD-RISC 10 Scale. We educated these providers about compassion fatigue through didactic and interactive discussions and provided an intervention via the reflective writing tool, Project 6-55.
Results: Our study found that nurses (n=13) scored highest on compassion satisfaction and burnout with 33.3% and 46.2% in the high range, respectively. For secondary traumatic stress, physicians (n=6) scored the highest with 40% in the high range. When compared to the general population of the U.S., resilience scores of both the nurses (n=12) and physicians (n=8) group fell to the bottom quarter, however, these scores rose to higher quarters when compared to nursing students in China. In addition, compassion satisfaction was positively correlated with resilience in the nursing group (p=0.005). The physicians (n=3) had the most positive change in attitude towards Project 6-55 as a tool for personal growth with 100% reporting an increase in favorability. A self-wellness opinion survey was also administered to determine what other proven stress relief activities would be helpful in order to design an individualized longitudinal intervention. Regular breaks and relaxation rooms/massages/meditation were ranked highest for both physicians (n=8) and nurses (n=12).
Conclusion: Lower resilience when compared to the United States, compassion fatigue and burnout are challenges that healthcare providers in Southern Vietnam face. Cultivating resilience as well as designing an individualized stress relief program appears to be beneficial for provider health, and in turn, may positively impact patient health.

Poster # 459

FEASIBILITY OF INPATIENT LOW-DOSE KETAMINE INFUSION FOR PAIN CONTROL IN HEMATOLOGY/ONCOLOGY PATIENTS

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Background: Although opioids remain the mainstay of pain management in the inpatient setting for pediatric hematology/oncology (PHO) patients, patients with chronic pain may be inadequately treated with side effects at increasing doses. Ketamine has been reported effective due to antagonism of the N-methyl-D-aspartate (NMDA) receptor which is up-regulated with chronic opioid usage. We therefore designed a protocol for utilization of low-dose ketamine infusion (LDKI) for inpatients with inadequate pain control with intravenous opioids.
Objectives: The primary aim was to determine feasibility and safety of implementing LDKI in the inpatient setting for PHO patients based on ability to administer LDKI on the PHO ward without notable side effects leading to infusion discontinuation. We secondarily hypothesized that LDKI would improve pain scores without need for opioid augmentation.
Design/Method: We retrospectively reviewed patients at UCSF Benioff Children's Hospital Oakland with a hematology/oncology diagnosis who received LDKI after protocol initiation March 2014 through October 2017 when institutional review board approval was obtained. The electronic health record was mined for patient demographics, opioid utilization per 24 hours in morphine equivalents, vital signs, pain scores, and subjective assessment. Data were collected for 24 hours prior to LDKI initiation and then for the first five days on the LDKI. Vital sign data were collected in 4-hour increments and averaged over 24-hour periods. We looked for side effects from the LDKI leading to decrease or discontinuation of the LDKI, benzodiazepine usage to treat LDKI side effects, and development of hypertension.
Results: Eighteen patients (11 male, 7 sickle cell, 11 oncology) with a median age of 14.6 years (interquartile range [IQR] 12.3 to 18.4) received LDKI for a median 7.5 days (IQR 4-12) at a median dose of 1.0 mcg/kg/min (IQR 1.0-2.5). No patient developed hypertension or discontinued the LDKI secondary to side effects. Five patients had side effects including dream-like feeling, blurry vision, and drowsiness, one of which required dose reduction. Median opioid doses (mg/kg/h morphine equivalents) remained statistically unchanged prior to the initiation of LDKI (median 0.04 mg/kg/h, IQR 0.01-0.08) through the first five days of LDKI (median 0.05 mg/kg/h, IQR 0.02-0.09). Pain scores (non-parametric) were a median of 4.8 (IQR 2.9-6.6) prior to LDKI with a median of 2.4 (IQR 0-4.4) for the five days thereafter (non-significant daily change based on Friedman test for repeated measures).
Conclusion: LDKI was feasible and safe for hematology/oncology patients. Utilization of LDKI allowed for stabilization of opioid dosing without impacting pain scores.

Poster # 460

USE OF VIRTUAL REALITY (VR) DURING MEDIPORT ACCESSING IN PEDIATRIC HEMATOLOGY ONCOLOGY PATIENTS

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Background: Pain and anxiety are prevalent symptoms among pediatric hematology oncology (PHO) patients, in part due to the underlying nature of their disease but also due to painful medical procedures. Use of VR as a potential innovative, non-invasive distraction technique has shown benefit in other settings.
Objectives: To test the usability and acceptability of immersive VR technology in PHO patients during Mediport access. Secondary objectives included: 1. Determining feasibility and acceptability of VR by nurses and child life specialists and 2. Piloting VR experience for future studies examining its efficacy in minimizing procedural pain and anxiety.
Design/Method: Patients age 5 -18 years undergoing outpatient Mediport access were approached for enrollment. Patients completed pre/post-simulator sickness questionnaires and validated self-reported measures of pain and anxiety. Patients aged 5-8 used the Faces Pain Scale-Revised and Children's Fear Scale. Patients 9 and older used Visual Analog Scales. Patients engaged in a 14-minute VR experience called Aqua LookUp using a stereoscopic head mounted display and hand controller. Use of topical numbing agents was allowed. The accessing nurse and child life specialist completed post- intervention surveys.
Results: Twenty-three patients were enrolled (13 males) with a median age of 9 years (range: 5-18). Six patients did not complete the intervention. Reasons included removal of headset once sterilization started (n=2), not wanting to put the headset on (n=1), not wanting to wear the required Bouffant cap (n=1), pre-simulator headache (n=1) and device malfunction (n=1). Only two of six patients aged 5-7 years completed the intervention. Of the 17 patients who used VR, 82.3% would want to play again and 66.7% reported playing Aqua made them feel better about coming to the hospital. Nurses reported no issues with sterility. In 15 of the 17 patient experiences, staff reported they would want to use VR again. All patients were able to answer self-validated questionnaires without parental proxy. Moderate to severe anxiety and pain regarding accessing were reported in eight and four patients respectively but in only one patient each while using VR. No major side effects were reported
Conclusion: The use of VR during Mediport accessing is feasible in a clinic setting and acceptable to patients and staff. It was well tolerated. Children age 5-7 were less accepting of the technology. Examining the role of VR as a means of distraction to reduce pain and anxiety is feasible and further study is warranted to determine its potential efficacy in reducing procedural pain and anxiety.

Poster # 461

A SINGLE-CENTER EXPERIENCE OFFERING ECMO SUPPORT TO CHILDREN WITH ONCOLOGIC DISEASE

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Background: As ECMO practice and technologies continue to evolve, concepts of indications/ contraindications and judgments of candidacy evolve in concert. Historically, adult and pediatric patients with active malignancy at the time of ECMO support have had poor survival.

Objectives: To review our institutional experience with the use of ECMO to support children with oncologic disease acutely suffering from refractory respiratory failure or shock.
Design/Method: We reviewed our ECMO Program consult list (Jan, 2014 - Dec, 2016) to identify all patients with active oncologic disease who were evaluated for ECMO. Medical records of identified patients were reviewed to determine decisions of candidacy based on ECMO consultant notes. The institutional pediatric ECMO patient list and individual patients' medical records provided information on cannulation and patient outcome. Data collected included underlying oncologic diagnosis, acute indication for ECMO, contraindications, reason(s) ECMO was not offered, and survival for ECMO and non-ECMO supported patients.
Results: Thirteen patients with oncologic diagnoses were evaluated for ECMO support, representing 28% of all ECMO consults. The ECMO consultation included evaluation of the severity of respiratory failure/shock, indications for procedure, and frank conversations with treating Pediatric Oncologists regarding underlying diagnosis/prognosis. Whenever possible, oncologists participated in the ECMO conversation with families. Of these patients, 8 (62%) were deemed ECMO candidates. Poor candidacy was based on terminal/refractory malignancy (n = 1), disseminated fungal infection (n = 1), subacute MODS (n = 2), and mechanical ventilation > 20 d (n = 1). No patient who was deemed a poor candidate was offered ECMO, and none survived. Of the 8 deemed candidates but not cannulated, 1 improved, 1 developed contraindications, and 1 family declined. Patients were supported with ECMO for shock (n = 4) and respiratory failure (n = 1). All 5 (100%) ECMO patients survived and are alive. During this period, children with oncologic diagnoses accounted for 30% of our total pediatric non-cardiac ECMO patients.
Conclusion: Although this case series is too small to support definitive conclusions regarding the role of ECMO in critically ill children with active cancer, the 100% survival rate at our center is notable and suggests careful selection enriches the ECMO population with patients likely to benefit. The balancing consideration is that potential beneficiaries may be excluded by a selection process that is too restrictive. To date there are no official ECMO criteria for pediatric cancer patients but our experience has motivated the development of such as an important feature of our ECMO program.

Poster # 462

IMPROVING ADHERENCE TO ORAL CHEMOTHERAPY IN ALL WITH MOTIVATIONAL INTERVIEWING: A FEASIBILITY PILOT

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Background: Non-adherence to oral chemotherapy during the maintenance phase of treatment for patients with acute lymphoblastic leukemia (ALL) is an instigating factor for relapse. Motivational interviewing (MI) is an individualized psychotherapeutic intervention that can evoke behavior change as previously shown in pediatric obesity, diabetes, and asthma.
Objectives: To assess the feasibility and acceptability of delivering a single MI session during a maintenance outpatient visit to English- and Spanish-speaking caregivers of children with ALL and adolescent patients with ALL.

Design/Method: Study personnel, including three English-speaking and two English- and Spanish-speaking practitioners, received ongoing training until they reached expert-level MI proficiency as described in the Motivational Interviewing Treatment Integrity Coding Manual (MITI) 4.2.1. From 06/2017 to 07/2018, 85 consecutive English- or Spanish-speaking caregivers of pediatric patients (ages 0-12) and adolescent patients (ages 12-14) with ALL in the maintenance phase of therapy were approached to participate in this 2:1 randomized pilot to either receive an individualized MI session or educational materials (without MI) during a regularly scheduled outpatient visit. Both the 20-60 minute MI individualized recorded sessions and the educational handout, in English or Spanish, focused on strategies to decrease barriers and increase motivation toward 6-Mercaptopurine (6-MP) adherence. Using a 6-point Likert-type scale, participants reported the acceptability of MI (1 = strongly disagree to 6 = strongly agree), with higher scores indicating greater acceptability of the intervention in either language. This pilot study focused on the feasibility and acceptability of MI, not the group differences. Caregivers also completed the 6-MP Adherence Questionnaire, a measure developed for this study, to assess understanding of 6-MP administration, taking behavior, knowledge, and delegation.
Results: Approached eligible participants included 69 English- and 16 Spanish-speaking caregivers and adolescent patients with ALL with 98% of both groups consenting and 55 (66%) randomized to MI. English- and Spanish-speaking caregivers had an average of 11.33±2.19 and 14.10±2.68 years of formal education, respectively. 6-MP knowledge fell into three categories: conceptual (46.7%), concrete (44.4%), or no knowledge/irrelevant response (8.9%). More than 75% of participants rated both English and Spanish MI sessions as acceptable interventions for improving adherence to oral medication.
Conclusion: This pilot study demonstrates that MI is a feasible interventional strategy in a real-life outpatient setting. It was acceptable to both English- and Spanish-speaking caregivers and adolescent patients with ALL. Randomized trials, with objective measures of adherence, are needed to determine the efficacy of MI in enhancing adherence to oral chemotherapy.

Poster # 463

FACTORS CONTRIBUTING TO PSYCHOSOCIAL DISTRESS IN CAREGIVERS OF CHILDREN WITH NEWLY DIAGNOSED CANCER

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Background: Children with newly diagnosed cancer and their family caregivers experience significant psychological distress, particularly post-traumatic stress symptoms (PTSS). Contextual factors, such as health literacy (HL), acculturation, ethnicity, language and socio-economic status (SES), contribute to the patient's ability to function effectively when faced with a cancer diagnosis. The association between HL and psychological distress in caregivers of children with cancer has not been well studied.
Objectives: To assess the role of contextual factors among Hispanics and non-Hispanics, particularly HL and acculturation, on PTSS in family caregivers of children with newly

diagnosed cancer.
Design/Method: Caregivers of children aged 0-17 y with a new diagnosis of cancer (n=61) were recruited between August 2017 and November 2018. HL, acculturation and PTSS were measured using the Newest Vital Sign, Short Acculturation Scale for Hispanics (SASH) and Impact of Events Scale-Revised (IES-R), respectively. The IES-R has three sub-scales: intrusion, hyperarousal and avoidance. Two-sample t-tests, univariate and multivariate linear regression were used for statistical analyses.
Results: Seventy-four percent of caregivers had adequate HL. Hispanics (n=32) had lower levels of HL compared to non-Hispanics (n=29), $p<0.001$. Both Hispanics and non-Hispanics reported high levels of PTSS (mean IES-R=31.2). Low HL ($p=0.010$), low acculturation ($p=0.029$), Hispanic ethnicity ($p=0.046$) and Spanish language ($p=0.049$) were associated with higher PTSS. Low SES ($p=0.032$), low acculturation ($p=0.033$), Hispanic ethnicity ($p=0.019$) and Spanish language ($p=0.034$) were associated with increased avoidance PTSS, characterized by numbness and diminished emotions. Likewise, low acculturation ($p=0.024$), Hispanic ethnicity ($p=0.050$) and Spanish language ($p=0.037$) were associated with increased hyperarousal PTSS, characterized by a state of heightened vigilance.
Conclusion: Our results show that caregivers of children with newly diagnosed cancer experience significant PTSS. Additionally, limited English proficiency and lower levels of HL and acculturation were correlated with increased PTSS. These findings underscore the importance of providing comprehensive psychosocial support to individuals with limited English-proficiency or low HL and acculturation, who may need supplementary resources and education about their child's diagnosis at an appropriate HL level. Given that Hispanic and Spanish-speaking caregivers were more likely to endorse avoidance and hyperarousal PTSS, this study may inform future psychosocial interventions tailored to the cultural and language needs of caregivers.

Poster # 464

RELIGIOUSNESS AND SPIRITUALITY AMONG ADOLESCENTS WITH CANCER

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Background: Understanding the religious/spiritual needs of adolescents with cancer and their families is imperative to providing goal congruent and effective care.
Objectives: To describe the religious/spiritual beliefs and needs of adolescents with cancer and examine relationship of Belief in spiritual healing with quality of life.
Design/Method: As part of a multi-site randomized clinical trial, 84 adolescents with cancer completed the Brief Multidimensional Measurement of Religiousness/Spirituality (BMMRS-revised) and the PROMIS-Brief measures of symptoms of anxiety and depression.
Results: Adolescents' (N=84) mean age 16.9 years (range ≥14-<21 years), 61% female, 81% Caucasian. 88% considered themselves religious/spiritual, 12% did not. 42% of adolescents reported they had a religious or spiritual experience that changed their life. When asked did they believe they will be spiritually healed from cancer by a miracle, 46% reported, Yes. Adolescents who believe in a miracle cure for their cancer were significantly more likely to have no anxiety, than those who did not believe (28.2% vs. 7.3%, $p=0.0186$) and were significantly more likely to

have no depression, than those who did not believe (46.2% vs. 24.4%, p=0.0414). 7% believed their cancer was a punishment from God. The belief cancer was a punishment from God was not associated with anxiety or depression.
Conclusion: Belief in spiritual healing protected adolescents with cancer from symptoms of anxiety and depression. Study findings support the value of spiritual assessment and care as a fundamental component of high quality psychosocial and spiritual care in AYA oncology. Integrated religious/spiritual care to meet the religious/spiritual needs of adolescents living with cancer provides support to the entire family and should be standard of care in pediatric hospitals, consistent with policy recommendations that spiritual care is part of holistic care for AYA patients with cancer.

Poster # 465

SHARED SPIRITUAL BELIEFS BETWEEN ADOLESCENTS WITH CANCER AND THEIR FAMILIES

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Background: FAmily CEntered (FACE) Advanced Care Planning (ACP) helps to inform family members and surrogate decision makers of patients' end of life care wishes.
Objectives: To understand if religious well-being and beliefs of adolescents with cancer are congruent with the religious well-being and beliefs of their families.
Design/Method: As part of multi-site (3) randomized controlled trial, the Spiritual Well-Being Scale of the Functional Assessment of Chronic Illness Therapy-Version 4 (FACIT Sp EX 4) was completed by 84 teens with cancer and 84 family members at baseline. Through the FACIT Sp EX 4, spiritual beliefs about the adolescent's cancer were assessed from both the family member and adolescents individually as well as total family congruence on religious/spiritual well-being. Statistical significance was analyzed using the Prevalence Adjusted and Bias Adjusted Kappa (PABAK).
Results: Adolescents (84) had a mean age of 16.9 years (range 14-20), and were 61% female and 81% Caucasian. Religious/spiritual classifications were identified as: Catholic (11), Protestant (60), Mormon (2), None/Atheist (7), and Other (3). Item analysis of agreement between spiritual belief of adolescents and families were assessed using a kappa statistic. Total agreement of "I have a reason for living," "I feel loved," and "I feel hopeful," received >90% congruence between adolescents and family member(s) with an Excellent PABAK score. Total agreement of "I feel peaceful," "I am able to reach down deep into myself for comfort," "I am able to forgive others for any harm they have ever caused me," and "I feel connected to a higher power (or God)," received <68% congruence with either a Fair or Poor PABAK score. Hypothesized social determinants of spiritual well-being for families were non-significant for gender, race, education, and poverty level.
Conclusion: When referencing spiritual well-being in the context of cancer, there is differentiation between connection to a higher power, forgiveness, comfort, and peacefulness. Findings confirmed family congruence in hopefulness despite prognosis.

Poster # 466

RELIGION'S AND SPIRITUALITY'S RELATIONSHIP TO DISTRESS IN PARENTS OF CHILDREN DIAGNOSED WITH CANCER

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Background: Parents of children diagnosed with cancer are known to exhibit high levels of distress and lower quality of life. Little is known about how parents manage the stress of caring for a child diagnosed with cancer. Parents of children with serious medical illness in other studies have self-reported that spiritual and religious beliefs are important for coping and decision making. We sought to determine if spiritual and religious beliefs are associated with distress in parents of children with cancer.
Objectives: The study has 2 objectives: First, to describe and explore the association between religiosity/spirituality and levels of distress in a sample of parents of newly diagnosed oncology patients during inpatient admission. Second, to determine if levels of distress are associated with levels of religious coping specifically, and with religiosity more generally, in the context of individual levels of psychological resilience and social support.
Design/Method: We are conducting a prospective cross-sectional study of parents with children diagnosed with cancer in the previous 6 months. Eligible parents completed the Kessler Scale of Distress as the outcome of interest. Religious coping (Religious-COPE scale), religiosity (Scale of Religiosity), resilience (Connor-Davidson Resiliency Scale), and social support (Krauss) were measured as predictors of interest. All measures were previously validated. We conducted a multivariable regression of the association between positive religious coping (secure relationship with the sacred), negative religious coping (tension/struggle/conflict with the sacred) and level of distress.
Results: At the time of submission, the study has reached 50% of the accrual goal with 35 mothers (70%) and 15 fathers (30%). Seventy-six percent of participants identified as Caucasian, 18% as African American and 6% as Hispanic. The average age of parents in the study is 38 years old (SD 8). Religious preferences of participants included 32 Christians (72%), 5 Jewish (10%), 7 with no religious preference (14%) and 2 who identify as other. The average score for the Kessler 10 distress scale is 21.6 (SD 6) indicating high levels of distress. Preliminary analysis suggest that, after adjusting for parent age and resilience, higher levels of negative religious coping are associated with increased levels of parental distress with no significant relationship was found between positive religious coping and parental distress.
Conclusion: Negative spiritual and religious beliefs of parents of children with cancer may contribute to increasing levels of distress. Exploring parental spiritual and religious beliefs may serve as a topic of conversation to identify families at high risk for distress.

Poster # 467

ATTENDANCE AT FUNERALS BY PEDIATRIC CANCER PROVIDERS

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Background: Medical provider wellness is an important emerging topic in medicine. Emotional stress and post-traumatic stress disorder (PTSD) are especially common among healthcare providers who frequently see suffering. One such group is pediatric oncology providers, who often have long-standing and close relationships with their patients. While bereavement practices - including attending patient funerals, has been studied in many medical settings - it has not been studied in pediatric oncology providers. Zambrano et al. studied adult providers from fields such as medicine, nursing, psychology, and social work, and found that 67% had attended at least one funeral of a patient and that the average number of patient funerals attended was 15 (Zambrano, J Ped Pall Med, 2018). Similarly, Borasino et al studied pediatric critical care providers and found that 66% attended children's funerals occasionally (between 1-25% of the time), with the other 33% of providers never attended (Borasino, Pediatrics, 2008).
Objectives: To estimate how common it is for pediatric oncology providers to attend their patient's funerals.
Design/Method: A REDCap survey was sent to healthcare professionals working in the pediatric oncology field across the nation, containing 27 questions about coping, one question about professional boundaries, and one question regarding funeral attendance.
Results: The response rate was 16% (362/2,332), of which 62% self-identified female, 78% Non-Hispanic white, 11% Asian, and 5% Hispanic-White. The average age is 47 years (27-75) and 17 years in the field (1-49), with 85% attending physicians and 12% nurses. Our preliminary data showed that 87% of providers make an effort to attend their patients' funerals, 9% choose not to attend, 4% state that they used to attend but do not anymore, and 0.4% state that they used to not attend but now do choose to attend. 89% felt that attending patient funerals did not violate professional boundaries.
Conclusion: Our preliminary data suggests that a larger number of pediatric oncology providers attend the funeral of their patients (87%) compared to 2/3 of adult providers or pediatric critical care providers previously reported. This study is part of an ongoing analysis to better understand what motivates pediatric oncology providers to attend or not attend their patients' funerals. We intend to further study the impact of attending funerals on ability to cope with psychological stress/loss of patients and symptoms of post-traumatic stress disorder (PTSD) in the future.

Poster # 468

DIETARY INTAKE AND MICRONUTRIENT DEFICIENCY IN CHILDREN WITH CANCER

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Background: Children with cancer often suffer from malnourished states secondary to cancer metabolic demand, cancer and treatment related hormonal disturbances, and complications affecting dietary intake and absorption. Malnutrition is associated with poorer treatment outcomes, reduced tolerance to chemotherapy, and higher rates of infectious complications or adverse events. This study assesses the relationship between dietary intake and micronutrient

deficiencies in children with cancer undergoing active treatment.
Objectives: Children with cancer suffer from micronutrient deficiencies despite high or adequate intake. Our objective is to increase awareness of the incongruence between micronutrient intake and deficiency in children with cancer.
Design/Method: This is a secondary analysis of an existing database of pediatric oncology patients in which serum micronutrient levels and dietary intake were collected in study participants. A 24-hour food, vitamin, and supplement recall was performed through the multiple pass method using the Nutrition Consulting Enterprise 2D Food Portion VisualTM. FoodWorks 8 was used to calculate macro- and micronutrients by percent recommended daily intake (RDI) corrected for age and gender. Additionally, quality of life was also measured using the Peds QL(TM) Pediatric Quality of Life Inventory Core Module and Cancer Module.
Results: Participants (n=150) were 1 – 30 years old (mean 11.5) and included CNS (n=13), blood (n=53), and solid tumors (n=83). Macronutrient analysis of the cohort resulted in 30% fat, 53% carbohydrate, and 17% protein consumption. Patients analyzed had less than the RDI of food groups compared to the average American child in all food groups except grains. Analysis of serum levels in a random subset of patients (n=23) revealed deficiencies in all micronutrients assessed: Vitamin A (4.3%), Vitamin C (83%), 25-OH Vitamin D (87%), Vitamin E (4.3%), selenium (4.3%), and zinc (45%). RDI of micronutrients was met or surpassed in Vitamin C (161% ± 107%), Vitamin E (455 ± 55%), selenium (136% ± 125%), and zinc (124% ± 112%). RDI of Vitamin A (43% + 71%) and 25-OH Vitamin D (11% ± 21%) was not met. Analysis comparing quality of life domains to micronutrient levels revealed a significant inverse correlation between Vitamin C and nausea ($p = 0.006$).
Conclusion: Children with cancer suffer from micronutrient deficiencies despite high or adequate intake. Understanding these deficiencies and the incongruence between intake and nutrition status will increase awareness of malnourishment as a contributor to adverse events and treatment related toxicities. Further work is needed to determine the physiologic mechanism for nutrient wasting or absorption inhibition in children with cancer.

Poster # 469

IMPROVING NUTRITIONAL SUPPORT FOR PEDIATRIC HEMATOLOGY & ONCOLOGY PATIENTS

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Background: Malnutrition affects nearly 50% of children and young adults with cancer during their treatment (1). Malnutrition can impair treatment tolerance leading to dose reductions, therapy delays, major organ dysfunction, and altered chemotherapy metabolism, all of which can adversely impact prognosis and overall survival (2). Additionally, malnutrition is associated with poor wound healing and impaired immune function, which increase susceptibility to infections (3). After treatment, malnutrition can have serious long-term consequences including impaired growth, cardiomyopathy, secondary cancers, neurocognitive difficulties, and reduced quality of life (4-7). While Duke employs several skilled Registered Dieticians (RD), guidelines for consultation with them are not established.
Objectives: The objective was to increase the number of interactions between patients with

hematology or oncology diagnoses and RD.
Design/Method: Two interventions were made. First, suggested criteria for RD intervention, including supplements, tube feeds, or total parenteral nutrition, were posted in provider workrooms (Step 1). Consultation was not mandatory. Second, a survey containing nutrition-related questions, including weight or appetite changes, parental concern, or desire to speak with RD, was completed by patients (or caregivers) and added to each visit (Step 2). After reviewing responses, a shared decision to consult RD was made. The average number of RD consults per day was calculated for three periods (baseline, Step 1, Step 2), and subsequently compared using two-tailed t-tests.
Results: The average number of RD consultation per day increased after each intervention from 0.1 (baseline) to 0.18 (Step 1) to 0.22 (Step 2). These equate to 8.7, 16.4, and 19.8 consultations per 90 days, respectively. Only the difference between baseline and Step 2 was statistically significant ($p = 0.03$).
Conclusion: These findings suggest that interventions at the provider level can increase RD referrals for patients needing consultation. Patient-driven intervention yielded the most measurable effect, suggesting that providers may respond better to active patient-proposed changes than to passive workplace suggestions. This highlights the importance of shared decision-making between providers and patients. Based on these findings, a third intervention featuring formal growth chart-derived criteria (8) mandating RD consultation were added to patient visits. This intervention will assess whether required objective criteria for RD consultation provide additional benefit to the patient survey. References:1. Sala, Cancer, 2004.2. Bauer, Adv Nutr, 20113. Picton, Int J Cancer Suppl, 19984. Warner, Lancet, 20005. Diller, J Clin Oncol, 20096. Glasser, Clin Orthop Relat Res, 19917. Mauer, J Parenter Enteral Nutr, 19908. Becker, Nutr Clin Pract 2015

Poster # 470

RISK FACTORS FOR WEIGHT LOSS IN INFANTS AND YOUNG CHILDREN UNDERGOING CANCER TREATMENT

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Background: Malnutrition is poorly characterized in pediatric oncology patients. Undernourished patients have more morbidity and mortality during cancer treatment. Despite interdisciplinary professional recommendations encouraging closer attention to malnutrition, little exists on risk factors and timing for weight loss during cancer treatment.
Objectives: We aim to better understand risk factors for weight loss, specifically in order to identify patients at risk for under nutrition during cancer therapy.
Design/Method: This observational, retrospective study utilized data from our cancer registry and medical record. Patients diagnosed less than 3 years old between 2007-2015 were included. We excluded patients with no accurate weight prior to treatment initiation, therapy started outside our institution, or incomplete treatment information. Weight was obtained at start of therapy and through 2 years after treatment initiation. Treatment intensity was assigned using the

validated Treatment of Intensity Rating Scale (ITR-3). Significant weight loss was defined by weight-for-age z-score loss greater than or equal to 1 at any time during the study. Age at diagnosis, sex, race, ethnicity, tumor type (brain tumor vs other malignancy), and treatment intensity were evaluated with univariate analysis and then significant factors were included in multivariate logistic regression.
Results: The 434 included patients were predominantly white (59%) and non-Hispanic (84%). Of patients, 51% were male with average age at diagnosis of 1.49 years. Diagnoses were consistent with expected distribution of malignancies for this age group; 57 patients had brain tumors and 377 had non central nervous system malignancies. Low intensity treatment was used in 44% of patients (ITR 1 or 2) and 56% of patients received high intensity therapy (ITR 3 or 4). Of patients, 167 had significant weight loss (38%) during the study with those less than 1 year old had 2.7 times higher odds than those diagnosed 1-2 years (95% CI 1.6-4.5, $p<0.001$) and 2.3 times higher than those diagnosed 2-3 years (95% CI 1.4-3.7, $p<0.001$). Higher intensity carried 2.8 times higher odds of significant weight loss compared to lower (95% CI 1.8-4.3, $p<0.001$). Weight-for-age Z-score trajectory declined for the first 6 months. Subsequently, patients older than 1 year at diagnosis gained weight back faster than those less than 1 year at diagnosis. There was no difference in likelihood of significant weight loss based on sex, race, ethnicity, or tumor type.
Conclusion: Infants are at the highest risk for significant weight loss during cancer therapy and lack of proper nutrition has lifelong implications for overall health and survival.

Poster # 471

INVESTIGATING THE NEED FOR A MULTIDISCIPLINARY CANCER PREDISPOSITION CLINIC

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Background: Cancer predisposition is a rapidly growing concern within pediatric oncology. It is estimated that up to 30% of children with a new cancer diagnosis are at risk of having an underlying genetic cancer predisposition. The diagnosis of a cancer predisposition syndrome impacts treatment choices, future screening for secondary malignancy, and genetic counseling for other members of the family. Currently, patients with known or risk for cancer predisposition syndromes are cared for in many different settings, both in primary care and sub-specialty clinics, without consistency.
Objectives: To better understand the need within the Southeast Wisconsin medical community for a cancer predisposition clinic from the perspective of primary care physicians.
Design/Method: We created an 18-question survey to gain understanding of the experience of primary care physicians who are referring physicians to the Children's Hospital of Wisconsin. This survey was designed to assess the comfort level with diagnosing and care of these patients, and to understand the current referral pattern in our region. The survey was delivered and collected electronically. Descriptive statistics were used in the analysis.
Results: The survey was completed in full by 61 primary care providers. Respondents were primary MD's (92%) who had been in practice for varying amounts of time (from <5 years to >20 years). Most providers reported feeling not comfortable (36%) or neutral (42%) in providing

care for patients with cancer predisposition syndromes, while only a small group reported feeling comfortable with caring for these patient (21%). About one third of providers are currently providing care for patients with cancer predisposition syndromes. These providers report managing surveillance in 40% of patients, while 60% made referrals to specialists who managed surveillance. However, over half of providers also not having access to current surveillance guidelines. When referrals are made, a majority of patients are being referred to the Genetics clinic (63%), with a separate population referred to Oncology clinic (23%).
Conclusion: This pilot survey demonstrates an ongoing need for the development of cancer predisposition clinics. Most community primary care providers are not comfortable providing care for these unique patients, and a majority do not have access to the available guidelines that exist for some of these patients. The divided referral pattern is also challenging; these patients would benefit from both genetic expertise and oncology care as they undergo regular cancer screenings. Based on this pilot survey, work will be done to build a multi-disciplinary clinic to provide care for this patient population.

Poster # 472

THE RISK OF SECONDARY CENTRAL NERVOUS SYSTEM TUMORS AFTER HEAD COMPUTED TOMOGRAPHY IN PEDIATRICS

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Background: Advanced diagnostic imaging has provided tremendous benefits in the management of intracranial disorders and emergencies. Nevertheless, the increased utilization of ionizing radiation modalities such as head/neck computed tomography (CT) scans may be associated with increased risk of developing central nervous system (CNS) tumors.
Objectives: To identify the available evidence of the association between the exposure to head/neck CT scans and secondary CNS tumors.
Design/Method: A literature review to identify studies that explored the association between head/neck CT scans and the risk of developing CNS tumors in pediatrics.
Results: Seven studies analyzing six cohorts were included. A positive correlation between exposure to head/neck CT scans and developing CNS tumors was evident in all cohorts. The strength of the association varied across the studies (relative risk 1.22 (0.84-1.61) - 2.82 (1.33-6.03); standardized incidence risk 1.35 (0.54-2.78)- 2.05 (1.48 to 2.83); incidence rate ratio 2.02(1.69-2.43); hazard ratio 2.56 (1.44-4.54)). The exclusion of patients with CNS tumors predisposing factors decreased the risk to develop CNS tumors in three studies, but it did not affect the risk in one study. The excess relative risk per mGy of brain dose (ERR/mGy) for all CNS tumors without adjusting for predisposing factors ranged from 0.0086 (95% CI: 0.2-2.22) to 0.23 (95% CI: 0.010-0.049). Two studies reported a non-significant reduction in ERR/mGy of brain dose after adjusting for predisposing factors, while the reduction was significant in one study. Two studies reported increased CNS tumors risks among patients who received two or more head/neck CT scans compared with one, but this association was not maintained in two other studies. The analysis of the calendar year at the time of imaging, referring to the different decades at which the imaging was performed, showed decreasing risk in those exposed to

head/neck CT scans after the year 2000 compared with prior decades. Three studies revealed that the exposure to head/neck CT scans at a younger age (0-6 years of age) was associated with higher CNS tumor risk. Four studies showed that the CNS tumor risk trended down after the first five years post-CT exposure, while two studies reported increased risk after 5-10 years and 10-15 years of exposure, respectively. Gender had no significant effect on the CNS tumor risk post-CT scan exposure.
Conclusion: Prospective epidemiological studies are needed to examine the precise carcinogenic effect of exposure to ionizing radiation and help tailor further preventive measures that have been implemented in the past two decades.

Poster # 473

EFFECTS OF CHEMOTHERAPY IN PEDIATRIC PATIENTS ON THE BRAIN'S GREY AND WHITE MATTER STRUCTURE

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Background: Improved cancer treatment protocols have resulted in increased survival in childhood cancer. Although many of the early side effects of treatment are understood, information on the late effects of chemotherapy, particularly in the realm of cognition, still remain to be elucidated. One such effect described is that of "chemobrain" or impairments in working memory, attention, cognitive switching, and concentration following chemotherapy.
Objectives: Chemobrain has only recently started to be addressed in the pediatric literature; this study aimed to further explore this phenomenon using structural MRI and neuropsychological tests. This study tested the hypothesis that chemotherapy-treated pediatric cancer survivors show reduced brain volumes and abnormal white matter connections when compared to age-matched controls.
Design/Method: Subjects underwent structural and DTI sequences using a 3.0T Siemens scanner. Structural volumes were normalized to MNI space, and segmented using tissue probability maps. Voxel-based morphometry (VBM) and cortical thickness analysis were performed using Computational Anatomy Toolbox for Statistic Parametric Mapping (SPM). Subcortical volumetric analysis was performed using FSL FIRST. DTI images were processed using DSI Studio. Fractional anisotrophy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were calculated for multiple areas. Statistical and correlation analysis were performed using SPSS.
Results: Cancer survivors had significantly smaller gray-matter volumes on VBM analysis in the right orbitofrontal area (T=-5.1, p=0.001), right anterior prefrontal cortex (T=-4.8, p=0.001), right parahippocampal gyrus (T=-4.5, p=0.030), left globus pallidum (T=-8.6, p=0.0001), left dorsolateral prefrontal cortex (T=-7.5, p=0.012), right thalamus (T=-6.3, p=0.0001), and left angular gyrus (T=-5.6, p=0.004) compared to controls. Regarding specific subcortical structures, patients revealed reduced volumes in the right thalamus (T=-4.01, p=0.003), left thalamus (T=-4.6, p=0.004), left caudate (p=0.010), right amygdala (p=0.026) and left nucleus accumbens (T=-3.2, p=0.021). Cortical thickness analysis showed thinning of the right parahippocampal gyrus in patients. MD and RD of the genu (p=0.027, p=0.048) and body of the corpus callosum (p=0.054,

p=0.052) and right corticothalamic tract (p=0.042, p=0.020) were increased in patients compared to controls.
Conclusion: Patients who had previously received systemic chemotherapy demonstrated reduced brain volume and abnormal white matter integrity compared to healthy age-matched controls. Many of the affected areas are known to be involved in working memory, higher order reasoning and decision making, as well as information processing. These decreased volumes as well as abnormal white matter connections between them, may help to explain some of the difficulties with executive function and working memory that survivors face.

Poster # 474

VISUOSPATIAL AND COGNITIVE CHANGES IN PEDIATRIC CHEMOBRAIN: A FUNCTIONAL CONNECTIVITY STUDY

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Background: Improvement in the treatment of childhood cancers has lead to an increase in the number of cancer survivors. While cognitive deficits are a known late effect of chemotherapy, limited data using fMRI exists in these patients. One such effect is impairment of cognitive function, called chemobrian, which is described as a deficit in working memory function, learning, and concentration.
Objectives: Few studies have explored the functional connectivity of survivors of pediatric cancer treated with chemotherapy. This study aimed to explore the neural correlates of functional deficits in chemotherapy treated pediatric cancer patients using resting-state fMRI (rsfMRI) technology. We hypothesized that patients would show reduced functional connectivity compared to non-chemotherapy exposed children.
Design/Method: Sixteen chemotherapy-treated childhood cancer survivors, diagnosed with a non-central nervous system tumor before the age of 18, and sixteen healthy controls were recruited. Subjects were scanned using a 3.0T Seimens PET/MR at Stony Brook Medicine. All subjects underwent a structural T1 weighted 3D MPRAGE and a seven minute rsfMRI sequence. Subjects were asked to keep their eyes closed and minds clear during scanning. rsfMRI scans were analyzed using the CONN toolbox for SPM. Pre-processing steps included realignment, slice time correction, co-registration, normalization, and smoothing. Seed based analysis was performed with seeds chosen based on anatomical analysis.
Results: Seed based analysis revealed three different connections in patients compared to controls. The right pallidum showed reduced connectivity to the left superior frontal gyrus (T= -4.74, p=0.028) and left middle frontal gyrus (T= -4.58, p=0.04). Patients also showed increased connectivity between the left inferior temporal gyrus and left paracentral lobule (T= 4.22, p=0.049).
Conclusion: The pallidum is primarily a structure that receives and projects information related to reward to the cortex. It is also necessary for reward learning. Reduced connections to the superior frontal and middle frontal gyri, both involved in forms of learning, represent a reduction in learning ability in patients. The left paracentral lobule is involved in movement while the

inferior temporal cortex is linked to semantic memory. The increased connectivity between these regions could point towards patients connecting movement to memory function.

Poster # 475

IDENTIFYING A NEED AND KNOWLEDGE GAP OF OSTEOPATHIC MEDICINE IN PEDIATRIC ONCOLOGY PROVIDERS

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Background: Children receiving chemotherapy often struggle with detrimental side effects including constipation, nausea, neuropathy, and decreased quality of life. As we continue to make great strides in medications to help minimize chemotherapy side effects, there remains a need for additional adjunctive supportive care. Since the advent of osteopathic medicine in the 1890's, this adjunctive therapy has been implemented successfully in both adult and pediatric populations for a myriad of illnesses. To date, there has been no literature on the need for osteopathic manipulative treatments (OMT) in oncology. Additionally, there have been no studies examining practitioner knowledge and implementation of osteopathic medicine specifically in the pediatric oncology population.
Objectives: To investigate a knowledge gap and potential need for osteopathic medicine in pediatric oncology.
Design/Method: Twenty-one pediatric oncology providers at Nationwide Children's Hospital were approached for participation. Of those approached, 20 total providers completed the survey. Following a description and video of OMT, participants completed quantitative surveys in REDcap and 1:1 semi-structured qualitative interviews. Providers were asked about their personal knowledge of OMT, hesitations and barriers regarding OMT utilization, and their experiences with difficult to control chemotherapy side effects. Interviews were audio-recorded, transcribed, and independently coded by two investigators to determine consensus thematic content. Descriptive statistics were used to summarize quantitative data.
Results: We surveyed 20 oncology providers (7 male), including 15 attending physicians and 5 nurse practitioners with a median of 6.5 years of clinical practice (range: 1-24 years). All attending physicians were allopathic trained pediatric oncologists and had knowledge of osteopathic medicine, with a varying degree of understanding. No provider reported they knew "a lot" about OMT. Providers supported further research to study the benefits of OMT, with 100% reporting a desire to have OMT available as a supportive care option. Family frustration secondary to uncontrolled symptoms requiring multiple failed medication regimens was an underlying theme from providers. Additional major themes included 1) provider frustration with current available treatments for managing chemotherapy side effects such as nausea, neuropathy, and constipation, 2) attractiveness of OMT as a non-invasive home intervention with low-risk and high reward, and 3) minimal provider hesitation for incorporating OMT into their patients' supportive care.
Conclusion: Pediatric oncology providers reported a need for better management of chemotherapy-associated side effects and an openness to non-pharmacological therapies with supporting data. These findings support the need to further investigate the safety and feasibility, as well as efficacy of OMT in the pediatric oncology clinical setting.

Poster # 476

MEDICATION UTILIZATION FOR SYMPTOM MANAGEMENT BY PEDIATRIC INPATIENTS WITH CANCER AT END-OF-LIFE

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Background: Despite advances in pediatric oncology care, most children that die each year from cancer report significant suffering at end-of-life. Commonly reported symptoms include pain, anxiety, and nausea. More than half of pediatric cancer patients die in the hospital, yet little is known about medication use for symptom management during their terminal hospitalizations.
Objectives: To describe the utilization patterns of opiates, benzodiazepines, and gastrointestinal (GI) related medications for commonly reported symptoms by pediatric cancer inpatients during their last week of life.
Design/Method: This retrospective study uses data from the Vizient clinical database/resource manager (CDB/RM™), a compilation of clinical and resource use data from over 100 academic medical centers and their affiliates nationally. Pediatric patients (ages 0-21) with a diagnosis of malignancy who died during an inpatient hospitalization from 2010-2017 were included (n=1,659). Patients admitted for less than 1 week were excluded. Individual medications were categorized as opiate, benzodiazepine, or GI-related. Exposure to each group was ascertained for all patients at two time points: one week and one day prior to death. Factors associated with the time of exposure were examined using generalized estimating equations. Results were summarized using adjusted odds ratios (aOR).
Results: Opiate exposure increased from 76% one week prior to death to 82% one day prior (aOR 1.5; $p<0.001$). Similarly, use of benzodiazepines also increased from 53% to 66% (aOR 1.3; $p =0.024$). Receipt of GI medications decreased from 92% to 89% (aOR 0.7; $p=0.001$). Opiates and benzodiazepines were more likely to be administered to patients with solid tumor diagnosis (aOR 1.4, 1.2), history of bone marrow transplant (BMT) (aOR 1.3, 1.4), and longer length of stay (LOS), respectively. Benzodiazepine utilization was lower among blacks (aOR 0.6) and Medicaid recipients (aOR 0.8). GI medications were also more likely to be received by patients with history of BMT (aOR 1.8) and longer LOS; additionally, exposure was higher in those age 5-9 (aOR 1.9) and of Asian race (aOR 2.5). Reported aORs are significant at $p<0.05$. Gender, ethnicity, study year, location in ICU, and DNR status did not significantly affect exposure in any category.
Conclusion: Not all patients are receiving medications typically used for symptom management in the week preceding death. Opiate and benzodiazepine exposure increased while GI medication use decreased. Earlier and more consistent intervention with these medications may reduce patient suffering. Furthermore, variability in utilization associated with patient characteristics suggests differences in symptomatology and provider/family decision-making warranting further study.

Poster # 477

MODELS OF PEDIATRIC PALLIATIVE ONCOLOGY OUTPATIENT CARE – BENEFITS, CHALLENGES, AND OPPORTUNITIES

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Background: Many children with progressive cancer receive their oncology care in the outpatient and home settings. Over half of children with cancer who die do so in the outpatient setting. Yet, a majority of current pediatric palliative care (PPC) services in the United States are concentrated in inpatient settings, and do not reach patients and families in the outpatient and home settings, where most clinical care, symptom assessment and management, decision-making, and advanced care planning occur. Integration of PPC services into the care of children with cancer is associated with improved symptom management, and quality of life (QOL) for children and families. Outpatient PPC often fills a gap that exists when patients have high symptom burden, and significant supportive care needs, and are not yet enrolled in hospice. As integrated PPC/pediatric oncology becomes the standard of care, novel pediatric palliative oncology (PPO) outpatient models are emerging. The optimal PPO model is unknown and likely varies based on institutional culture, resources, space, and personnel.
Objectives: To describe the unique PPO clinic development process and expected difficulties, and present novel PPO outpatient clinical models such that additional pediatric oncology centers can improve access to outpatient PPC services.
Design/Method: We convened a group of experts to offer pragmatic guidance regarding PPO clinic development, implementation, and resource allocation. Additionally, we present five institutions' unique outpatient PPO clinical models with their respective staffing models, available clinic metrics, benefits and challenges.
Results: Recommendations on clinic development including issues of staffing, coverage, space, operations, information technology, finances, referrals, communication, and marketing are presented. The five outpatient PPO models featured include a floating clinic model, embedded PPC experts within oncology clinics, consultative or trigger-based supportive care clinics, and telehealth clinics. These models vary in their institutional support, personnel, resources, and patient populations.
Conclusion: Although PPC possesses an inherent adaptability to a wide variety of ambulatory oncology practices, this diversity makes comparative analyses of patient and provider outcomes across models difficult. The description of varying models presented with opportunities and challenges will allow for formal investigation. Clinically, in the absence of a one-size-fits-all model, pediatric oncology and PPC groups with a spectrum of available personnel and resources can select, tailor, and implement the model that best suits their respective needs and capacities. Emerging PPO clinics must balance the benefits and burdens unique to their organization, and focus on achieving high quality PPC for children with cancer and their families across all care settings.

Poster # 478

IMPROVING PEDIATRIC PALLIATIVE CARE IN A COMMUNITY-BASED SETTING THROUGH AN ONGOING EDUCATION SERIES

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Background: Community hospitals represent a unique setting to provide pediatric palliative care (PPC), given their usual proximity to a patient's home. Texas Children's Hospital, The Woodlands (TCH-TW) is a community-based campus that opened in April 2017. Hospital staff have varying experience in PPC and are unfamiliar with available resources. Absence of focused training on PPC and relative paucity of exposure to PPC necessitates an urgent need for improvement.
Objectives: 1. To understand baseline comfort of TCH-TW staff members in delivering PPC in a community-based setting and identify areas of improvement and knowledge gaps. 2. To pilot a campus wide ongoing education series that improves overall comfort and knowledge of TCH-TW staff members in delivering PPC in a community-based setting.
Design/Method: An electronic survey (using a 5 point Likert scale) was sent to 350 staff members including physicians, mild-level providers, nurses, social workers, child life specialists, chaplains, pharmacists, and administrators to conduct a needs assessment. Results were analyzed to design a quarterly education series, utilizing didactic presentations, simulations, and small group discussions. Feedback tools included pre- and post-assessment questions, audience response system, and competency checklists.
Results: One-hundred forty three participants (40%) completed the survey. Staff members reported an average score ~3.16 when asked if they felt the campus was "palliative care friendly." They reported a comfort level ~2.90 with regards to having end-of-life discussions with patients and their families, and a rating ~2.33 when it came to placing "do-not-resuscitate" orders. An average comfort level ~3.28 was reported when caring for an actively dying patient and acute symptom management. Additional areas of improvement included understanding essential differences between palliative, concurrent, and hospice care (average score ~3.39), as well as logistics and information accessibility to identify PPC resources within the campus (average score ~2.85 and ~2.93, respectively). The inaugural lecture- "Hospice 101: Providing Palliative Care in the Community Hospital Setting: An Interprofessional Approach-" was launched in October 2018, with 37 participants reporting an overall activity quality score ~4.53. Additional lectures planned over the academic year include: having difficult conversations; logistics of when a patient dies at TCH-TW; and management of an actively dying patient.
Conclusion: Community hospitals have a unique opportunity to provide PPC services due their closer proximity to a patient's own home. Through an ongoing campus wide educational series initiative, we aim to provide a high-quality palliative care experience that better serves our patient population.

Poster # 479

IMPROVEMENT IN PATIENT TRANSITION PROCESS FROM MAIN CAMPUS TO COMMUNITY CAMPUS SITE

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Background: All new leukemia and lymphoma patients at Texas Children's Hospital are initially diagnosed at our Main Campus (MC). Our Texas Children's Cancer Center has now established a clinic at our new community West Campus site (WC), to which patients can transition their care after initial diagnosis if desired. However, there is not a standardized transition process and there is a knowledge gap for both MC providers and nurse coordinators (NCs) as to how to transition a patient's care.
Objectives: We aim to create a standardized transition process and to achieve >95% average knowledge score for MC providers and NCs for how to transition a patient from MC to WC during a six month period (June 2018-December 2018).
Design/Method: In order to improve our providers' and NCs' knowledge for how to transition a patient from MC to WC, we initially assessed providers' and NCs' knowledge with a baseline survey. We then created a new transition process, using input from both MC and WC providers and NCs. For our plan-do-study-act (PDSA) 1, we provided education for this new process for MC providers and NCs. We performed a repeat knowledge survey for MC providers and NCs three months after initiating PDSA 1.For our PDSA 2, we focused on any patient who originally presented at WC and was subsequently transferred to MC for initial diagnostic work-up, which is centralized at MC, by placing a copy of a transition form in these patients' chemotherapy charts. We also initiated monthly education emails to MC providers and NCs with key points to remember about the transition process. We performed a repeat knowledge survey for MC providers and NCs three months after initiating PDSA 2.
Results: The average baseline knowledge score for MC providers and NCs was 62%. The average knowledge score for MC providers and NCs after PDSA 1 was 82%. The average knowledge score for MC providers and NCs after PDSA 2 was 85%.
Conclusion: Our goal was create a standardized transition process and to improve the average knowledge score to >95% for MC providers and NCs within six months. Although we did not yet meet this goal, we witnessed dramatic improvement from baseline knowledge score of 62% to 85% at the end of our PDSA 2. We have now expanded this process to our second community campus, and we will plan to continue ongoing education for providers and NCs for the transition process.

Poster # 480

INPATIENT DEATHS OF CHILDREN WITH CANCER - HOW COMMON IS CPR?

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Background: Death in children with malignancy may result from refractory disease or acute complications during therapy. In this population, end-of-life research commonly focuses on palliative care, however little is known about the medical interventions received in the last week of life from the overall cohort of children who die from cancer or related complications in the inpatient setting. Perceptions of undertreatment or overtreatment can cause distress among families and clinical staff, yet the prevalence of do-not-attempt resuscitation (DNAR) orders and the use of CPR and other supportive therapies on inpatient oncology units remains poorly described.
Objectives: To describe the medical management of children with cancer or serious hematologic

disorders during the last week of life.
Design/Method: We performed a single-institution retrospective chart review of all oncology patients who died as inpatients between February 2005 to March 2017, examining the medical record for interventions at the time of death as well as 24-hours, 48 hours, and 7 days prior to death. The medical record was reviewed in its entirety for any acute code event (cardiac and non-cardiac), intensive care unit (ICU) admissions, and limitations on medical therapy (i.e. DNAR).
Results: We identified 344 inpatient deaths with a mean age of 11.32 years. Hematologic malignancies and solid tumors occurred most commonly (49%, 29% respectively); 48% had a stem cell transplantation, 51% of deaths occurred in the ICU. In this cohort 86% had evidence of disease with 20% receiving any chemotherapy 7-days prior to death. DNAR orders were common (76%), with only 3 designated as unilateral. In the 83 without DNAR, 32 (39%) did not receive CPR at death due to guardian request. In this cohort, 20% had ever received CPR, with 11% receiving CPR only at death and <2% receiving CPR more than once, including at death. Of those who received CPR at death, 51% were thought to be due to a potentially reversible cause.
Conclusion: Our findings showed that very few patients received CPR at the end of life and lack of a formal DNAR did not guarantee that potentially non-beneficial CPR would be performed. The most common reason for CPR at death was for a potentially reversible cause of arrest. Having previously had CPR decreased the likelihood of CPR at death, either due to written DNAR or parent refusal. Further analysis is needed to better understand other factors that impact the decision to have a DNAR or initiate CPR at death.

Poster # 481

THE 'GOOD DEATH' IN PEDIATRIC ONCOLOGY

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Background: Empirical descriptions of a "good death" exist for older adults with cancer, and these have served as the foundation for providing quality end of life care. In contrast, little is known about what, if anything, constitutes a "good death" from the perspective of Adolescents and Young Adults (AYAs) with advanced cancer, their caregivers, or their medical teams. Pediatric oncology clinicians care for numerous patients at the end of life and can offer a breadth of insight regarding these difficult situations. Incorporating clinician experience can identify common pitfalls as well as successful strategies to inform and improve the delivery of patient-centered end of life care. Ultimately, understanding the intersection between patient, family, and provider values is critical to providing high quality end of life care for AYAs. This study provides a first step toward achieving this goal.
Objectives: This sub-analysis is part of a larger project that includes AYA patients, their parents, and bereaved parents. The objective of the present analysis was to identify factors that healthcare clinicians considered important at the end of life for AYA patients and their families.
Design/Method: In this prospective qualitative cohort study, semi-structured interviews were conducted with n=19 (74% female) oncology medical staff at a large academic pediatric hospital. Staff members included physicians (n=7), advanced practice providers (n=6), and other multidisciplinary providers including physical therapists, music/art therapists, and chaplains (n=5). Interviews were audio-recorded verbatim, de-identified, and transcribed. Two primary

coders conducted content analyses to identify relevant themes related to quality end of life care. Coding was reconciled iteratively with each transcript to inform subsequent thematic development and ensure saturation. Data were analyzed using ATLAS.ti software.
Results: Twenty-seven major themes and 66 sub-themes emerged from provider interviews. Major themes included 'Acceptance,' 'Communication,' 'Meeting Families Where They Are,' and 'Protection.' Providers identified early and transparent communication within families, parental acceptance, and AYA/families maintaining a sense of control as features of a 'good death.' Lack of open communication, an unexpected/sudden death, and family denial or avoidance correlated with providers' experiences of a 'bad death.'
Conclusion: Healthcare clinicians agree that compassionate and transparent communication are common denominators in good end of life care for AYAs with cancer. These insights may help clinicians caring for patients during a very difficult period of the cancer care trajectory. Future analysis of patient and parent interviews will guide recommendations for the practice of end of life care that is most aligned with patient/family values.

Poster # 482

FACTORS CONTRIBUTING TO "GOOD" AND "BAD" DEATHS IN AYA ONCOLOGY PATIENTS: PHYSICIANS' PERSPECTIVES

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Background: Oncologists face many challenges in discussing end of life (EOL) care with patients and acknowledge struggling with communication on this topic. While EOL discussions are presumably difficult at any age, unique challenges are presumably present in the adolescent and young adult (AYA) cancer population that likely inhibit oncologists' willingness and ability to effectively communicate. In fact, and likely for that reason, reports show that EOL discussions in this population overwhelmingly occur very late in relation to time of death. Yet, available evidence says these patients want to be involved in EOL care decisions. Little data is available that describes physicians' challenges.
Objectives: Determine physicians' perspectives on optimum timing surrounding EOL care communication in AYA oncology patients and factors they identify as contributing to more acceptable EOL care outcomes.
Design/Method: Providers within medical oncology, medical critical care, pediatric oncology and pediatric critical care at the University of Chicago Medical Center were interviewed to discuss their experiences with EOL care for AYA oncology patients, specifically describing "good" and "bad" patient deaths they could recall and factors they think contributed to the outcome. Two questions specifically focused on their opinion of optimal timing of first EOL discussion.
Results: Among 45 patient deaths identified as "bad" among 22 different healthcare providers, lack of EOL discussions with the patient or markedly late EOL discussions were contributing factors in 21. Other identified factors included family members' anger at providers, prolonged hospital stays, unrealistic family expectations and futile care. Physicians named knowing patient wishes and early EOL discussions as major contributing factors in 25 of 31 deaths identified as "good." Notably, some of the same deaths identified as "bad" by some providers were identified

as “good” by others. Regarding opinions on optimum timing of EOL discussions, answers spanned from at time of diagnosis to at time of a life-threatening situation. There was noted variability both within and between specialties, with oncologists choosing later time points in course of treatment and critical care providers choosing earlier.
Conclusion: Lack of EOL discussions or EOL discussions occurring too late was noted as the most common factor contributing to “bad” patient deaths in AYA oncology. Early EOL discussions were noted as the most common factor contributing to “good” patient deaths. There is a wide range in identified optimum timing of EOL discussions in AYA oncology patients among physicians.

Poster # 483

EXPERIENCES OF YOUNG WOMEN WITH CANCER REGARDING MENSES/MENSTRUAL SUPPRESSION DURING CHEMOTHERAPY

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Background: Adolescent and young adult (AYA) women undergoing multi-agent chemotherapy are at risk for heavy menstrual bleeding due to thrombocytopenia, coagulopathy, disruption of the hypothalamic-pituitary-gonadal axis, and/or secondary effects of chemotherapy. Any blood loss may complicate cancer treatment, thus menstrual suppression may be advised. There is a paucity of data on the menses of AYA women with cancer, their risk for heavy bleeding, and how they perceive menstrual suppression.
Objectives: This study aims to 1) describe the attitudes and experiences of AYA women with a history of cancer regarding their menses and menstrual suppression, and 2) investigate facilitators and barriers to patient-provider communication around this topic.
Design/Method: AYA women ages 15 – 29 years with a diagnosis of cancer in the last 1-5 years completed individual, semi-structured interviews regarding their experiences and preferences around menstrual health. Two independent reviewers conducted a thematic analysis of transcribed interviews.
Results: We interviewed 20 participants. Emerging themes include the following: 1) of the women who experienced menses during chemotherapy, many reported strong negative feelings and worry about having menstrual bleeding due to fear of blood loss. 2) Many young women had misconceptions around what it means to have a menstrual period during chemotherapy and subsequent menstrual suppression, linking cessation of menses with menstrual suppression to future infertility. 3) Patients desired menstrual suppression during chemotherapy and want more conversations with their clinical team about suppressive options, safety, and side effects.
Conclusion: AYA women with cancer desire enhanced patient-provider communication and education around menstrual health and menstrual suppression during chemotherapy. Future directions include enhanced provider training around menstrual suppression and development of guidelines and tools to assist in conversations with adolescents.

Poster # 484

SPERM CRYOPRESERVATION PRIOR TO GONADOTOXIC THERAPIES IN ADOLESCENTS AND YOUNG ADULTS WITH CANCER

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Background: Fertility preservation allows young men and women to freeze gametes or embryos prior to therapy with gonadotoxic medications or radiation. In post-pubertal boys, semen cryopreservation is considered the most effective form of fertility preservation and is now recommended as standard of care. The utilization and outcomes of sperm cryopreservation in adolescents and young adults has not been well studied.
Objectives: There is limited data on the semen analysis parameters of adolescents and young adult (AYA) men with cancer who cryopreserve semen. This study aimed to assess whether their age or diagnosis affects the quality of the sperm that will be cryopreserved based on density, volume, and morphology.
Design/Method: A cohort of 79 AYA men aged 21 and younger with a diagnosis of cancer requiring gonadotoxic therapies who were referred to the Fertility Preservation Program (FPP) In Pittsburgh for semen cryopreservation between 2010-2018 were included. Patient demographics, malignant diagnosis, and semen analysis results were collected and analyzed using descriptive statistics and ANOVA using STATA software.
Results: The average age of participants were 17.2 years (range 12-21). Diagnosis include leukemia (12.7%), Hodgkin Lymphoma (21.5%), Non-Hodgkin Lymphoma (12.7%), Sarcoma (27.8%), Germ cell tumor (20.2%), and Other (5.1%). The tumor type had no significant effect on sperm mean volume, mean density or morphology prior to receiving gonadotoxic therapy when controlling for age and correcting for multiple comparisons. When comparing AYAs to patients >21 years of age evaluated at the same center and controlling for tumor type, the AYA patients had statistically significant lower mean volume of sperm (-0.9 mL ± 0.2) with a p value of <0.001 when using Tukey's method to adjust for multiple comparisons. Patients <21 also trended toward lower morphology and density, but these results were not statistically significant.
Conclusion: For AYA patients, there was no difference in sperm quality based on tumor type. Younger patients with cancer who underwent semen cryopreservation prior to gondadotoxic therapy had lower semen when compared to patients to patients >21 years of age. Given these results, it is important to find ways to optimize semen collection and cryopreservation to ensure that these patients can meet their reproductive needs in the future.

Poster # 485

FERTILITY CHALLENGES FACING THE AYA CANCER POPULATION FROM THE SURVIVOR'S PERSPECTIVE

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Background: Treatment advancements in pediatric cancer have led to an increased 5-year survival rate for over 80%, igniting a conversation regarding late-effects. Reproductive health, a previously neglected topic in childhood cancer, has become a priority to address before initiation of chemotherapy. Studies report up to 80% of survivors desire to have children yet these patients have no recall of receiving reproductive counseling. We embarked on a study to evaluate the experience of AYA cancer survivors in regards to reproductive counseling.
Objectives: Our objectives were to: (1) describe the experience of AYA cancer survivors who were counseled about reproductive health prior to treatment, (2) to collect data regarding their fertility preservation methods, and (3) to identify challenges in pursuing fertility preservation.
Design/Method: The REI team created a survey of 19 open-ended questions about fertility and counseling. Inclusion criteria included individuals treated for pediatric solid tumors between 2004-2014, ages 18-30 years at the time of survey, and who had no signs of relapse at the time of study enrollment. 12 of 33 patients who qualified for enrollment opted to participate.
Results: Participants (n=12) were 18-30 years old, diagnosed between ages 12 and 25 years, and had completed treatment. All participants had history of sarcoma. 58% of participants ranked fertility as their top priority while 83% expressed a desire to have children. 58% were in a relationship at diagnosis. 66% recalled receiving fertility counseling. 75% reported satisfaction with the education provided, though three subjects made comments regarding changes they would have preferred to see in the discussion. Comments included receiving fertility preservation options immediately after diagnosis to maximize collection time; wanting data regarding possible outcomes; and feeling that their oncologist did not know the potential effects of chemotherapy to future reproductive health. 58% opted for sperm cryopreservation. 58% viewed costs as their primary challenge.
Conclusion: Our data confirms fertility is a top priority for AYAs facing cancer treatment. The trends suggest women were overall more dissatisfied with the counseling they received while their male counterparts were all satisfied with the information they received. We postulate that this difference might be due to the lack of availability of rapid fertility preservation methods for women. Fertility costs and lack of time emerged as primary barriers. We propose a collaborative multidisciplinary approach to develop reproductive health curriculums for patients. This curriculum should include data about fertility late-effects, information about approved and investigative fertility preservation methods, potential funding, and local providers.

Poster # 486

RECOLLECTION OF FERTILITY DISCUSSION IN ADOLESCENT AND YOUNG ADULT ONCOLOGY PATIENTS

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Background: With medical breakthroughs in childhood cancer treatment, the number of childhood cancer survivors has drastically increased. With this, focus has shifted in the recent years to improving future quality of life and long term complications, such as infertility. Despite national guidelines, fertility preservation is discussed in less than half of the eligible patients. With our survey, we sought to discover if education gaps regarding fertility exist within our practice, in efforts to address these gaps and improve the quality of cancer care we provide.

Objectives: Primary objectives were to determine if the impact of anti-neoplastic therapy on fertility was discussed before, during, or after treatment, as well as if fertility services were offered. Secondary objectives were to assess the patient's knowledge about their fertility as well as if they felt adequately educated about risks of infertility and services provided.
Design/Method: A retrospective electronic survey was administered to eligible adolescent and young adult (AYA) oncology patients. Eligible patients included those that were ≥ 12 years of age at the time of cancer diagnosis and were 6 months to 5 years post completion of therapy. Patients with anti-neoplastic therapy lasting longer than 3 years, whom were in maintenance, were also included.
Results: Of the 63 patients approached, 47 responded to the survey. 22/47 (46.8%) stated they were concerned about their fertility to some degree, however only 11/47 (23.4%) report having been offered services. When asked why they decided against steps to preserve fertility, 15/32 (46.9%) reported that they did not know they had options. There was no evidence of a significant difference in age for those who did receive fertility services as compared to those who did not (p-value = 0.05). Of all patients that completed the survey, 28/47 (59.6%) requested additional information regarding their fertility.
Conclusion: As a retrospective study, the sample size was not large enough to demonstrate a statistical significance of a particular hypotheses. However, the preliminary findings do suggest room for improvement in the fertility education provided to our patients. Though not necessarily generalizable to larger/differing populations, it can serve to inform future research. This study has resulted in development of a standard operating policy for fertility preservation referrals, at our institution, as well as education materials for all newly diagnosed oncology patients.

Poster # 487

IF IT WASN'T DOCUMENTED, IT DIDN'T HAPPEN: INFERTILITY RISK DISCUSSION IN PEDIATRIC CANCER PATIENTS

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Background: Over 80% of children and adolescents diagnosed with cancer become long-term survivors. In order to be cured, patients are exposed to chemotherapy, surgeries and/or radiation treatment. As a result, cancer survivors are at risk for late effects affecting health in general and reproductive health in particular, such as premature ovarian insufficiency and infertility. Based on American Society of Clinical Oncology (ASCO) guidelines health care providers (HCPs) caring for adult and pediatric patients with cancer should address the possibility of infertility as early as possible before treatment starts and refer patients who express an interest in fertility preservation to reproductive specialists. Despite these recommendations, a significant gap in care exists.
Objectives: SMART aim: To improve infertility risk discussion and documentation of this conversation in the electronical medical record (EMR) to over 80% among all eligible newly diagnosed oncology patients at Rady Children’s Hospital-San Diego in San Diego, CA by June 2018.
Design/Method: Plan-Do-Study-Act (PDSA): P: EMR and newly-diagnosed patients tracking

methods were utilized to collect information on infertility risk discussion documentation; 10/2017-01/2018 baseline data, Ishikawa results, process map, and resources available in the community were assessed. Barriers identified via published literature, direct communication with the HCPs were 1) HCPs discomfort discussing infertility risk at the time of cancer diagnosis, 2) knowledge gap in addressing infertility risk and in resources available in the community. A smart phrase to make documentation easier for providers was developed, resources available in the community were communicated to HCPs, educational sessions with the reproductive endocrinologist were conducted. SA: Team reviewed data at least monthly during implementation phase between 02/2018-06/2018. All newly diagnosed oncology patients, who were anticipated to receive therapy were included (chemotherapy and/or radiation). Patients not expected to survive were excluded. Descriptive statistics presented. SPSS v25 software used.
Results: Baseline: N= 34 patients (23 hematologic, 11 solid tumors). Only 11 (32%) had fertility risk discussion documented in the EMR at the time of diagnosis (6 females, 5 males). Post intervention: N=29 (22 hematologic, 7 solid tumors). 27 (93%) had infertility discussion documented in the EMR. During implementation phase patients with hematological malignancies were more likely to have infertility risk discussion documented in the EMR compared to patients with solid tumors (p=0.05).
Conclusion: We exceeded our aim for documenting infertility discussion in the EMR for newly diagnosed pediatric oncology patients via interdisciplinary collaboration of Pediatric Hematology/Oncology, Reproductive Endocrinology, Information Technology and use of QI methods. Next cycles will address sustainability.

Poster # 488

IMPROVING FERTILITY PRESERVATION CONSULTATION IN NEW-DIAGNOSIS PEDIATRIC CANCER PATIENTS

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Background: Fertility counseling in new-diagnosis pediatric oncology patients has been recommended by clinical guidelines, and is important to preserve quality of life in pediatric patients as they reach reproductive adulthood. This process can be challenging in a pediatric institution, however a successful protocol can be developed with the collaboration of multiple reproductive specialties and the oncology team.
Objectives: Quality Improvement methodology was implemented with the goal of increasing the rate of patients receiving fertility preservation consultation from 30% up to 80% of all eligible patients by December of 2018. Patients who were pre-pubescent males or females, or who had a diagnosis of a brain tumor or other non-chemotherapy diagnoses were excluded from the study and protocol.
Design/Method: The measure that was tracked monthly was eligible patients that ended up receiving fertility preservation consultations. Interventions included: development of multidisciplinary fertility preservation consultation algorithm, educational seminars related to developed algorithm for identified stakeholders and fertility preservation counseling process seminar for Staff oncologists. Plan, Do, Study, Act (PDSA) cycles followed every intervention to assess need for changes and impact on desired goal.

Results: Out of 60 new-diagnoses oncology patients 40 were excluded, as they did not meet criteria for fertility preservation consultation (e.g. pre-pubescent males, non-systemic chemotherapy). For patients at risk of infertility without a specific fertility preservation opportunity, a discussion occurred outside of the fertility consultation protocol. Following implementation of interventions, data was collected monthly. Median of data showed that 100% of eligible patients were receiving fertility preservation consultation.
Conclusion: Through a team-based approach and development of multiple interventions followed by PDSA cycles, significant improvement can be made in the rate of fertility consultation for newly diagnosed pediatric oncology patients. Developing an algorithm describing the steps to achieve our goal was successful. Following development of this algorithm, together with educational sessions, there was a shift in the data, signaling a non-random pattern and establishing intentional special-cause variation. Fertility consultation is an extremely important conversation to be had with each new-diagnosis pediatric oncology patient, and can be challenging in smaller institutions The challenges and successes we faced can now be used to create fertility programs in other institutions with limited resources, to bring this vital discussion to the forefront for all pediatric oncologists with their patients.

Poster # 489

A QI PROJECT TO DEVELOP AN ONCOFERTILITY ROADMAP FOR CHILDREN AND ADOLESCENTS WITH CANCER

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Background: Cancer treatment impacts male and female fertility. Fertility counseling and referral to reproductive specialists prior to initiation of chemotherapy are recommended. Barriers to implementation of these recommendations include patient factors (poor prognosis and age), physician discomfort, time constraints, and lack of institutional resources or guidelines.
Objectives: The aims of this quality improvement (QI) project were to 1) develop a roadmap to standardize fertility counseling for pediatric oncology patients before, during, and after therapy; 2) to determine the rate of fertility counseling prior to treatment; and 3) determine the rate of successful fertility preservation in a large pediatric oncology center.
Design/Method: A multidisciplinary team of physicians (oncology, urology, reproductive endocrinology, pediatric endocrinology, adolescent medicine), advanced practice providers, nurses, and psychologists used QI methodology of process mapping to determine desired process and workflow to achieve counseling and access to fertility preservation with a focus on clear identification of patient options, referral process, and clear provider roles. Root cause analysis methodology was used to review the proposed map with multidisciplinary stakeholders. The roadmap was implemented 12/1/2017. Retrospective chart review of patients diagnosed from 12/1/2017 – 12/1/2018 were completed to (1) define the proportion of patients who received fertility counseling and (2) determine rate and type of fertility preservation completed. Data analysis included descriptive statistics according to age, cancer subtype, and in- or outpatient status.
Results: Roadmaps specific to gender (male, female) and pubertal status (pre, post) were developed and implemented.115 patients were identified, with exclusion of 25 due to exclusive

surgical management or prior chemotherapy. 90 patients were included in analysis. These were analyzed by age, 41% <7, 23% 7-12, 29% 13-17, and 6% >/= 18 years of age. Patients were analyzed according to cancer diagnosis, 19% brain tumor, 32% solid tumor, 49% leukemia and lymphoma. For all patients, 90% had documented fertility counseling. Within the oldest age groups, 100% of patients received counseling. 13 patients underwent fertility preservation procedures of sperm cryopreservation, testicular tissue harvest, or oocyte harvest. 7 additional patients received referrals to adolescent medicine per protocol.
Conclusion: Development of roadmaps to address fertility preservation in pediatric and adolescent cancer patients from diagnosis through survivorship is the first necessary step to standardize and improve practice. Publication of these roadmaps may help other institutions to develop a similar process. Within our department, this has allowed for high rates of fertility preservation counseling. We plan ongoing work to focus on supporting fertility following treatment.

Poster # 490

DEVELOPING AN ADOLESCENT AND YOUNG ADULT ONCOLOGY PROGRAM AT A CHILDREN'S HOSPITAL

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Background: Adolescents and young adults (AYA) with cancer have unique needs requiring services distinct from those traditionally available in children's hospitals. To better address the specific care needs of AYA patients undergoing cancer therapy, a growing number of programs are implementing various strategies and organizational models.
Objectives: To describe the strategies and resulting outcomes associated with the development of the comprehensive and multidisciplinary AYA oncology program at Cincinnati Children's Hospital Medical Center.
Design/Method: Metrics for developing AYA oncology programs as described by Ferrari et al. (JCO 28:4850, 2010) regarding treatment (i.e., research, provider education), psychosocial care, and fertility were used to measure program development.
Results: In 2009, the AYA Program at Cincinnati Children's was established. Led by a multi-disciplinary team, it aims to improve quality of life and survival for patients 15-39 years of age by prioritizing four cornerstones of care: Treatment, Fertility, Psychosocial Care, and Survivorship. From 2009 to 2018, the number of AYAs seen at Cincinnati Children's increased by 39%, with a total of 104 new AYAs seen in 2018. From 2012 to 2018, the number of open treatment trials for AYAs has increased from 85 to 94, with over 40 currently open trials for AYAs older than 25y. Twenty inpatient rooms were allocated to AYAs and a separate outpatient clinic space was created for AYAs. In 2017, a monthly AYA Grand Rounds series was developed to provide didactic education to staff. To date, there have been 13 sessions with an average of 20 attendees per session. The fertility team was established in 2009, with database records starting in 2013. Since that time, 501 AYAs have been offered consultation with our fertility team. In 2018, 100% of AYA patients were assigned a Social Worker and a standardized order set was implemented in the electronic medical record to automatically refer all AYA

patients for an initial intake evaluation with a psychologist. To inform clinical initiative development and implementation, a web-based AYA Advisory Program was developed in 2017. To date, a total of 80 AYAs have provided feedback on four clinical initiatives which, in conjunction with discussions prompted by the AYA Grand Rounds, has been used to inform the development of wellness, physical activity, and sexual health programs.
Conclusion: Coordinated efforts directed by a multi-disciplinary leadership team in conjunction with hospital administration and staff have resulted in a robust and unique program designed to meet the specific needs of AYAs with cancer.

Poster # 491

INTEGRATING FRAGMENTED ACTIVITIES: THE USE OF SYSTEMS ENGINEERING IN CREATING AN AYA CANCER PROGRAM

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Background: Adolescent and young adult or AYA patients age 15 to 39, have had the lowest improvement in survival when compared to other ages. This disparity is thought to be independent of biology and instead a product of the immense fragmentation of AYA specific services. Systems Engineering (SE) is a discipline used in aerospace and automotive industries as a way of integrating fragmented systems with the goal of improved safety, quality and cost. Healthcare Systems Engineering (HSE) is a new academic program developed to bring these successes to healthcare. UCLA is in the process of creating an integrated AYA cancer program using SE methodology to help improve survival outcomes and to meet AYA needs.
Objectives: - To introduce the topic of HSE and the general methodology that can be used in a healthcare setting - To demonstrate a novel approach to improving quality care amongst the highly vulnerable AYA population
Design/Method: SE approaches a complex problem through formalized methodology. For this project we will use with following sequential steps crucial to SE: Defining a problem statement and scope of the project, investigation of the objectives as well as interrogatives, formulation and analysis of the program requirements, evaluation of the measures of effectiveness, risk identification and mitigation, program design steeped in systems architecture as well as Lean methodology, and finally verification and validation of the requirements along with continuous improvement.
Results: A detailed list of required "AYA Activities" have been established and the main outcome/quality measures that will be targeted will be the completion of these activities for every new AYA patient in the system at UCLA. . We will also be looking at a variety of metrics that will show the return on investment (ROI) for this type of quality work.
Conclusion: While the importance of systems thinking has become more prominent in healthcare it is often difficult to conceptualize in terms of management, implementation and facilitation. HSE is an emerging field that looks to take the idea of “systems thinking” and operationalize it in a way that allows for improvement at the local, regional and national level. This project is a way of working to translate the SE methodology into a practical format for healthcare. The fragmentation that exists within the care for AYA cancer patients is not unique to

this population and with successful use of HSE in this setting this information could be expanded to other clinical environments.

Poster # 492

DEVELOPING A SUCCESSFUL ONCOFERTILITY PROGRAM AT A CHILDREN'S HOSPITAL

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Background: With continually improving survival rates for pediatric, adolescent and young adult (AYA) cancers, minimizing late effects of therapy is paramount. One important late effect is gonadotoxicity and resulting infertility. The field of oncofertility has grown immensely and is now part of pediatric/AYA oncology. Pediatric centers have struggled to identify patients at risk and provide fertility consultation and preservation options. Likewise, the ability to offer fertility preservation measures has been challenging.
Objectives: We describe the efforts, evolution, and outcomes in the development of the Comprehensive Fertility Care and Preservation Program (CFCPP) at Cincinnati Children's Hospital Medical Center.
Design/Method: Using an IRB-approved CFCPP REDCap database, the following metrics were obtained: new patient encounters in the Cancer and Blood Diseases Institute (CBDI) for oncology and bone marrow transplantation, appropriateness of fertility consult, completion of fertility consult, and fertility preservation option pursued. Patients were considered inappropriate for a fertility consult if they met one or more of the following criteria: surgery/observation only, second opinion only, Phase I or palliative care, prior fertility consult, and family refusal. CBDI administrative databases and weekly patient lists were used to ensure completeness of CFCPP database in capturing new patient encounters.
Results: In September 2013, the multidisciplinary CFCPP team and database were established. The team consists of oncology, reproductive endocrinology, pediatric/adolescent gynecology, urology, research, pathology, ethics, quality improvement (QI), and a fertility navigator. Fertility consults were obtained via a new patient order set in the electronic medical record, outpatient consult order, or email. The fertility navigator role was designed as the main point of contact. Education sessions were routinely provided to all CBDI staff and providers. QI evaluation occurred monthly. Since September 2013, a total of 2,165 patients have been reviewed. A total of 1,041 patients were found to be eligible, of which 981 (94.2%) received a fertility consult. The percentage of eligible patients receiving a fertility consult has increased from 80% (28/35) in 2013 to 98.7% (229/232) in 2018. A total of 214 patients (21.8%) have pursued a fertility preservation option, including 109 ovarian tissue cryopreservation, 2 oocyte cryopreservation, 32 testicular tissue cryopreservation, and 71 sperm cryopreservation. No patient has used any cryopreserved specimens to date.
Conclusion: Integrated efforts led by a multi-disciplinary team and in conjunction with education, ease of consultation, and attention to QI efforts have resulted in a fertility consultation program equipped to meet the oncofertility needs of this pediatric and AYA population.

Poster # 493

HIGH DOSE METHOTREXATE TOXICITY AND CONCOMITANT ADMINISTRATION OF SUPPORTIVE CARE MEDICATIONS

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Background: High dose methotrexate (HDMTX) is widely used in the treatment of certain pediatric malignancies. Well-known side effects associated with HDMTX infusions include renal injury, mucositis, myelosuppression and leukoencephalopathy. Significant toxicity can result in delays in subsequent scheduled chemotherapy. Several supportive care measures are taken to reduce toxicity which includes vigorous hydration, urine alkalization, and the administration of supportive medications. Despite these efforts, patients continue to experience significant toxicity.
Objectives: To determine the incidence of toxicity associated with HDMTX administration in pediatric patients at St. Louis Children's Hospital and to identify modifiable risk factors that can reduce toxicity.
Design/Method: We performed a retrospective chart review of patients in which HDMTX was a major component of their care. Patients receiving 5 g/m2 (leukemia) and 12 g/m2 (osteosarcoma) of methotrexate who were treated from 2010-2017 were included in the study. Data was extracted from both the electronic medical record and paper chemotherapy roadmaps. Data extracted included demographic information, concurrent intravenous (IV) medications, IV fluid administration details, and type of central line. Outcome measures collected included vital sign abnormalities, abnormal laboratory values (white blood cell count, platelet count, alanine aminotransferase elevation, and methotrexate levels), and any imaging results obtained subsequent to the administration. Additional outcome measures included episodes of delayed clearance (>48 hours and >72 hours for leukemia and osteosarcoma patients respectively), length of stay, and readmission to the hospital with admitting diagnoses.
Results: Data was extracted from 461 HDMTX administrations (213 leukemia, 248 osteosarcoma). Delayed clearance was observed in 78% of leukemia administrations and 56.5% of osteosarcoma administrations. Patients with delayed clearance were more likely to have received more doses of supportive care IV medications including leucovorin, ondansetron, ciprofloxacin, and metoclopramide than those with normal clearance. The average number of IV doses in patients with leukemia experiencing delayed clearance was 18.4 doses ± 5.2 versus 12.4 ± 3.5 for those without delays and 24.3 ± 11.7 versus 17.5 ± 7 in patients with osteosarcoma ($p<0.0001$ for both populations). Additionally, delays in future chemotherapy cycles were seen in 27.7% and 34.3% of encounters for patients with leukemia and osteosarcoma respectively. Readmission rates were the same across the two populations at 6.1%; the most common readmission diagnoses were mucositis, fever, and neutropenia.
Conclusion: HDMTX infusions continue to cause significant morbidity to patients. Supportive care practices, including administration of IV medications with interruptions to hydration may be contributing to delayed clearance and increased toxicity.

Poster # 494

MANAGEMENT OF HIGH-DOSE METHOTREXATE INFUSIONS DURING AN INTRAVENOUS SODIUM BICARBONATE SHORTAGE

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Background: High-dose methotrexate (HDMTX) plays a critical role in modern treatment protocols for a variety of pediatric malignancies. Standardized supportive care practices including hyper-hydration, urinary alkalinization, and leucovorin rescue have led to improved HDMTX tolerance. However, national shortages of chemotherapy and supportive care agents may require alterations in standard regimens.
Objectives: We describe our institutional experience in the management of patients receiving HDMTX during an intravenous (IV) sodium bicarbonate shortage.
Design/Method: We performed a retrospective chart review of patients admitted to Texas Children's Hospital for HDMTX during a national shortage of IV sodium bicarbonate from March to October 2017. All patients received 5 g/m2 of IV methotrexate over 24 hours with standard hydration of 125-200ml/m2 followed by leucovorin rescue. All patients received IV hydration consisting of either D5 1/2 NS (Group A), D5 1/4 NS (Group B), or D5 1/4 NS + 4meq NaHCO3 (Group C). During the shortage all patients were either Group A or Group B and received urinary alkalinization with enteral sodium bicarbonate, enteral sodium citrate, bolus parenteral sodium bicarbonate, or a combination of the above. Group C received entirely IV urinary alkalinization. Mean 24-hour methotrexate levels (CPss) in our cohort were compared to pre-drug shortage institutional methotrexate levels (Group C).
Results: Twenty-five patient charts were reviewed for a total of 79 infusions of HDMTX administered during the IV sodium bicarbonate shortage. Forty-eight infusions were administered in Group A, and 31 infusions were administered in Group B. These were compared to 952 historical infusions in Group C. The mean CPss was significantly different among the groups, at 25 µM + 16 µM for Group A, 53 µM + 38 µM for Group B, and 62 µm + 24 µM for Group C ($p<0.001$). CPss was <20 µM in 21 (44%) Group A infusions, nine (29%) Group B infusions, and nine (0.01%) Group C infusions. Of note, one patient received all infusions per Group B with all 4 CPss <20 µM. Patients had a median of 2 (range 1-4) HDMTX infusions during the study period.
Conclusion: Drug shortages effecting chemotherapy and supportive care for oncology patients occur frequently. Our series demonstrates that in the setting of IV sodium bicarbonate shortage, the composition of hydration IV fluids may impact methotrexate clearance.

Poster # 495

ORAL BICARBONATE SUPPLEMENTATION TO DECREASE TIME TO HIGH DOSE METHOTREXATE ADMINISTRATION

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Background: High dose methotrexate (HD MTX) is an integral chemotherapy in childhood acute lymphoblastic leukemia (ALL), lymphoma, and osteosarcoma treatment. Due to toxicity and excretion profile, HD MTX cannot be started until the patient's urine is sufficiently dilute and alkaline. Unfortunately, delays to starting HD MTX are common. This timing is often further complicated by administration of intrathecal (IT) chemotherapy under sedation several hours earlier, before which patients are NPO and unable to self-hydrate.
Objectives: In this QI project, we seek to address these delays with the following SMART aims: 1) To reduce average length of time from start of IV alkalinization to administration of HD MTX by 3 hours in 12 months 2) To increase the % of patients who start HD MTX within goal of 6 hours of IT MTX by 20% in 12 months.
Design/Method: An interdisciplinary effort including inpatient and outpatient nurses and providers identified several key drivers impeding the administration of HD MTX in a timely manner.Our first PDSA cycle focused on education and other interventions during the patients' inpatient stay. The medical providers and the inpatient and outpatient nursing teams were educated on the importance of starting HD MTX within 6 hours of IT MTX. IV fluid orders were also modified to optimize urine alkalinization and dilution. During our second PDSA cycle, all HD MTX patients were prescribed oral sodium bicarbonate to take on the day prior to admission. Other institutions have given oral bicarbonate for urine alkalinization during IV bicarbonate and acetate shortages, so we hypothesized that home oral bicarbonate would alkalinize urine ahead of admission, thus decreasing the time needed for IV alkalinization, and also empower patients and their families to self-alkalinize even when NPO. Due to positive results from our second cycle, our 3rd PDSA cycle optimized administration of oral bicarbonate.
Results: We have achieved a statistically significant (p=0.017 Cycle 1 vs. Cycle 3) decrease in the time to alkalinization in our osteosarcoma patients. Furthermore, the proportion of patients who received HD MTX within 6 hours of their IT MTX increased from 51.6% in Cycle 1 to 66.7% after Cycle 2. Oral bicarbonate supplements were generally well tolerated.
Conclusion: By identifying and addressing key drivers, specifically the lack of education amongst providers and our patients' tendency to have acidic urine upon admission, we were able to decrease the time to alkalinization, and more patients received HD MTX in a timely manner.

Poster # 496

PEDIATRIC DESENSITIZATION PROTOCOL FOR ETOPOSIDE: PREVENTING DRUG OMISSION DURING DRUG SHORTAGES

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Background: Etoposide is part of many clinical trials within the COG. Etoposide is known to produce hypersensitivity reactions during administration. Substitution with etoposide phosphate, a water soluble prodrug that is rapidly converted to etoposide in plasma, and has less potential for hypersensitivity reactions is usually the next step. Desensitization protocol for etoposide has been reported for adult oncology patients. Drug shortages could result in elimination of a drug from treatment protocol and could compromise patient outcomes.
Objectives: To describe an institutional pediatric focus protocol for desensitization of Etoposide to prevent drug omission in treatment of pediatric malignancies.

Design/Method: Case report
Results: A 17 year old female with high risk HL enrolled in AHOD1331 experienced a severe hypersensitivity reaction to etoposide after the second dose of etoposide during cycle 1. Patient experienced chest pain, shortness of breath, tingling/numbing sensations to her face and full body flushing after twenty-three milliliters of etoposide had infused. Etoposide was discontinued and substituted for etoposide phosphate for the remainder of the cycle. Due to the drug shortage and inability to procure the etoposide phosphate for subsequent cycles our team devised an institutional etoposide desensitization protocol adapted from what was reported in the adult literature. Premedication with prednisone, albuterol, montelukast, and ranitidine was started 24 hours prior to the start of chemotherapy. Etoposide was prepared in three 10-fold dilutions, a 12-step incremental approach was taken with escalating infusion rates, and the total dose was given over 6 hours. The desensitization protocol was well tolerated and the patient was able to complete 5 cycles with no reactions while remaining on study.
Conclusion: In the presence of etoposide phosphate drug shortage, a pediatric focused 12-step desensitization protocol and premedication helped in the successful completion of drug administration and prevented drug omission from the treatment protocol.

Poster # 497

AERO-DIGESTIVE REACTIONS TO INTRAVENOUS PENTAMIDINE INFUSION FOR PNEUMOCYSTIS JIROVECI PROPHYLAXIS

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Background: Intravenous pentamidine (IVP) is used for Pneumocystis jiroveci prophylaxis in children who cannot not tolerate standard trimethoprim/sulfamethoxazole therapy. Side effects observed during IVP infusion are reported in low frequencies and often retrospectively, leading to great subjectivity and possible underreporting. The most frequently reported side effects in children include nausea (12%) and perioral paresthesias (<5%). The incidence of symptoms associated with IVP has appeared higher in our patient population. We designed a prospective study utilizing a survey platform to minimize the recall bias.
Objectives: We investigated the incident and characteristics of aero-digestive reactions observed during intravenous pentamidine infusion for Pneumocystis jiroveci prophylaxis in patients undergoing chemotherapy or following hematopoietic stem cell transplantation (HSCT).
Design/Method: Patients actively receiving IVP or those who have received in 2018 (4mg/kg, infused over 1 hour) for pneumocystis jiroveci prophylaxis were included. Each patient was asked to complete a one-time survey, which included thirty-one questions. Both participating patients and their parents have contributed to the completion of the survey.
Results: In this ongoing study, 27 patients participated, and 4 declined. Median age was 8 (1-19), 4 were younger than 4 years of age, 20 were male, the most common diagnosis was leukemia in 19 cases, 21 were chemotherapy cases and 6 HSCT recipients. All patients were given ondansetron prior to infusion. Reactions were observed in 24 (89%) patients surveyed and 20 (83%) reported onset of symptoms within the first 30 minutes of infusion. Symptoms did not

subside upon infusion completion in 22 (92%) patients and recurrence of symptoms was seen in 20 (83%) cases. The five leading reported symptoms were congestion (n=11; 46%), lip tingling (n=8; 33%), nausea (n=7; 29%), tongue tingling (n=4; 17%), and throat swelling (n=4; 17%). A single symptom was reported in 10 (42%) cases. One participant experienced as many as 8, 1 patient had 7, 2 cases reported 5 symptoms. No patients discontinued IVP due to side effects. Two patients were given diphenhydramine without resolution of the symptoms.
Conclusion: Aero-digestive side effects of IVP are very common, typically starting early during infusion, generally mild and tolerated, self-limited and tend to be recurrent. Advantages of this study include low possibility of recall bias and obtaining direct answers to specific questions in the survey. It is possible that these aero-digestive symptoms are not mediated through a type-1 hypersensitivity reaction.

Poster # 498

INVESTIGATING POTENTIAL DRUG-DRUG INTERACTIONS IN CHILDREN RECEIVING CHEMOTHERAPY

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Background: Pediatric oncology patients receive numerous medications during chemotherapy admissions, increasing the risk of potential drug-drug interactions. Although it is well documented in adult literature that the incidence of patients receiving interacting medications is high, evidence regarding the incidence in pediatrics remains limited.
Objectives: To evaluate the incidence of potential drug-drug interactions among pediatric oncology patients admitted for chemotherapy.
Design/Method: One hundred admissions for chemotherapy at Texas Children's Hospital from November 2016 to May of 2017 were reviewed. All medications causing QT prolongation were counted. EKGs for all patients were reviewed in the medical record. Twenty-eight of the admissions were further analyzed using lexi-com with significant interactions being defined as either a risk rating of D or X.
Results: Of the 100 patients evaluated, nearly half (n=44) received chemotherapy for a diagnosis of leukemia or lymphoma. Only 4 of the 100 patients received an interacting combination of an antifungal and an antineoplastic medication. The most commonly seen interaction was Etoposide with either Fluconazole or Voriconazole. Importantly, however, all 4 of these patients had their antifungal appropriately held until at least 24 hours after completion of Etoposide, decreasing their risk of interaction. Only 2 patients admitted for chemotherapy did not receive any QTc prolonging medications. The other 98 patients received between 1 and 8 (with a mean of 3) QTc prolonging medications. One third (n=33) of patients received 4 or more QTc prolonging medications. Of those children, one-fourth (n=8) did not have a documented EKG prior to or during admission. Twenty-eight of the 100 admissions were further evaluated with lexi-com. Over one-fifth (n=6) of those admissions were flagged as having a "D" risk rating interaction. The majority of those interactions (n=4) were flagged for use of numerous CNS depressants, the most in one admission being up to 7. One admission received an "X" rating for the use of both a beta agonist and beta antagonist. The beta antagonist additionally had a "D" rating for reaction with doxorubicin in the same patient, potentially increasing the concentration of doxorubicin

with concomitant use.
Conclusion: Pediatric patients admitted to the hospital for antineoplastic therapy are at high risk for drug-drug interactions. The additive effects of multiple agents that cause QTc prolonging or respiratory depression should be carefully monitored.

Poster # 499

NAVIGATING THE MEDICAL SETTING FOR PARENTS OF YOUTH DIAGNOSED WITH SOLID TUMORS

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Background: Families of those diagnosed with cancer often face challenges with care coordination, finances, unmet medical services, and access to non-medical services. Patient navigation aims to provide individualized assistance to families to help overcome barriers and facilitate timely access to quality care through the cancer journey. Few studies involving patient navigation have been done in the pediatric oncology setting. To date, no literature exists on the potential role of patient navigation in pediatric patients diagnosed with solid tumors.
Objectives: Determine whether families of pediatric patients with solid tumors feel the use of a patient navigator would be beneficial with regards to psychosocial needs, communication with the medical team, and overall healthcare satisfaction.
Design/Method: Parents of 20 pediatric patients diagnosed with a solid tumor were contacted to complete 2 surveys after informed consent was obtained. The first survey was created to include center-specific questions regarding diagnosis, treatment, psychosocial needs, communication with the medical team, and the potential roles of a patient navigator. The second survey was the PedsQL Healthcare Satisfaction Generic Module Version 3.0. All data was analyzed using SPSS and a p-value ≤ 0.05 was considered to be significant.
Results: Upon diagnosis, 20% of families reported receiving inconsistent information from various medical team members. Twenty-five percent of families indicated additional information about community resources would have been helpful. Twenty percent of caregivers also reported a lack of information on available hospital support groups and another 20% of caregivers also reported wishing they had received more opportunities for financial assistance. Families reported significantly lower satisfaction with the medical team's ability to address their emotional needs than all other domains except satisfaction with information provided. With regards to the use of a patient navigator, 90% of families indicated a navigator would be helpful to address needs and identify who to contact for assistance and 70% felt a navigator would be helpful to discuss strategies on how to take a more active role in their child's care.
Conclusion: Families of youth diagnosed with solid tumors face a number of barriers to quality care. The results of the current study demonstrate families believe the use of a patient navigator would aid with these barriers. Incorporation of patient navigators in the care of pediatric patients with solid tumors warrants further investigation.

Poster # 500

SATISFACTION WITH INTERPERSONAL RELATIONSHIP WITH NAVIGATOR AMONG CAREGIVERS OF CHILDREN WITH CANCER

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Background: Patient Navigators are trained to provide support and guidance to patients throughout the cancer care continuum. They help "navigate" through the maze of doctors' clinics, outpatient centers, insurance and payment systems, patient-support organizations, and other components of the health care system. Yet, there is no existing patient satisfaction tool to assess the patient navigation program in the Philippines for pediatric cancer.
Objectives: This study aims to evaluate satisfaction with the patient navigation program using a validated Satisfaction with Interpersonal Relationship with Navigator (SN-I-Ph) Measure among Filipino caregivers in a tertiary referral center for childhood cancer. Other goals of the study were to describe the demographics of the participants, to validate (English/Filipino) the tool for use among Tagalog-speakers, and to determine socio-demographic and clinical factors associated with satisfaction among caregivers.
Design/Method: The translation process consisted of three phases. Phase I was the modification of the questionnaire for cultural appropriateness. Phase II included the translation into Filipino and the testing of its content validity. Phase III was the road test on the evaluation of the internal consistency and the reliability of the Interpersonal Relationship with the Navigator (SN-I) measure. Caregivers of Filipino children with cancer were then recruited to answer the survey.
Results: The SN-I-Ph was modified for cultural appropriateness; content validity for all 9 items was acceptable with score of 4.5-5 and internal consistency showed satisfactory results with cronbach alpha of 0.9067. A total of 202 participants were recruited to join the survey. Results showed mean±SD of 42.6±7.8. All of the 9 items showed excellent satisfaction. Socio-demographic and clinical factors were analyzed using odds ratio in logistic regression. A cut off score of 4.5 was set to categorize as the participant as very satisfied and less than 4.5 as somehow satisfied. Out of the 202 participants, 187 (92.6%) were categorized as very satisfied and 15 (7.4%) as somehow satisfied. The socio-demographic and clinical factors showed no clinical significance with p value showing >0.05.
Conclusion: This study showed good satisfaction with the interpersonal relationship of the navigators among caregivers. Participants enrolled in the patient navigation program reported a positive overall experience with the medical care.

Poster # 501

TCRαβ/CD19 DEPLETED HAPLO-HSCT + ZOLEDRONATE FOR PEDIATRIC MALIGNANCIES: PRELIMINARY FINDINGS

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Background: For many children with hematologic and high-risk solid tumors, hematopoietic stem cell transplant (HSCT) may be the only curative option. T-cell depleted haploidentical (haplo-) HSCT is a good option for patients lacking an HLA-matched donor. A novel graft preparation method selectively depletes TCRαβ+ and CD19+ cells, which reduces the incidence of graft-versus-host disease (GVHD) and post-transplant lymphoproliferative disease while retaining TCRγδ and NK cells in the graft, which have potent effects against tumors and infectious agents. TCRγδ cells can be activated, in vivo, with zoledronate to further promote graft-versus tumor/leukemia activity.
Objectives: The objective of this clinical trial is to evaluate the safety of TCRαβ+/ CD19+ depleted haplo-HSCT in conjunction with post-transplant zoledronate to treat hematologic malignancies and high-risk solid tumors in children.
Design/Method: In this single institution, ongoing phase 1 clinical trial, patients receive a conditioning regimen prior to TCRαβ/CD19-depleted haplo-HSCT on Day 0. The first three subjects were transplanted without zoledronate verifying that engraftment was comparable to that of patients receiving TCRαβ/CD19-depleted grafts at other institutions. Zoledronate was administered on Day +63 to three subsequent subjects, one patient receiving a second dose on Day +91. Patients enrolled after 2018 will receive five doses of zoledronate at 28-day intervals, beginning on Day +28.
Results: Six children (3 males, 3 females, ages 3-17) have been treated (3-neuroblastoma, 1-rhabdomyosarcoma, 1-B-cell ALL, 1-AML & osteosarcoma). All received reduced intensity conditioning, post-transplant GVHD prophylaxis and tolerated the graft infusion well. Median cell doses infused were 8.3 x10^6 CD34+/kg (range 7.3 - 22.9 x10^6) and 4.6 x10^4 TCRαβ+/kg (range 3.0 - 7.7 x10^4) with all subjects engrafting rapidly; the median day for engraftment was Day +16 (range 13-19) for neutrophils and Day +18 (range 16-23) for platelets. Two subjects experienced viral reactivation (CMV and adenovirus, respectively) and one died from complications of fulminant EBV infection on Day +84. Acute GVHD was limited to skin-only (grades 1 and 3) in 2 patients resolving with brief steroid treatment. Two subjects with neuroblastoma who responded to treatment (no zoledronate) went off study at Day +100 to receive other therapy. Three subjects received zoledronate but went off study following relapse. One subject (rhabdomyosarcoma) experienced a complete response after transplant (no zoledronate), and is now 2 years in remission.
Conclusion: Preliminary findings show this transplant procedure is well tolerated and results in rapid engraftment with a low incidence of skin-only GVHD. Support from UWCCC, UWICTR, Cannonball Kids

Poster # 502

HAPLOIDENTICAL STEM CELL TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE IN PEDIATRIC CANCERS

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Background: Haploidentical stem cell transplantation (haplo SCT) with post-transplant cyclophosphamide (PTCy) for malignant disorders represents a cost-effective mode of in vivo T cell depletion with resultant disease-free survival rates similar to or superior to matched donor

transplants in some series.
Objectives: We present data over 5 years in children who underwent haplo SCT with PTCy for malignant disorders
Design/Method: We performed a retrospective analysis of case records of children up to the age of 18 years from January 2014 to April 2018 at the paediatric blood and marrow transplant unit, Apollo hospitals, Chennai, India.
Results: A total of 24 children underwent haplo SCT during the study period of which 11 (45%) were diagnosed to have acute lymphoblastic leukaemia (ALL), 10 (41%) with acute myeloid leukaemia (AML) and one child each with mixed phenotype acute leukaemia (MPAL), chronic myeloid leukaemia with ALL blast crisis and relapsed Hodgkins lymphoma after autograft. Disease status at the time of HSCT was CR1 in 8 (33%), CR2 in 15 (62%) and active disease in one child with AML M7. Source of stem cells were predominantly peripheral blood in 22 (91%) children and bone marrow in 2 (9%). Donors were siblings in 5 (20%), mother in 2 (8%) and father in 17 (70%) children. Engraftment by D+17-21 was achieved in 21/24 (90%) children with primary graft failure in 2 (8%) and one child dying before engraftment from sepsis. Among those who engrafted, acute GvHD was noted in 13/21 (61%) and CMV reactivation in 15/21 (71%) transplants. Donor lymphocyte infusions were given pre-emptively in 11 (45%) children. Relapse was noted in 2/21 (9%) children who engrafted with disease free survival of 91% in our cohort. However, overall survival was 16/24 (66%) in our cohort with varied causes of death. Among the 8 children who died, 6 (75%) were in CR2 while 2 (25%) were in CR1.
Conclusion: Excellent relapse free survival can be achieved with haplo SCT and PTCy in children with malignant disorders particularly in those in CR1. Post-transplant strategies including early withdrawal of immunosuppression and pre-emptive donor lymphocyte infusions will further aid in improving relapse free survival. Conditioning needs to modified based on patient characteristics and tolerability with myeloablative conditioning being well tolerated. PTCy priced at USD 25 is an excellent cost-effective modality of T cell depletion with tolerable rates of GvHD.

Poster # 503

INCIDENCE RISK FACTORS, OUTCOME OF BLOODSTREAM INFECTIONS DURING FIRST100 DAYS POST PEDIATRIC HSCT

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Background: Bloodstream infections (BSI) are a frequently observed complication after hematopoietic stem cell transplant (HSCT) and are an important cause of morbidity and mortality.
Objectives: To identify the incidence, risk factors, causative organisms, susceptibility pattern, and related mortality rate of BSI post HSCT in pediatric cancer patients
Design/Method: We retrospectively collected the clinical and microbiological data during the first 100 days from 302 pediatric patients who underwent HSCT for a malignant disease at our institute between January 2013 and June 2017. The median age at transplantation was 8.4 years. A total of 164 patients underwent autologous and 138 allogeneic HSCT.
Results: The overall incidence of BSI was 37% with 92% of infectious episodes occurring

during the pre-engraftment phase. Amongst the 112 patients who developed BSI (median 5.2 days after HSCT), 141 separate pathogens were isolated from the blood cultures. Gram-positive bacteria (GPB) accounted for 54.6% of 141 isolates, Gram-negative rods (GNR) for 43.9% and fungi for 1.4%. Staphylococcus Hominis and Staphylococcus Epidermidis were the most commonly isolated GPB, while Escherichia Coli and Klebsiella Species were the most commonly isolated GNB. 45% of GNB were Extended-Spectrum Beta-Lactamase (ESBL) positive and 19% were MDR organisms. All patients received routine fluoroquinolone prophylaxis and fluoroquinolone-resistance was common, both among GPB and GNR (92 % and 69%, respectively). Risk factors for BSI in univariate analysis were allogeneic HSCT, delayed time to engraftment more than 12 days and previous BSI within 6 months before HSCT, while in multivariate analysis only HSCT type (Allo versus Auto P= 0.03) and previous BSI within 6 months before HSCT(P= 0.016) were significant. Overall survival at day 100 was 97.68%. Overall survival did not differ significantly between patients with and without BSI.
Conclusion: Allogeneic HSCT recipients, delayed time to engraftment more than 12 days and previous BSI 6 months before HSCT are associated with increased risk of post-transplant BSI.

Poster # 504

CYTOMEGALOVIRUS REACTIVATION IN PEDIATRIC PATIENTS AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT

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Background: Cytomegalovirus (CMV) infection represents a significant complication following allogeneic hematopoietic cell transplant (allo-HCT). Although there have been notable advances in detection methods and treatment, CMV reactivation remains a prominent problem following allo-HCT affecting 12 - 40% of pediatric patients and contributing to increased morbidity and mortality. Risk factors for CMV reactivation include donor-recipient CMV serostatus, graft source, and human leukocyte antigen (HLA) match. Few studies have explored CMV reactivation and its effect on clinical outcomes in pediatric patients.
Objectives: To evaluate the effect of CMV reactivation on clinical outcomes of survival and relapse among pediatric patients undergoing allo-HCT at a single institution.
Design/Method: We conducted a retrospective analysis of pediatric patients who received an initial conventional or T-cell depleted allo-HCT for malignant or non-malignant diseases from related or unrelated donors from 2010 – 2018 at Memorial Sloan Kettering Cancer Center. Clinical Research Database and Clinical Information System were utilized to identify patients and collect clinical data. CMV reactivation was defined as ≥ 1 measurement of CMV polymerase chain reaction >500 in whole blood or >137 in plasma. This study was approved by Institutional Review Board.
Results: From January 2010 to June 2018, 227 pts (age 54 days – 26.6 years) received allo-HCT on the pediatric service for malignant (N=143) and non-malignant (N=84) diseases. Patients at risk of CMV reactivation (N=157) were analyzed by serostatus (D+/R+ N=90; D+/R- N=29; D-/R+ N=38). Forty-nine patients (22%) reactivated CMV, including 42% of D+/R+ (N=38) and 29% of D-/R+ (N=11) recipients. The median time to reactivation was 25 days (IQR 14.5 – 35.5)

and median CMV maximum viral load was 3,407 copies/mL (IQR 730 - 5620). Six patients (12%) with reactivation developed CMV disease. Malignant disease relapse was seen in 8 of 29 (28%) patients reactivating CMV compared to 17 of 113 (15%) patients who were known to not reactivate CMV. One-year overall survival for reactivated and non-reactivated CMV patients was 82% and 87%, respectively.
Conclusion: CMV reactivation remains a significant complication in pediatric allo-HCT. CMV reactivation occurred in 22% of all patients and 31% of those at risk for reactivation. Surprisingly in this cohort, no recipients on D+/R- serostatus reactivated CMV, which may reflect passive transfer of CMV antibody rather than true prior infection in this pediatric cohort. Further evaluation of risk factors and treatment thresholds will help stratify patients for novel prophylactic treatment and could translate into improved outcomes.

Poster # 505

PREVALENCE OF VIRAL DISEASES AND COMPLICATIONS IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Viral infection or reactivation in immunocompromised patients is a serious complication in pediatric hematopoietic stem cell transplant recipients. Severe viral disease can lead to encephalitis, liver failure, and engraftment failure, in addition to toxicity from antiviral drugs. There is still debate as to which viruses contribute most to serious complications and require prophylactic treatment.
Objectives: Evaluation of the prevalence of viral diseases and serious complications in pediatric stem cell transplantation to support the development of procedures for screening and treatment of viral infections.
Design/Method: We utilized a historical database of all pediatric hematopoietic stem cell transplant patients cared for in the Division of Pediatric Hematology/Oncology at UCLA and report a retrospective assessment of these patients focusing on viral diseases and clinical outcomes. Along with demographic data, patients were characterized by potential risk factors for viral disease, such as primary disease, transplant graft, match status, time to engraftment and pre-engraftment viral serology. We report 172 transplants in 161 patients performed at the service in the period from January 2008 through September 2017. Pre-transplant screening included serologies for CMV, HSV, EBV, HIV and hepatitis viruses. Prophylaxis was administered to patients seropositive for CMV and HSV, consisting of ganciclovir 6 mg/kg over days -7 to -2 and acyclovir 10-20 mg/kg/dose BID or TID from day 0 to +100, respectively.
Results: Of the 42 patients who died, we have identified 17 cases in which infections by CMV, HSV, adenovirus and HHV-6 had a relevant role in their demise. The incidence of seven common viral diseases was also documented (CMV (n=31, 18.0%), EBV (n=2, 1.2%), HSV (n=12, 7.0%), adenovirus (n=15, 8.7%), BK (n=24, 13.9%), HHV-6 (n=25, 14.5%)). Among patients who received prophylaxis, the incidences of CMV viremia and HSV infections were 15.8% and 5.6%, respectively; CMV disease occurred in 25.0% of CMV seropositive patients. Graft failure occurred in 7.1% of patients. Of 127 transplants for malignant disease, 10.2% patients died of relapse. Of 42 reported deaths, GvHD was the cause of death in 14.3% of these

cases. Infections in the absence of relapsed disease, graft failure, SOS or GvHD contributed to 30.9% of deaths. Respiratory viral infections contributed to the death of 6 patients (14.2%).
Conclusion: Infection or reactivation of these viruses contribute to substantial morbidity and mortality in this patient population, and further studies should investigate susceptibilities to reactivation, as well as potential prophylactic methods, to improve patient care.

Poster # 506

VITAMIN D SUPPLEMENTATION IN PEDIATRIC PATIENTS UNDERGOING TRANSPLANT: ROOM FOR IMPROVEMENT

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Background: Up to 70% of pediatric patients have low vitamin D (VD) levels (VDL) prior to hematopoietic stem cell transplantation (HSCT). Studies have found that patients with VD deficiency before HSCT and at day +100 have significantly lower 1-year overall survival and increased mortality associated with graft-versus-host disease (GVHD). VDL <20ng/mL are considered deficient, <30ng/mL are insufficient, ≥30ng/mL are sufficient, and >50ng/mL are optimal.
Objectives: This study assessed practices of VD evaluation and VD supplementation (VDS), and investigated the association between VDL and complications (GVHD, veno-occlusive disease [VOD]). This is one of the largest retrospective studies investigating practices surrounding VD, and the association between VDL and complications in the pediatric population.
Design/Method: Patient records were abstracted for VDL through a retrospective review of patients that received HSCT at CHLA between January 2013 and April 2018. Overall survival (OS) time is defined as the time between HSCT and the time of death, from any cause. Those who remained alive were censored at the time of last contact.
Results: Of 314 encounters included in the study, baseline (BL) VDL were available for 135 patients. Of these, 61% had insufficient or deficient BL VDL, and 9% had optimal VDL. VDS was higher among those with insufficient or deficient BL VDL ($p = 0.008$). Only 16% of patients achieved an optimal VDL during the HSCT process, regardless of supplementation status. There was no difference in demographics between those with and without BL VD assessments or between those who did and did not develop GVHD or VOD. There was no difference in VDS by GVHD or VOD status. There was no difference in survival by baseline VDL or by VDS.
Conclusion: We found that only 43% of patients had BL VDL assessed. Patients with insufficient or deficient VDL were significantly more likely to receive VDS, but still less than half received supplementation and only 16% ever achieved optimal VDL. There was no association between BL VDL or VDS and HSCT complications or survival, which is expected since such few patients achieved, and none sustained, optimal VD levels. This demonstrates that regular supplementation is not adequate to achieve or maintain the optimal VDL that may be associated with improved outcomes. VD deficiency is a known and, importantly, modifiable risk factor that may be implicated in transplant outcomes. Further prospective studies are required to establish effective practices for monitoring and sustaining optimal VDL and to examine how this affects outcomes.

Poster # 507

QUALITY IMPROVEMENT OF ENTERAL NUTRITION IN PEDIATRIC PATIENTS UNDERGOING STEM CELL TRANSPLANTATION

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Background: Most pediatric patients undergoing stem cell transplantation (SCT) require nutrition support. Historically, parenteral nutrition (PN) has been the nutrition support of choice for SCT patients. Recent research indicates enteral nutrition (EN) is feasible and beneficial for this population, but uniform approaches in EN implementation are often lacking.
Objectives: To standardize and increase the utilization of EN over PN by implementing a standard of practice (SOP) guideline for nutrition support in a single institution's pediatric SCT population.
Design/Method: A retrospective chart review was completed on 32 patients who underwent SCT at our institution prior to implementation of the SOP and compared to 26 patients transplanted after the SOP. Data capture included the use of PN and EN, length of time on PN and/or EN, whether the patient was discharged on PN and/or EN and per patient PN or EN charges. Rates of complications with feeding tube placement, number of tubes placed, incidence of bacteremia, gut graft versus host disease (GVHD), and TPN cholestasis was collected. A descriptive analysis was completed.
Results: Pre-SOP, PN was initiated on 31 patients (97%) compared to only 18 patients (69%) post-SOP. For those started on PN, the average number of days on PN decreased from 18 days pre-SOP to 7 days post-SOP. EN initiation increased post-SOP with 20 patients (77%) having EN started post-SOP while only 14 patients (44%) had EN started pre-SOP. For those started on EN, the average number of EN days did not change from pre to post SOP, with both groups having an average of 19 days of EN. Four patients required no nutrition support post-SOP, while pre-SOP, all patients received some kind of nutrition support during their transplant period. No patients were discharged home on PN post-SOP while 16 patients (50%) were discharged home on PN pre-SOP. The average PN charge decreased from pre- to post-SOP by $14,074.16/patient. The average EN charge increased by $251.18/patient from pre- to post-SOP. Overall, the average amount charged per patient for nutrition support (EN+PN) decreased by $13,852.98 (59%) from pre- to post-SOP. No adverse events with the placement of NG or NJ tubes were observed.
Conclusion: EN in pediatric SCT is safe to use. With the help of an SOP we were able to provide a uniform nutritional support system and standardize care with increased utilization of EN and fewer patients discharged on PN. This resulted in a cost-savings for our population.

Poster # 508

ACTH STIMULATION TEST TO DIAGNOSE ADRENOCORTICAL INSUFFICIENCY IN PEDIATRIC HCT RECIPIENTS

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Background: Children undergoing hematopoietic cell transplantation (HCT) are at high-risk of developing adrenocortical insufficiency (AI).
Objectives: Primary objective of this study was to determine prevalence of AI in pediatric HCT recipients.
Design/Method: Under an IRB approved study, we identified HCT recipients who were tested for AI at our institution. Adrenocortical function was evaluated by ACTH stimulation tests ("stim test"). A low-dose stim test was performed by giving 1 mcg cosyntropin intravenously and measuring serum cortisol levels at 0, 10, 20 and 30 minutes. A high-dose stim test was performed by giving 15 mcg per kg (max 250 mcg) cosyntropin and measuring serum cortisol levels at 0, 30 and 60 minutes. AI was diagnosed if peak serum cortisol level was below 18 mcg/dL. AI was classified as (1) adrenal suppression from the effects of exogenous glucocorticoids or other medications on hypothalamic-pituitary (HP) axis, (2) central AI due to direct effect on HP region by tumor, surgery, or cranial radiation therapy; or (3) primary AI due to adrenal gland pathology.
Results: Between years 2006 -2017, 269 patients, median age 10.2 years (range 0.1 – 22.4) underwent 349 transplants (59% allogeneic, 41% autologous). Of these, 66 patients who had 87 transplants underwent adrenocortical function testing. In those tested, a majority of the transplants were allogeneic (73.6%) and were performed for malignant diseases (66.7%); and 38 patients had prior glucocorticoid exposure (57.6%). A total of 83 stim tests were performed, and no adverse effects were noted. Of these, 63 were high-dose, 6 were low-dose, and 14 were low-dose followed by high-dose. AI was observed in 14/66 patients (21%). The most common cause of AI was adrenal suppression (12/14 cases, 86%); 10 had exposure to glucocorticoids and 2 to megestrol. One patient had primary AI related to MIRAGE syndrome, and another from adrenal gland resection. There was a higher rate of AI in patients with acute GVHD (29%) compared to those without acute GVHD (12%). Of the 31 children with acute GVHD, 23 (74%) were found to have normal adrenal gland function despite prior glucocorticoid exposure.
Conclusion: We observed a high prevalence of AI in pediatric HCT recipients. The stim tests demonstrated recovery of HPA axis in a majority of patients with acute GVHD and prior glucocorticoid exposure. ACTH stimulation testing is a useful, objective measure of HPA axis function; it should be used to guide replacement and stress dosing of glucocorticoids in high risk HCT recipients.

Poster # 509

EXAMINING THE UTILITY OF AMMONIA LEVELS IN SINUSOIDAL OBSTRUCTION SYNDROME

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Background: Sinusoidal Obstruction Syndrome (SOS) is a rare but medically significant complication, which can occur following conditioning for hematopoietic stem cell transplant (HSCT). SOS is characterized by the clinical criteria of weight gain, jaundice, and

hepatomegaly. SOS is a challenging diagnosis, as there is no laboratory value that is diagnostic of SOS. The main lab value used at this time is total bilirubin, which correlates with the clinical criteria of jaundice. It is known that elevated blood ammonia levels reflect liver problems. SOS is a dysfunction of the liver so we hypothesize that hyperammonemia correlates with the course and severity of SOS.
Objectives: Our objective was to evaluate the potential relationship between ammonia levels and the disease course of SOS.
Design/Method: This is a retrospective chart review of twenty-three children from 2014-2018 who underwent HSCT at Riley Hospital for Children and had a diagnosis of SOS. In patients who had ammonia levels checked, we correlated ammonia levels with bilirubin and creatinine levels as well as with clinical course including the need for critical care interventions, including dialysis and mechanical ventilation.
Results: Eight of twenty-three patients had ammonia levels drawn during their clinical care and all were found to have hyperammonemia. Five of these patients had ammonia levels above 100. Ammonia levels peaked around the time of SOS diagnosis and resolved as the course improved with defibrotide treatment. This pattern is distinct from idiopathic hyperammonemia, and has not previously been described in pediatric SOS patients. Ammonia levels correlated with total bilirubin and creatinine level trends. The length of hyperbilirubinemia was shorter in the four of eight patients who were started on ammonia scavengers. Seven of the eight children required PICU management and six of the eight required critical care interventions of ventilation and dialysis. One patient with significant hyperammonemia did not require intubation or dialysis but was started on ammonia scavengers early in her course.
Conclusion: SOS continues to be a rare but potentially lethal complication following transplant. We found that eight children with severe SOS also had hyperammonemia, which correlated with their SOS courses. Routine monitoring of ammonia levels prospectively in patients at high risk for SOS may be useful in determining the development and progression of SOS as well as provide an opportunity for earlier intervention. Ammonia scavengers and/or dialysis may be indicated as additional therapy in selected patients with SOS and multi-organ failure with hyperammonemia.

Poster # 510

MOBILE TECHNOLOGY FOR PEDIATRIC BLOOD AND MARROW TRANSPLANT PATIENTS: INSIGHTS FROM MISSING DATA

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Background: Mobile applications (apps) and wearable devices are increasingly used to provide real-time access to patient symptoms and physiologic measurements. However, missing data is a constant issue in acutely ill patients.
Objectives: We aim to evaluate potential differences between time-periods with data and time-periods missing data.
Design/Method: We used data from 10 Pediatric Blood and Marrow Transplant (PBMT) patients enrolled in a longitudinal feasibility study using an app to collect self-reported symptom

data and a wearable tracker (Apple WatchTM) to collect physiologic data. Electronic health record (EHR) vital sign data was also collected. Patients were enrolled pre-transplant; remained in the study up to 120 days; were asked to record in the app once per day and wear the watch at least 8 hours/day. Data for each patient was divided into 4 categories, corresponding to all combinations of whether or not wearable or app data was collected. EHR data was analyzed to compare time periods with and without data from the sources. Statistical parameters of each category were calculated for heart rate (HR), blood pressure (BP), and temperature data to identify differences.
Results: Four patients and their HR were initially used to pilot our missing data methodology. Their analyses yielded trends across time periods with and without data. In three patients, a general trend was found for lower HR during time-periods where data was recorded. One patient displayed an opposite pattern (higher average HR during time-periods with recorded data). Overall, average HR was higher in instances of missing data: 100.3 when missing wearable data, 101.4 when missing app data, and 103.4 when missing data from both sources. Conversely, average HR was only 87.7 for instances in which patients were not missing data. Further analysis observing more variables in a higher population will be available at presentation.
Conclusion: Missing data from mobile technologies may provide important insights. Our initial analysis revealed patients with missing data had higher HR. Higher HR is often reflective of increased complications and/or symptoms, and therefore may lead to patients being less likely to record in an app or wear a device. Therefore, missing data may help inform clinicians of changes in patients' conditions and lead to earlier intervention. Future plans include expanding our dataset and using identified characteristics to develop systematic methods to accurately supplement missing data from mobile technologies. This methodology could increase the amount of usable data for analysis to better understand PBMT patients' complications/symptoms.

Poster # 511

HEALTH LITERACY AND PATIENT OUTCOMES FOLLOWING BONE MARROW TRANSPLANTATION

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Background: Health literacy (HL) is the degree to which individuals can understand basic health information to make medical decisions and to access needed services. Low health literacy, which affects 36% of the US population, has been linked to poor outcomes in many chronic diseases. No studies have investigated outcomes associated with health literacy in a bone marrow transplant (BMT) setting, where patients require complex outpatient self-care.
Objectives: To determine the association between HL and clinical outcomes (overall survival, and each of the following within 6 months of transplant: hospital readmission, number of hospitalizations, total hospital days, acute graft-versus-host disease (GVHD), and chronic GVHD) in patients who underwent BMT.
Design/Method: English- and Spanish-speaking patients ≥18 years of age, and the primary caregiving parent of pediatric patients <18, were recruited while admitted for a first allogeneic BMT. Low HL was defined as either a total Newest Vital Sign (NVS) score ≤3 or a total Short Test of Functional Health Literacy in Adults (S-TOFHLA) score ≤22. Univariate tests of

association were performed using chi-squared tests (binary endpoints), t-tests (continuous endpoints), or log-rank tests (time-to-death). Multivariable analyses controlled for key clinical factors: age, treatment center, donor type, stem cell source, and conditioning regimen.
Results: One patient with missing HL data was excluded. Of the remaining 198 patients, 54 (27%) had low HL and 144 (73%) had adequate HL. There were 18 (9%) patients <18 years old. The proportion of patients with one or more hospital readmissions within 6 months of transplant was similar for low (63%) versus adequate (55%) HL (p=0.3). Those with low HL had lower overall survival (OS) (59% versus 68% at 2 years) and higher 2-year cumulative incidence of non-disease deaths (14.8% versus 8.3%), but these differences did not meet statistical significance (OS p=0.14, non-disease death p=0.29). Rates of acute and chronic GVHD within patients with low HL (53% acute, 8% chronic) were similar to those with adequate HL (41% acute, 16% chronic) (p=0.1 acute, p=0.2 chronic). In multivariable analyses, there was no significant association between HL and clinical outcomes.
Conclusion: In this cohort of patients undergoing BMT, there was no evidence to support a relationship between health literacy and hospitalizations. Those with low HL had lower absolute overall survival and higher non-disease death, but these findings did not reach statistical significance in univariate or multivariable analyses.

Poster # 512

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN PEDIATRIC ONCOLOGY AND POST BONE MARROW TRANSPLANT

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Background: Posterior reversible encephalopathy syndrome (PRES) is a clinical radiologic disease described over twenty years ago and is becoming more recognized due to increased index of suspicion and early brain imaging.
Objectives: Describe a cohort of pediatric patients with oncologic diseases and post bone marrow transplant (post-BMT) and incorporate them in a systematic review of the literature to describe risk factors contributing to PRES.
Design/Method: We retrospectively analyzed 11 patients in a single center in Saudi Arabia and conducted a systematic review of literature published between January 1996 to December 2016.
Results: A total of 62 case reports and series were evaluated, 43 met the inclusion criteria in addition to our 11 patients for a total of 129 patients of which 27 were post-BMT. PRES was more common in males 69/118 (60.5%) in general, however more common in females post-BMT (17/27, 63%, p=0.011). We studied immunosuppression and history of systematic hypertension (S-HTN) as risk factors for developing PRES. There were 38 patients on immunosuppression; 68.4% were post-BMT and the remaining had hemophagocytic lymphohistiocytosis (HLH). The most commonly used medication was cyclosporin in 86.8% followed by 19.2% on tacrolimus. The articles on patients with HLH were more likely to report details on the immunosuppression compared to those post-BMT. Of the 22 patients with reported presence or absence of drug toxicity, 45.5% had elevated levels. There were 21 patients with reported management of the immunosuppressive medication after PRES; 10 were resumed on cyclosporine and 30% had recurrence (16.7%, 50% of the patients with HLH and post-BMT respectively, p=0.08). The

remaining 11 patients were shifted to other medications and 27.3% developed recurrence.We analyzed 78 patients with reported S-HTN prior to development of PRES. The presence of S-HTN as a risk factor was more common in the post-BMT group compared to the non-BMT group (69.2%, 24.6% respectively, p=0.001). There were 13 patients were on cyclosporin and S-HTN was present in 69% compared to 24.6% of patients not on CsA (p=0.002).Recurrence of PRES occurred in 11 patients (8.5%) with no differences related to underlying disease, clinical presentation, or imaging. There were 29 deaths (22.5%), none were due to PRES.
Conclusion: From our review of the literature, risk factors for PRES include male gender in oncology, females post-BMT, and S-HTN particularly with cyclosporin. Toxic level and previous exposure to immunosuppression does not seem to increase the risk and changing the immunosuppressive medication is not protective against recurrence.

Poster # 513

CASE-CONTROL STUDY OF PNEUMOMEDIASTINUM IN PEDIATRIC ALLOGENEIC HSCT PATIENTS

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Background: Pneumomediastinum has potential for significant morbidity and mortality. Limited information is known regarding risk factors and outcomes.
Objectives: To identify risk factors and outcomes for Pneumomediastinum in pediatric allo-HSCT patients.
Design/Method: We conducted a retrospective case-control study of pediatric allo-HSCT at our institution from July 2007 – July 2018. Comparisons of categorical and continuous variables between cases (Pneumomediastinum) and controls (no Pneumomediastinum) were done via Fisher's exact tests and two-sample t-tests. Overall survival was compared via a log-rank test.
Results: We identified 117 HSCT events for 113 patients. Pneumomediastinum occurred in 6% (n=7) transplants. For the entire cohort, mean (SD) age at HSCT was 8.70 (5.94) years with 61% (n=71) HSCT events occurring in males. Malignant disease was the predominant indication for HSCT (77% n= 90). Donor sources varied, including 28% (n= 33) MRD, 37% (n= 43) MUD/MMRD/matched CBU, 29% (n=34) MMUD/mismatched CB, and 6% (n=7) haplo. Predominant graft source was BM in 72% (n=84), followed by CB 23% (n=27), and PBSC 5% (n=6). MAC regimens were most common with TBI-based in 44% (n=51) and Bu-based in 39% (n=46). Other conditioning regimens were RIC in 11% (n=13) and Cy/ATG in 6% (n=7). AGVHD and cGVHD were noted in 39% (n=46) and 13% (n=15), respectively. During the first 100 days, 54% (n=63) had a documented infection. There were no statistically significant associations between sex, race, diagnosis, HLA match, or conditioning regimens and pneumomediastinum. There was a trend towards a significant association of pneumomediastinum with older mean age at transplant (12.55 yr cases, 8.5 yr controls, p=0.08), PBSC as graft source (28.6% cases, 3.7% controls, p=0.06), aGVHD (71.4% cases, 38% controls, p=0.1), and infections 85.7% cases, 52.8% controls, p=0.1). Although there was no statistically significant difference in survival (p=0.1) between cases and controls, the Kaplan-Meier indicates that overall survival trended to be better for controls than for cases. Median survival time for the cases was only 7 months while median survival time for controls could not

be estimated as more than 50% of patients remained alive at time of analysis. Only 28.6% of cases are alive, with deaths attributable to infections and relapse.
Conclusion: Pneumomediastinum was related to poor median survival and had suggested relationships with older age, PBSC graft source, aGVHD, and infections. Due to the small number of cases, lack of power likely contributed to the difficulty in identifying clear statistically significant associations needing future multi-institutional studies with larger cohorts.

Poster # 514

OUTCOMES OF SUBSEQUENT TRANSPLANT FOR PATIENTS WITH HEMATOLOGICAL MALIGNANCIES WHO RELAPSE

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Background: Relapse remains a major cause for failure after hematopoietic stem cell transplantation (HSCT). Although the prognosis is grim, subsequent transplant from a different donor may offer the chance of long-term survival.
Objectives: To determine the long-term outcomes of this population, we reviewed the outcomes of pediatric patients who were recipients of an allogeneic HSCT due to post-transplant relapse at Duke University from 2000-present
Design/Method: We conducted a retrospective review of 30 patients, ages 0.9-18yr (median 5.5yr) at time of the second transplant, who relapsed 1-30 months (median 9.5 months) following allogeneic HSCT. Diagnoses included AML (N=16), ALL (N=11) and MDS (N=3). Graft sources for the first HSCT included unrelated umbilical cord blood (UCB, N=15), matched siblings (MSD, N=11) and matched unrelated donors (MUD, N=4). Second transplant graft sources were UCB (28), MUD (1) and MSD (1). All subjects received myeloablative conditioning (MAC). Seventeen patients had active disease at the time of second transplant. Descriptive statistics, Kaplan-Meier (KM) estimates of survival and cox regression to identify predictors of survival were utilized.
Results: The KM probability of 5-yr overall survival was 27.16% (95% CI: 10.79%, 43.53%) with a median follow-up of 7.6 years for survivors (range 1-18 years). Three of 9 survivors had disease (2 AML, 1 MDS) at the time of conditioning. Most survivors (N=5) had a MSD graft for the first HSCT followed by UCB for second graft. Three survivors received UCB grafts for both transplants, and one had a MUD followed by double UCB transplant. Of the 9 survivors, 5 received TBI with the first transplant, 3 with the second, and one received 200cGy with the first transplant and 400cGy with the second. Of the 21 deceased patients, 12 died of relapse. Additional causes of death were infection and organ failure. Time to death ranged from 0.5-24 mos (median 4.86 mos). Median time to relapse after first transplant was 9.25 months. The median interval between the 2 transplants was 12 months for the surviving patients and 15 months for the deceased patients. No outcome predictors were identified.
Conclusion: Subsequent transplant from a different donor can be a viable option for treatment of relapse following HSCT. The mortality rate remains high, with the most common cause of death being relapse. Novel therapeutic strategies are needed to further improve outcomes.

Poster # 601

GATA2 HAPLOINSUFFICIENCY: NOVEL PULMONARY STIGMATA AND RAPID MYELODYSPLASTIC TRANSFORMATION

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Background: Leukemia-predisposing conditions, such as GATA2 haploinsufficiency, have high penetrance and expressivity profiles. Prompt recognition of key clinical features and laboratory abnormalities is critical to directing surveillance or initiation of therapy.
Objectives: Describe an instructive case of non-tuberculous mycobacterial infection (NTM), pulmonary granulomatous vasculitis, and rapid transformation to myelodysplastic syndrome (MDS).
Design/Method: Retrospective chart review along with direct multidisciplinary patient care.
Results: A 17-year old Caucasian male presented with a one-month history of fever, 30-lb weight loss, cytopenias, and diffuse lung disease resistant to outpatient antibiotics. He had leukopenia with profound monocytopenia, chest x-ray findings of interstitial opacities and prominent hilar adenopathy in both lungs, as well as a reactive PPD, but negative IFN-γ release assay, concerning for possible NTM infection. Extensive infectious evaluation was otherwise negative. Despite empiric antibiotic and antifungal therapy, the patient's cytopenias and clinical status deteriorated with persistent fevers, further weight loss, and a CT chest with worsening appearance of hilar lymph nodes, prompting evaluation for malignancy. Bone marrow (BM) examination was normocellular with minimal megakaryocytic dysmorphology and normal cytogenetics, while lung biopsy revealed a fibrinoid granulomatous vasculitis with focal bronchiolocentric organizing pneumonitis. Due to the clinically evolving diagnosis of MonoMac syndrome, immunologic evaluation was pursued and revealed a pathogenic GATA2 frameshift variant (c.17_18del, p.Glu6Alafs*178). Progressive pancytopenia and this new genetic information urged a repeat BM exam demonstrating a hypocellular marrow now with overt multilineage dysplasia and a new t(X;12)(q24;q24.1) in 8/12 cells. Family history obtained in conjunction with genetic counseling was unrevealing for a familial pattern of acute myeloid leukemia (AML) or MDS. Empiric treatment for NTM infection and a therapeutic trial of steroids for pulmonary vasculitis was completed. The patient underwent a 10/10 matched unrelated hematopoietic stem-cell transplant (HSCT) with adequate engraftment. However, >1year post-transplant, after many complications including cardiopulmonary, skin, and gut GVHD, as well as CMV colitis, our patient succumbed to his disease without evidence of relapse.
Conclusion: This case report highlights a novel pulmonary finding which may represent a new stigmata of the disease spectrum. Furthermore, given the often subclinical spectrum of presentation of GATA2 haploinsufficiency and rate of de novo mutations, we recommend dedicated GATA2 screening when next generation sequencing is not performed.

Poster # 602

PRIMARY MYELOFIBROSIS WITH AML TRANSFORMATION IN A CHILD: RARE PRESENTATION AND POOR THERAPY RESPONSE

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Background: There is limited literature of primary myelofibrosis with acute myeloid leukemia transformation in the pediatric population. Within the literature, only few pediatric cases express objective clonal markers like JAK2 that are the basis for the diagnosis of myeloproliferative neoplasms.
Objectives: To describe a case of Primary Myelofibrosis (PMF) in pediatric patient with Acute Myeloid Leukemia (AML) transformation receiving JAK1/2 inhibitor therapy along with cytototoxic treatment for AML.
Design/Method: A PubMed search was conducted for queries including "Primary Myelofibrosis" "Ruxolitinib", and "Pediatrics." Relevant papers were selected for literature review.
Results: 13-year-old previously healthy Hispanic male with pertinent family history of follicular lymphoma in his father was admitted with persistent fevers, nodular rash on his bilateral lower extremities and pancytopenia. Work up included a bone marrow biopsy showed hypocelllularity with no myelodysplastic changes, but abnormal trisomy 21 clone in 94% of his cells. He was placed on steroids for 4 months, and azathioprine for 1 year with good response to his cellular counts and clinical course. Due to recurrent fevers and pancytopenia, a repeat bone marrow biopsy demonstrated myelodysplasia with concern of AML transformation. His myeloproliferative gene panel harbored JAK2, RAD21, and RUNX1 mutations. He was started on AML based therapy combined with Ruxolitinib for his refractory disease with an initial tentative plan to proceed with allogeneic hematopoietic cell transplantation from an unrelated donor.
Conclusion: We hereby present an unusual presentation of PMF with AML transformation in a child that has shown resistance to cytotoxic chemotherapy and JAK1/2 inhibitor. PMF in pediatric patients could represent an inferior outcome with refractory disease compared the adult counterpart might warrant further investigation.

Poster # 603

EPSTEIN-BARR VIRUS LYMPHOPROLIFERATIVE DISEASE AFTER IMMUNOSUPPRESSIVE THERAPY FOR APLASTIC ANEMIA

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Background: Acquired aplastic anemia (AA) is a form of bone marrow failure that is treated with immunosuppressive therapy (IST) and/or allogenic hematopoietic stem cell transplantation. AA is also associated with risk of development of paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndromes (MDS), and leukemia. While the development of Epstein-Barr virus-

associated lymphoproliferative disorders (EBV-LPD) is well described in the post-transplant period of a variety of disorders including AA, it is extremely rare in the non-transplant setting of IST for AA.
Objectives: To recognize the development of immunodeficiency associated EBV-LPD as a risk in patients receiving non-transplant IST for AA and PNH.
Design/Method: We discuss a case of a 19-year-old female who developed EBV- LPD, diffuse large B cell lymphoma (DLBCL) type, in the setting of IST for severe AA, eculizumab treatment for symptomatic PNH, and presence of a somatic ASXL1 mutation.
Results: Patient was initially diagnosed with severe AA at thirteen years of age. She was treated with horse antithymocyte globulin (ATG) and cyclosporine A with good response and was weaned off immunosuppression over two years. Approximately four years after her initial diagnosis she had a relapse of AA and was treated with rabbit ATG, tacrolimus, and eltrombopag. She remained on chronic immunosuppression with tacrolimus for severe refractory AA. At the time of her AA relapse, she was found to have a somatic mutation in ASXL1 bone marrow evaluation and the mutant allele frequency increased on subsequent evaluations, suggestive of clonal expansion, and later remained stable. Additionally, at the time of her AA relapse, she developed symptomatic PNH and was started on eculizumab. Twenty months after receiving ATG for her AA relapse, and while still on tacrolimus and eculizumab, she developed right upper quadrant abdominal pain and was ultimately diagnosed with EBV-positive DLBCL, non-germinal center phenotype. She was treated with three cycles of dose adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab). She was conditioned with cyclophosphamide and total body irradiation and received a 10/10 matched unrelated bone marrow transplant. She is currently two months post-transplant, has fully engrafted, and has declining percentages of PNH clones that are being monitored closely.
Conclusion: Although it is rare, we must consider development of EBV-related LPD as a risk in patients receiving IST for AA. Continued reporting and evaluation of such cases is needed in order to further our understanding of this association and to guide monitoring and management of these patients.

Poster # 604

ELTROMBOPAG IN PEDIATRIC SEVERE APLASTIC ANEMIA: THE ST. JUDE EXPERIENCE

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Background: Immunosuppressive therapy (IST) with horse anti-thymocyte globulin and cyclosporine currently remains the initial standard of therapy for children with severe aplastic anemia (SAA) who lack an HLA-identical sibling. Thrombopoietin receptor agonist, eltrombopag (EPAG) has been recently approved by the FDA for treatment of SAA in patients 2 years and older. However, there are limited data for EPAG efficacy and safety in pediatric SAA.
Objectives: To assess outcomes and adverse events with the addition of EPAG to standard IST in pediatric SAA.
Design/Method: We conducted a retrospective study in patients with SAA <18 years old

diagnosed at our institution between 2000 and 2018. Patients were grouped into 2 cohorts; those receiving IST with GM-CSF (cohort A) and those receiving IST with EPAG (cohort B). The primary outcome was the objective response, ranging from partial to complete response (CR) at 6 months, as defined by the response criteria of the North American Pediatric Aplastic Anemia Consortium.
Results: We identified 16 patients in cohort A (median age 12, range 1-17 years) and 9 patients in cohort B (median age 11, range 4-18 years). In cohort B, EPAG with standard IST was administered as first-line therapy in 6 patients and second-line in 1 patient; while 2 patients received EPAG in refractory setting after 2 failed IST attempts. All patients were evaluable at 6 months with median duration of follow up of 86 and 13 months in cohort A and B, respectively. The objective response in cohort A was 75%, with CR in 4 patients (25%). In cohort B, all 7 patients treated concurrently with IST and EPAG responded, with 2 patients (28%) achieving CR, while no response was seen in the 2 patients who were refractory to IST after two attempts. Infections requiring hospital admission within 6 months of treatment were reported in cohort A and B at 81% and 44%, respectively (not significant). No renal insufficiency of grade 3 or greater occurred in either cohort and the incidence of hypertension was comparable (31% vs. 44%). Only one patient in cohort B developed grade 3 transaminitis which subsided after reducing the EPAG dose. No cutaneous toxicity was observed in patients receiving EPAG. Finally, there was no increase in PNH clones in both cohorts.
Conclusion: The addition of EPAG to standard IST was well tolerated and resulted in satisfactory hematological response at 6 months. A longer follow-up is warranted to assess response durability.

Poster # 605

NAPAAC MULTICENTER SURVEY ON PEDIATRIC MYELODYSPLASTIC SYNDROME (PMDS1)

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Background: Pediatric myelodysplastic syndrome is a rare life-threatening clonal hematopoietic disorder. As pediatric MDS is frequently driven by germline predisposition, inherited bone marrow failure syndromes (IBMFS), and/or secondary to exposures to cytotoxic agents, the disease definition continues to evolve uniquely from adult MDS. Management is thus complicated by the heterogeneity of disease etiology, clinical presentation and lack of standardization of diagnostic criteria.
Objectives: North American Pediatric Aplastic Anemia Consortium (NAPAAC) created a working group to establish a baseline understanding of the range of clinical practice regarding pediatric MDS in North America as a foundation for the identification of areas for future research to improve the evaluation, diagnosis and treatment of this rare condition.
Design/Method: A comprehensive pediatric MDS survey (pMDS1) was distributed to members of the MDS working group. The survey consisted of questions categorized into the following domains: MDS Background (I), Diagnosis (II), Definition (III), Treatment (IV), and

Transplantation (V). Institutional representatives were instructed to complete a single survey incorporating multidisciplinary consensus when appropriate.
Results: 12 of 13 institutions completed the survey. Incidence of pediatric MDS ranged from 0 to 6 newly diagnosed patients/institution/year, with a mean of 2-3 patients/institution/year. Surveys demonstrated notable discrepancies in cytogenetic testing and sequencing platforms used to define somatic genetic aberrations, but was uniformly consistent in screening for Fanconi anemia and telomere disorders. 75% reported following the revised 2016 WHO diagnostic criteria; however, only 50% reported utilizing the term Refractory Cytopenia of Childhood (RCC) in relation to MDS diagnosis. Although most institutions agreed that pediatric MDS can be diagnosed without a somatic genetic lesion, 8 of 12 believe that multi-lineage dysplasia is not essential for diagnosis. For early stage pediatric MDS defined by morphologic criteria (<5% blasts), 45% would observe monitoring bone marrow, 36% would transplant with best available donor, 18% would transplant only if a matched sibling were available. For initial therapy in early stage pediatric MDS with excess blasts, 33% would use a demethylating agent, 33% would transplant with best available donor, 9% would transplant only with a matched sibling, 25% would use intensive AML induction followed by transplant.
Conclusion: Results reveal a lack of North American consensus in the definition and clinical management of pediatric MDS. This pilot survey will be extended to an additional 20 North American centers. These data support the need for focused research into pediatric MDS as well as consensus approaches to the diagnosis and treatment of this disease.

Poster # 606

TARGETED EXOME SEQUENCING IDENTIFIES NOVEL GENETIC VARIANTS IN CLINICALLY AMBIGUOUS IBMFS

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Background: Inherited bone marrow failure syndromes (IBMFS) are a diverse group of rare genetic disorders characterized by insufficient production of blood cells, congenital anomalies, and an increased risk for malignancy. In a significant number of cases the clinical presentation and screening tests are ambiguous or unavailable and a causative pathogenic variant is unknown. Most commercially available gene panels for IBMFS are disease specific, requiring a presumptive diagnosis, and include only the most common causative genes. We therefore created a custom comprehensive panel containing all currently known and investigational genes associated with IBMFS to see if we could increase the diagnostic yield.
Objectives: To determine whether a custom-created panel of genes associated with IBMFS was able to identify the genetic etiology for patients with clinical features consistent with an IBMFS, in most cases not previously detected using disease specific IBMFS gene panels available from commercial labs.
Design/Method: Proband-only targeted exome sequencing of a custom list of 101 genes associated with IBMFS and exon array of select genes on the list was performed on 24 undiagnosed patients followed at our institution with clinical symptoms consistent with an IBMFS.
Results: Variants of uncertain significance in genes that fit the patients' phenotype were

identified in 8 out of the 24 (33%) patients tested and thought to be disease causing (3 dyskeratosis congenita, 2 Diamond-Blackfan anemia, 1 Fanconi anemia, 1 ADA2 deficiency, 1 congenital amegakaryocytic thrombocytopenia). Functional, biochemical, or enzyme analysis is pending to confirm loss of protein function.
Conclusion: The overlapping features of many IBMFS often makes disease specific gene panel testing an inefficient and costly way of searching for a genetic diagnosis. While more comprehensive IBMF gene panels are offered by some commercial labs, they do not contain all rare and investigational genes. With our custom, comprehensive targeted exome panel, we have identified a likely genetic diagnosis for such patients not previously detected by genetic or other testing.

Poster # 607

HEMATOPOEITIC STEM CELL TRANSPLANTATION FOR FANCONI ANEMIA - 15 YEAR EXPERIENCE FROM SOUTH INDIA

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Background: Fanconi anaemia in India is highly underreported with an incidence higher than that published due to the high prevalence of consanguineous marriages. Haematopoietic stem cell transplantation (HSCT) in children with FA carry unique challenges and need modified conditioning protocols.
Objectives: We present data over 15 years in children diagnosed to have FA, who underwent HSCT from 2002 to April 2018 at the paediatric blood and marrow transplantation unit, Apollo hospitals, Chennai, India.
Design/Method: Data was analysed for graft and donor source, rates of engraftment, GvHD, overal survival rates.
Results: A total of 51 children with FA have been transplanted at our centre where the donor source was matched family donor (MFD) in 28 (54%), matched unrelated donor (MUD) 2 (4%), umbilical cord blood (UCB) 7 (13%), haploidentical stem cell transplantation (haplo SCT) with post-transplant cyclophosphamide (PTCy) in 14 (27%). Source of stem cells was PBSC in 39 (76%), UCB 7 (13%), bone marrow in 5 (10%). Engraftment by D+16-21 was achieved in 72% with 6 (11%) children dying before engraftment. Overall rate of acute graft versus host disease (GvHD) was 13 (25%) and chronic GvHD 6 (11%). GvHD was seen in 14% of those with MFD of which 3 / 4 (75%) died due to GvHD. Both the children with MUD HSCT died due to severe GvHD. Among those who received UCB, GvHD was seen in 2 and both died due to GvHD. Among the haplo SCTs, GvHD rates are high at 42%, of which 2/6 died due to GvHD and 70% of these were responsive to steroids. Cytomegalovirus reactivation was noted post engraftment in all children who underwent haplo SCT and all were responsive to valganciclovir and ganciclovir. Overall mortality rate is 25 (49%) with survival rate of 51%. Causes of death are varied with GvHD in 9, primary graft failure in 2, sepsis in 8, AML in 2, AML 8 years post HSCT in 1, PTLD 3 years post HSCT in 1, intracerebral haemorrhage in 1 and peliosis hepatis in 1 child. In our cohort among FA patients, survival rates are 54% with MFD, 29% with UCB, 0% with MUD and 65% with haplo SCTs.
Conclusion: FA needs trained paediatric transplant physicians with paediatric intensivists to

provide optimal care and outcome. Haplo SCTs with PTCy provide a feasible and cost-effective alternative in case of unavailability of matched family donor with survival rates of 65% in this cohort and acceptable GvHD rates.

Poster # 608

PERIPHERAL BLOOD STEM CELL TRANSPLANT IN SEVERE APLASTIC ANEMIA IN DEVELOPING COUNTRIES

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Background: With the increasing incidence of drug resistant infections particularly in developing countries and risk of sudden onset life-threatening bleeds in acquired aplastic anaemia, early and sustained engraftment is imperative. Peripheral blood stem cells (PBSC) provide the earliest engraftment albeit with a risk of graft versus host disease (GvHD).
Objectives: We present our experience where capping CD34 cell dose to 5x106/kg recipient body weight in PBSC grafts can result in excellent disease free, event free and overall survival.
Design/Method: This retrospective, uncontrolled study was conducted at the Paediatric blood and marrow transplantation unit at Apollo Hospitals, Chennai, India. All children less than 18 years of age who were diagnosed to have SAA and VSAA and underwent HSCT from 2002 to February 2018 were included in the study. Data was collected on their source of stem cells, the CD34 cell dose infused, pre- and post-transplant clinical course and outcome in terms of engraftment, incidence of GvHD, DFS, EFS and OS.
Results: A total of 29 children diagnosed to have SAA and VSAA underwent HSCT including 13 girls and 16 boys, median age being 10 years. 12 had received more than 15 PRBC and platelet transfusions prior to HSCT, 11 children had more than 1 admission for febrile neutropenia. Source of stem cells included matched sibling donor in 20/29 (68%), haplomatched donor in 9/29 (31%). PBSC was used in 26/29 (90%) and bone marrow in 3 (10%). Average CD34 cells infused were 5.68 x 106/kg recipient body weight. Engraftment by D+14 was note in 24 (82%) children with sustained complete chimerism in 23/24 (95%) transplants. Of the 24 that engrafted, 6 (25%) have chronic GvHD requiring low dose steroids. Two children died of sepsis prior to engraftment, two of primary graft failure, two of late sepsis and one of HHV6 encephalitis, with 87% of these having received more than 25 transfusions prior to HSC. Mortality in this cohort is 27% with an EFS 75% and OS 73%.
Conclusion: PBSC grafts in children with acquired aplastic anaemia ensure early engraftment rates of 82%. A 25% risk of chronic GvHD can be minimised by capping CD34 stem cell dose to 5 times. With increasing drug resistant organisms, PBSC as a source of stem cells would provide improved survival rates in this high risk but curable condition, particularly in developing countries.

Poster # 609

INFANTILE PANCYTOPENIA DUE TO VITAMIN B12 DEFICIENCY

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Background: The differential for pancytopenia in infants includes viral suppression, bone marrow failures syndromes, leukemia, and nutritional deficiencies. Pancytopenia requires urgent evaluation, often necessitating a variety of blood tests and a bone marrow evaluation. Vitamin B12 deficiency is one nutritional cause of pancytopenia, which typically presents in infants with non-specific symptoms such as developmental delay, hypotonia, and feeding difficulties. The characteristic CBC finding is megaloblastic anemia, but thrombocytopenia and leukopenia may also be present.
Objectives: We describe a patient who presented with pancytopenia and was found to have vitamin B12 deficiency secondary to maternal pernicious anemia.
Design/Method: A 3-month old male was being followed for failure to thrive by his pediatrician. Over the past month, he had been losing weight, and had dropped from the 5th percentile to <1st percentile. CBC ordered by the pediatrician was notable for pancytopenia. He had been exclusively breastfed. Recently he had been eating less than usual, and would refuse to drink from a bottle. He had diarrhea over the previous week, but no fever or other symptoms. Patient was born full-term and pregnancy was uncomplicated, though mother was on levothyroxine. She has a history of Graves' disease, which had been treated with radioiodine therapy.
Results: WBC 3.7 ANC 340Hemoglobin 4.5MCV 86Platelets 34Reticulocytes: 0.7%Smear: +1 schistocytes, +2 teardrop cellsLDH: 2,052Haptoglobin <10Vitamin B12: <150Flow Cytometry and Cytogenetics (Bone Marrow): normalBone Marrow Exam: Trilineage hematopoiesis, normal granulopoiesis, mild erythroid hyperplasia, decreased megakaryocytes, no blasts
Conclusion: This case describes a 3-month old infant with pancytopenia secondary to vitamin B12 deficiency. This was not a leading differential initially, based on CBC findings, which showed normocytic anemia without any megaloblasts noted. The only clues were the patient being exclusively breastfed and mother's history of an autoimmune condition (Graves disease), although she had no history of anemia herself. Maternal testing ultimately revealed pernicious anemia, with vitamin B12 deficiency and positive intrinsic factor antibodies.Vitamin B12 deficiency is known to cause anemia in two ways: megaloblastic changes and intramedullary hemolysis. The latter likely accounts for the findings of a relatively normocellular bone marrow, elevated LDH, and presence of schistocytes in this patient. This case highlights the importance of maintaining a high level of suspicion for nutritional deficiency in an infant presenting with pancytopenia. Despite initial concerns for leukemia and bone marrow failure, repletion of a single vitamin rapidly corrected this infant's cytopenias and feeding difficulties.

Poster # 610

ASSOCIATION OF ELEVATED VITAMIN B 12 LEVELS WITH MALIGNANCY OR OTHER COMORBIDITIES IN CHILDREN

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Background: Vitamin B12 (B12) is essential for DNA synthesis and cell metabolism. While B12 deficiency is extensively studied and linked to hematological, neurological, and gastrointestinal disorders, the importance of elevated B12 is still under investigation. High B12 levels are described in adults with malignancies, liver, renal, autoimmune and infectious diseases. However very limited and conflicting data exists pertaining to children with elevated B 12.
Objectives: To determine if there is an association of elevated B12 and malignancies or other hematological and non-hematological conditions in children.
Design/Method: An IRB-approved, single institution retrospective study was conducted. Patients younger than 18 years with abnormal B12 levels during the period of 2010-2018 were included. Patients with history of, or concurrent B12 therapy were excluded. Vitamin B12 levels, complete blood counts with prior and concurrent diagnoses were collected. Demographics and clinical characteristics of the patients are described using mean and standard deviation or median for continuous variables, and frequency and percentages for categorical variables, as appropriate. A multiple linear regression was calculated to predict abnormal vitamin B12 levels based on age, sex and hematological parameters: hemoglobin, white blood cell (WBC) and platelet counts. P-value of less than 0.05 was considered as statistically significant.
Results: A total of 270 patients with abnormal B12 were identified. Ninety four percent (n=255) had high B12 levels. Fifty three percent (n=149) of the patients with high levels were female. The overall mean age of the patients was 11.02 ± 5.04 years. The highest number of abnormal vitamin B12 levels were observed for gastroenterology diagnoses (22%, n=53), followed by psychiatric diagnoses (14%, n=35), constitutional (11%, n=26) and hematology/oncology (9%, n=21). From the hematology/oncology patients, only 28.56% had reported malignancies. Malignancies included Diffuse Large B Cell Lymphoma, lytic lesion, medulloblastoma, precursor B-cell acute lymphoblastic leukemia, Rosai-Dorfman and Wilms tumor. The most common indication for obtaining a B12 level was for reported fatigue (6%, n=16), followed by failure to thrive (5%, n=14). Of the predictors, age was a significant predictor of abnormal B12 ($B = -13.76$, $p = 0.01$). In contrast, sex, hemoglobin, platelet count and WBC were non-significant predictors of abnormal B12 levels.
Conclusion: While elevated B12 levels have been associated with various malignancies in adults, our study demonstrated that there does not appear to be any significant association with a particular disease process in children. More studies are needed to further delineate the importance of elevated B12 in different medical conditions in the pediatric population.

Poster # 611

BLOOD PRODUCTS AND BRONCHOPULMONARY DYSPLASIA IN EXTREMELY LOW BIRTH WEIGHT NEONATES

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Background: Transfusion of red cells in preterm newborns has been associated with bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP) and necrotizing enterocolitis (NEC). Similar data in extremely low birth weight (ELBW) neonates is scarce.

Objectives: To assess effect of transfusion volume of packed red blood cells (PRBC), fresh frozen plasma (FFP) and platelets in first 28 days of life on the severity of BPD in ELBW neonates.
Design/Method: We retrospectively identified all ELBW (<1000 gm) babies admitted to Metrohealth Medical Center Neonatal Intensive Care Unit between 2010-2016. Neonates who died before 36 weeks post-menstrual age and those without BPD were excluded. BPD was divided into "severe" (Grade 3) and "non-severe" (Grade 1-2) categories. Socio-demographic, co-morbidities and transfusion data were collected. Chi-square test and Student's t test and Multinomial logistic regression analysis were performed. The P value of 0.05 was considered significant.
Results: A total of 128 patients were included out of which 45% neonates(n=57) developed severe BPD. Severe BPD was seen more in males than females (71.9% vs 28.07%, p 0.006). No racial association was seen (p 0.41). Birth weight was significantly lower in severe BPD compared to non-severe BPD (631.8-714.2 gms vs 788.8-847.4 gms, p <0.001). Mean gestational age was significantly less in severe BPD group compared to non-severe BPD group (24.2-25.1 vs 25.8-26.6 week, p <0.001). Apgars at 1 and 5 minutes were significantly lower in severe BPD group with p of 0.0132 and 0.0201 respectively. Significant association was present with severe BPD and PDA (p 0.017), need for surgical ligation of PDA (p <0.001), postnatal days of O2 supplementation(p <0.001), postnatal days of steroids (p 0.0001), development of ROP (p 0.055) and IVH (p 0.002). Significant association was also seen with severe BPD and Hb at birth (p 0.003), volume of PRBC transfusions(p <0.0001), platelet transfusions (p <0.001), FFP transfusions (p 0.005), total doses of EpO received (p 0.0012) and total no IV iron doses received (p 0.07). On multivariate analysis platelet transfusion (in units) (OR 2.131, 95%CI 1.26-3.61) and PRBC transfusion vol/kg (2.7, 95%CI 0.39-4.7) were independently associated with severe BPD.
Conclusion: This study shows that increasing amounts of transfusion of PRBC (vol/kg) and platelets (in units) are independently associated with severe BPD in ELBW neonates. The reason for the relationship between transfusions and BPD is unclear, further studies are needed to define if transfusion associated lung injury is a possible cause of association.

Poster # 612

EVALUATION OF THE INTRINSIC HEPCIDIN IDX™ TEST TO DETECT IRON DEFICIENCY IN ADOLESCENTS/YOUNG ADULTS

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Background: Adolescents/Young adults (AYA) are at risk for iron deficiency (ID). Hemoglobin (Hb) and ferritin, which are commonly employed for ID screening, are not optimal given their lack of sensitivity. Hepcidin is the central iron regulatory hormone and its clinical measurement could facilitate accurate ID screening.
Objectives: To demonstrate the diagnostic accuracy of the Intrinsic Hepcidin IDx Test for ID in AYA.
Design/Method: Single center, prospective, observational study enrolled AYA patients ≥11

years old from the Boston Children's Hospital (BCH) AYA clinics. We excluded patients if they had known acute or chronic inflammatory illness, hemoglobinopathy, recent iron supplementation or transfusion, or pregnancy. Subjects provided blood for iron studies, hemoglobin (Hb) and hepcidin (Intrinsic Hepcidin IDx Test). We defined ID as ferritin <20 ng/mL. We calculated sensitivity (Se) and specificity (Sp) for the full sample and for age (<18, ≥18) and sex subgroups, with diagnostic accuracy defined as lower 95% confidence interval (CI) on Se and Sp ≥70%. We secondarily examined alternate definitions for ID: 1) ferritin <15ng/mL and 2) ferritin <20ng/mL or transferrin saturation (TfSat) <15%.
Results: Of 501 eligible patients, 494 (143 males, 351 females; mean age=19.6 years, range=12.1-26.5years, 27.5% <18 years) had complete data for analysis. Mean Hb was 13.2g/dL (range: 6.7-21.7g/dL), ferritin 63.7ng/mL (range: 1.4-528.2ng/mL), TfSat 22.4% (range: 2.3-89.7%) and hepcidin 14.5ng/mL (range: 2.0-196.3ng/mL). Females were older, and had lower ferritin, hepcidin, hemoglobin, and TfSat than males ($p<0.05$, per t-test). For ID=ferritin<20ng/mL, Intrinsic Hepcidin IDx Test Se=98% (95%CI: 92%-100%) and Sp=40% (95%CI: 35%-45%). Alternate ID definitions did not dramatically alter Se/Sp. For ID=ferritin<15ng/mL, Intrinsic Hepcidin IDx Test Se=98% (95%CI: 91%-100%) and Sp=37% (95%CI: 32%-42%). For ID=ferritin <20ng/mL or TfSat<15%, Intrinsic Hepcidin IDx Test Se= 85% (95%CI: 79%-90%) and Sp= 42% (95%CI: 36%-47%). The observed Se was also high within age and sex subgroups; however, the 95% lower CI fell below 70% in the smaller subgroups including males (n=143), males <18years (n=44), and males ≥18years (n=99).
Conclusion: Sensitivity of Intrinsic Hepcidin IDx Test was >85%, regardless of biochemical definition of ID. The 95% lower CI for sensitivity exceeded the diagnostic accuracy threshold of 70% except within smaller size male subgroups Specificity of Intrinsic Hepcidin IDx Test was low regardless of how ID was defined. Funding for this work was provided by a NIDDK Small Business Innovation Research (SBIR) mechanism awarded to Intrinsic Life Science and Boston Children's Hospital.

Poster # 613

A 4YO WITH ZOLLINGER-ELLISON SYNDROME: A NOT SO SIMPLE CASE OF IRON DEFICIENCY ANEMIA

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Background: Zollinger-Ellison syndrome (ZES) is a rare entity first described in 1955 caused by excess gastrin secretion by a duodenal or pancreatic neuroendocrine tumor called a gastrinoma, typically resulting in severe acid-related peptic disease and diarrhea. They are rare in the general population with an incidence of 0.5-2 per million per year and even more so in pediatric patients with this group comprising only 1-2% of all cases.
Objectives: This case should underline the importance of continuous reassessment of a patient's case despite having a working diagnosis.
Design/Method: We present a case of a 4yo with iron deficiency anemia complicated by underlying ZES.
Results: Our patient was a 4yo F who initially presented to our institution with a history of chronic constipation and gastric ulcers diagnosed the year prior and pancreatitis three months

before at a different institution. The patient complained of pain and nausea with food, causing her to withhold stool and to be very particular about her diet. After discharge she presented again a month later with a hemoglobin of 4.1 with an MCV of 75.8. During this stay the working diagnosis for her anemia was iron deficiency with a diet of mainly dairy products, imaging and endoscopy negative for active bleeding, and a ferritin of 3. However, a CBC done two months prior had been normal; and such a severe drop would be unusual in such a short time without active bleeding. Another part of the diagnostic challenge was a concern for parental medical neglect. Child Protective Services had opened a case at the prior institution, causing her to come to us initially out of frustration. The concern worsened with a history of patterned bruising and concern for malnutrition. During her workup, though, a gastrin level was drawn and found to be >10,000. She was ultimately diagnosed with metastatic gastrinomas but, unfortunately, acutely exsanguinated and died from a perforated previously unseen ulcer prior to starting therapy.
Conclusion: While the overall outcome may not have changed, the overall stress and morbidity for this family surrounding their daughter's suffering and ultimate diagnosis would certainly have been lessened by an earlier diagnosis of ZES. Although our patient's symptoms were not ignored, the focus on the psychosocial issues certainly delayed her diagnosis. Hopefully this case will serve to highlight the need to constantly reassess patients as their clinical courses evolve and to critically question whether our diagnoses are accurate.

Poster # 614

ANEMIA AND RESPIRATORY DISTRESS IN A TWO-YEAR-OLD BOY

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Background: A 2-year-old boy with past medical history of asthma and iron deficiency anemia, presented with shortness of breath and was found to have severe anemia with a hemoglobin (Hb) of 5.6 g/dL. He was doing well until the morning of presentation when he started experiencing of shortness of breath. Parents denied any fever, trauma or bleeding from anywhere. On examination he was afebrile, but in mild distress. Lungs were clear for auscultation, and rest of the physical exam was unremarkable except for tachycardia and a systolic flow murmur. Chest X-ray was concerning for diffuse opacification suggestive of pulmonary edema. In light of his persistent respiratory distress, pulmonary hemorrhage was suspected and hence a bronchoscopy was performed, which helped in diagnosis.
Objectives: To describe a case of idiopathic pulmonary hemosiderosis (IPH) and use the case to describe clinical features, pathogenesis, diagnosis, prognosis and management principles of IPH.
Design/Method: Review of medical chart and literature was performed to write this case report.
Results: Peripheral blood smear showed significant anisocytosis and marked hypochromia of erythrocytes with normal appearing white cells and platelets. We performed Coombs test to rule out immune-mediated hemolysis, iron studies, erythrocyte folic acid level and serum vitamin B12 level to rule out nutritional causes of anemia, all of which were unremarkable. Broncho-alveolar lavage (BAL) samples showed hemosiderin-laden macrophage, which suggests pulmonary hemorrhage. Lung biopsy and serological tests were used to rule out rheumatological causes of pulmonary hemorrhage such as Goodpasture syndrome, eosinophilic granulomatosis with polyangiitis, mixed connective tissue disorder, while infectious causes such as tuberculosis,

viral, fungal, and bacterial pneumonia were also ruled out after negative interferon-gamma release assay, respiratory viral panel and culture of BAL sample. Eventually, the patient was diagnosed with idiopathic pulmonary hemosiderosis (IPH) and started on a pulse of methylprednisolone with 30 mg/kg/day for 3 days, followed by daily prednisone taper.
Conclusion: IPH is an uncommon pediatric disorder that was first described in 1975. IPH is characterized by recurrent and diffuse pulmonary hemorrhage with the frequent bleeding resulting in hemosiderosis and secondary fibrosis from chronic inflammation and superoxide-mediated toxicity. This results in pulmonary fibrosis and iron deficiency anemia. IPH is a diagnosis of exclusion, frequently requiring bronchoscopy and extensive testing to rule out other causes of pulmonary hemorrhage. It can be associated with celiac disease and milk protein allergy. Corticosteroid burst and supportive care, with close long term follow up are the mainstay of treatment.

Poster # 615

NOVEL MUTATION OF ALAS2 IN CONGENITAL SIDEROBLASTIC ANEMIA NON-RESPONSIVE TO PYRIDOXINE - NEXT BMT

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Background: Congenital sideroblastic anemia (CSA) is a dyserythropoietic disorder that leads to anemia and potentially iron overload. With the use of molecular diagnostic technologies, there is a better understanding of the different genotypes-phenotype presentations, thus guiding better treatment strategies. X-linked CSA (XLSA) caused by a mutation in the ALAS2 gene located in the Xp11.21 region, affecting mainly boys, unless a skewed x-inactivation favors the phenotype in women. Half of those mutations has been historically responsive to pyridoxine.
Objectives: We hereby describe a pediatric female patient with a mutation in exon 2 of ALAS2 gene with XLSA for which pyridoxine did not correct anemia. Patient is undergoing allogeneic bone marrow transplant
Design/Method: A PUBMED search was conducted for queries including ALAS2 gene, XLSA, pyridoxine, BMT, lionization/skew x inactivation. Relevant papers were selected for literature review.
Results: A 14-year-old pre-pubertal girl with history of intrauterine growth retardation and congenital anemia presented for transplant evaluation after her anemia has progressed over the past year. Patient presented at birth with anemia requiring one transfusion with further stabilization of her hemoglobin (9-11g/dL) upon one year prior to transplant evaluation. Patient had short stature with no dysmorphic features, musculoskeletal abnormalities, cardiac problems, nail dystrophy, skin rashes nor hypopigmented hair. Family history was negative for consanguinity or history of anemias. Laboratory evaluation showed worsening anemia of 6 g/dL, with mild neutropenia (ANC 1000 cells/uL), normal platelet count, and elevated ferritin (450 ng/ml). Bone marrow biopsy showed erythroid hyperplasia with dyserythropoiesis, adequate and normal megakaryocytes with normal reticulin distribution, and the presence of more than 10% sideroblast. No evidence of malignancy or dysplasia with negative cytogenetics. Whole exome sequencing showed a heterozygous nonsense mutation for c.70A>T (p.Lys24*)

(g55052364T>A) in the ALAS2 gene, causing a substitution of the lysine codon for a stop codon in exon 2. In addition, a variant of unknown clinical significance was found on the CSR3F gene. Patient received a trial on pyridoxine with no improvement. She is undergoing allogeneic unrelated bone marrow transplant.
Conclusion: More than 60 mutations have been detected up-to-date affecting the catalytic region, and the regulatory regions from exon 5-11. Our patient had a novel nonsense mutation in exon 2, not allowing the catalytic part of the protein to develop, and hence administration of pyridoxine was not helpful. More discoveries of gene mutation profiles can help us to better understand the mechanism of XLSA, and guide available therapy such as hematopoietic stem cell transplant.

Poster # 616

DIAGNOSTIC CHALLENGES IN A UNIQUE CASE OF ERYTHROCYTOSIS AND PARAGANGLIOMA

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Background: Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors that account for approximately 0.3 cases per million per year. Twenty percent of PPGLs are diagnosed in childhood. Erythrocytosis can manifest in a subset of patients secondary to dysregulation of the VHL pathway leading to overproduction of erythropoietin. While the gold standard for diagnosis is the detection of excess circulating catecholamines, current imaging modalities may fail to localize these tumors.
Objectives: To review the unique clinical presentation, diagnostic challenges, and treatment course of a child presenting with hypertension and erythrocytosis.
Design/Method: A 6-year-old female was incidentally found to have high blood pressure (184/125) and elevated hemoglobin (21.4g/dL). She was admitted for BP management and therapeutic phlebotomy.
Results: Further evaluation was conducted according to the consensus algorithm of the Congenital Erythrocytosis Working Group. She was noted to have elevated erythropoietin (63.7 [normal 2.6-18.5milli-units/mL]) and normal p50 (oxygen affinity). JAK2 V617F mutation testing by PCR was negative. A hereditary erythrocytosis panel was negative for mutations in EGLN1, EPAS1 (HIF2-alpha), and EPOR. VHL full-gene sequencing was negative. No evidence of renal artery stenosis was detected on ultrasonography. Serum and urine normetanephrines were elevated (2.47 [normal 0-0.89nmol/L] and 660 [normal 0-450ug/d], respectively); however, abdominal MRI/MRA and MIBG revealed no abnormalities. Over the ensuing 18 months, her BP was managed medically, but she required intermittent phlebotomies with increasing frequency for symptomatic erythrocytosis. She re-presented with hypertensive urgency, and repeat serum and urine normetanephrines were markedly elevated (8.4 and 2,980.0, respectively). Repeat MRI demonstrated 3 retroperitoneal masses (2cm in largest diameter) that were non-avid on MIBG. Surgical resection of the masses revealed paragangliomas. Post-operatively, her normetanephrines and hemoglobin normalized, and her antihypertensive medications were tapered. Six months after surgery, her hemoglobin and BP began to rise again, necessitating recurrent phlebotomies. Subsequent MRI and whole-body FDG-PET/CT did not

reveal any recurrent or new lesions, and she continues on a trimonthly imaging surveillance protocol. Whole-exome sequencing of her serum revealed no causative variants in genes associated with PPGLs or erythrocytosis. Targeted sequencing of her tumor is underway.
Conclusion: We present the challenging case of a patient with paragangliomas and recurrent erythrocytosis and hypertension. Our case highlights the limitations of current imaging modalities in the early detection of these tumors, despite their biochemical activity and clinical manifestations. While genomic testing for reported causative variants were negative in our patient's serum, routine sequencing of PPGL tumors warrants consideration to elucidate the biology of this disease.

Poster # 617

WISKOTT ALDRICH SYNDROME - COMPARISON OF TRANSPLANT VS SUPPORTIVE CARE

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Background: Wiskott Aldrich syndrome (WAS) is a rare X linked disorder with poor prognosis without hematopoietic stem cell transplant (HSCT). HSCT in children < 5 years of age have survival rates >80%.
Objectives: Our study aims to compare outcomes, associated complications and health care utilization (HCU) in patients with WAS who underwent HSCT vs those who received supportive care.
Design/Method: We conducted a cross-sectional analysis of outcomes and HCU in pediatric patients with WAS in the Healthcare and Utilization project (HCUP) database from 2007-2012. Discharges with WAS were identified using ICD 9 code (279.12) and HSCT identified using CCS procedure code 64 or DRG code 481. Socio-demographic data, mortality rates, complications, and HCU data were compared. Continuous data was compared using two tailed independent sample t-test, categorical data was compared with the Rao-Scott adjustment for chi-square test.
Results: 382 discharges with WAS were identified and of these 38 were associated with a HSCT during that admission. All patients who underwent HSCT were male, but interestingly 2% of the non- HSCT group were female indicating possible X chromosome inactivation. Mean age at admission was significantly lower in the HSCT group versus non-HSCT group (1.31+/-0.32 years vs 5.44+/-0.78 years, $p<0.0001$). In the HSCT group, 92.2 % of discharges were below 5 years of age. In the non-HSCT group, majority (44.98%) were below 5 years of age and older age groups were significantly lower (6-10 years: 15.3%, 11-15 years: 13.11%, 16-20 years: 14.18%). Only patients in the non-HSCT group developed lymphoma (4.41%). Non-HSCT group had more ED visits compared to HSCT group (37.73% vs 8.14%, $p=0.0097$). Of 85 centers, only 10% centers had 42% (2.8-9.1% each) of the hospitalizations and 90% of the centers had less than 2.5% of hospitalizations each. Death during hospitalization was significantly higher in HSCT vs non-HSCT group (8.14% vs 0.89%, $p=0.0003$). Although payer source and median household income were not significantly different between the HSCT and non-HSCT group, the total charge for each admission was higher in the HSCT group (695,697+/-

118,520 vs 79,489+/-21,928; p<0.0001).
Conclusion: Considering the natural course of disease progression without HSCT and fewer non-HSCT patients over 5 years seeking active inpatient care, this could be an indirect indicator of increased mortality in older patients despite advances in supportive care. Post HSCT admissions were a very small number. Very few centers have experience in taking care of WAS patients and a much smaller number of centers have HSCT expertise for WAS.

Poster # 618

THROMBOCYTOPENIA AND ECZEMA DUE TO A NOVEL RUNX1 MUTATION

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Background: Familial platelet disorder with propensity to myeloid malignancy (FPDMM) is an autosomal dominant hereditary cancer syndrome caused by mutations in the hematopoietic transcription factor RUNX1 and is characterized by mild-moderate thrombocytopenia, platelet dysfunction, and increased risk of hematologic malignancies.
Objectives: We report a novel de novo deletion in RUNX1 predicted to alter the 3'carboxyl terminal end of the protein leaving intact the runt and transactivation domains in a boy with easy bruising, thrombocytopenia and eczema.
Design/Method: Case Report
Results: A 3-year old boy presented with life-long bruising and eczema. Laboratory findings revealed thrombocytopenia (~40,000/μL, normal mean platelet volume). Family history was unremarkable for cytopenias or hematologic malignancies. Sanger sequencing of the coding exons of WAS to evaluate for Wiskott-Aldrich Syndrome was negative (WAS expression was not performed). Marrow examination was normocellular and notable for atypical megakaryocytes. Targeted capture and next generation sequencing (NGS) panel testing of skin fibroblast DNA for mutations in known inherited bone marrow failure and AML/MDS predisposition genes (http://web.labmed.washington.edu/tests/genetics/MRW) revealed a novel heterozygous, likely pathogenic RUNX1 deletion (NM001754.4:c.1208_1322del, p.Tyr403Cysfs*153). This 115 base pair deletion occurs in exon 9, (chr21:36,164,553-36,164,667; hg19) and is predicted to lead to a fusion protein with intact runt and transactivation domains and a mutant tail of 153 residues starting at codon 403 and terminating at codon 555, which bypasses the normal stop codon at 481 (located at hg19; chr21:36,164,095-36,164,097). Sanger sequencing of parental DNA confirmed this variant as de novo. In 2 years of follow-up, he has required platelet transfusions twice for bleeding related to soft tissue injury. Marrow examination 15 months after presentation was unchanged with no evidence of myelodysplasia or leukemia.
Conclusion: This is the first description of eczema presenting in FPDMM in the absence of a family history of hematologic disorders. Notably, a FPDMM kindred with eczema and history of hematologic disorders was previously reported (p.Leu472fsX123) [1]. This mutation results in the same mutant STOP as caused by our patient’s deletion and was shown to impact RUNX1 binding to its co-repressor, TLE1, and to impair megakaryocytic differentiation [2]. Our report

emphasizes that eczema is a phenotypic finding in FPDMM and underscores the value of NGS to investigate the etiology of moderate thrombocytopenia and bruising/bleeding. The RUNX1 mutation places our patient at increased risk of hematologic malignancy providing rationale for close clinical surveillance. [1] Sorrell A. et al. International Journal of Clinical Medicine 2012; 3.[2] Alkadi H. et al. Blood 2018;132.

Poster # 619

ATYPICAL PRESENTATION OF WISKOTT ALDRICH SYNDROME IN AN INFANT

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Background: Wiskott-Aldrich Syndrome (WAS) is an x-linked primary immunodeficiency disorder characterized by thrombocytopenia, atopic dermatitis and increased susceptibility to infections. WAS typically presents with thrombocytopenic purpura with normal appearing megakaryocytes but small defective platelets, with normal sized platelets thought to exclude the diagnosis.
Objectives: This case report describes an unusual presentation of WAS in an infant with congenital thrombocytopenia.
Design/Method: Our patient had severe thrombocytopenia requiring multiple IVIG and platelet transfusions. Work-up for TORCH infections and a head ultrasound were negative. There was no family history of bleeding disorders. He continued to receive IVIG and platelet transfusions after birth for thrombocytopenia and a consistently normal mean platelet volume (MPV) noted on peripheral smears, until around 4-5 months of life when he started to develop worsening eczema and bloody diarrhea with subsequent iron deficiency anemia. Further work-up was initiated to determine the etiology of this patient's thrombocytopenia.
Results: Genetic testing demonstrated an approximately 112 kb loss of Xp11.23 including the entire WAS gene; further testing on the patient's mother is pending to determine if this deletion arose de novo or was inherited. Quantitative immunoglobulin testing revealed elevated IgE, low IgM, and further evidence of immunodeficiency was demonstrated by low T cell and B cell counts on flow cytometry. Due to his underlying immunodeficiency, he requires IVIG transfusions, IV pentamidine for PCP prophylaxis, and bone marrow transplant and immunology evaluations are in process. He also requires frequent platelet transfusions and romiplostim to maintain platelet counts. He is being followed closely with weekly complete blood counts to determine the need for transfusion.
Conclusion: Despite consistent findings of thrombocytopenia with a normal MPV, our patient was diagnosed with Wiskott Aldrich Syndrome with complete deletion of the WAS gene. Failure to perform early testing for WAS, particularly in males with congenital thrombocytopenia and a normal MPV, may result in delayed diagnosis. This is clinically significant because early evaluation by a bone marrow transplantation team, with subsequent curative treatment, results in significantly improved survival in these patients. Our case provides another example of the heterogeneity of the genetic and clinical findings in WAS.

Poster # 620

A NOVEL WISKOTT-ALDRICH SYNDROME GENE MUTATION MANIFESTING AS ISOLATED MACROTHROMBOCYTOPENIA

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Background: Wiskott-Aldrich Syndrome (WAS) is a rare X-linked disorder caused by mutations in the gene that encodes the Wiskott-Aldrich syndrome protein (WASp). The WASp protein regulates the actin cytoskeleton remodeling in the cytoplasm of hematopoietic cells. When absent, the immunologic synapse between T cells and antigen-presenting cells become defective, leading to immune dysfunction. The original clinical features described in patients with WAS include susceptibility to bacterial and viral infections, microthrombocytopenia and eczema. More recently, novel mutations in the WAS gene have been discovered, leading to a wide range of phenotypes. These phenotypes can be classified anywhere from mild (X-linked thrombocytopenia, X-linked neutropenia) to severe (Classic form). This is important clinically, as severe forms can lead to life threatening infections, autoimmune complications, and hematopoietic malignancies.
Objectives: To present a case of an infant and his family pedigree to describe the phenotype associated with a novel WAS gene mutation.
Design/Method: This is a case report of an infant found to have macrothrombocytopenia since birth. Next Gen Sequencing (NGS) for giant platelet syndromes revealed an unexpected novel mutation in the WAS gene in our patient.
Results: This case report presents a novel mutation of WAS within our 3-year-old male patient and other family members. Our patient initially presented with macrothrombocytopenia after birth and a significant family history involving his mother, grandmother and uncle, who were all previously diagnosed with Immune Thrombocytopenic Purpura (ITP). Our patient was evaluated for Giant Platelet Syndromes with Next Gen Sequencing and found to have a hemizygous mutation of c. 869T > C (p.lle290Thr) in the WAS gene. Due to this finding, our patient's mother and uncle were also tested and found to have an identical mutation. Maternal history is only significant for chronic ITP which worsens during pregnancy. Patient's uncle's history includes chronic macrothrombocytopenia and neutropenia, but no significant immunodeficiency nor eczema.
Conclusion: There have been no case reports of a family with the novel mutation c. 869T > C (p.lle290Thr) in the WAS gene, nor a description of the inheritance pattern. The mutation appears to be x-linked with a similar phenotype in males and females. This macrothrombocytopenia syndrome is distinctly unique when comparing to other Giant Platelet Syndromes or other phenotypes associated with different WAS gene mutations. Further observation of this first reported family will be needed to fully describe the long-term impact of this mutation.

Poster # 621

ISOLATED THROMBOCYTOPENIA AS INITIAL PRESENTATION OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Immune thrombocytopenia (ITP) is the most common diagnosis of isolated thrombocytopenia. The dilemma for pediatricians is missing diagnosis of acute lymphoblastic leukemia (ALL) in children with isolated thrombocytopenia.
Objectives: We present the prevalence of isolated thrombocytopenia in a series of childhood ALL confirmed by bone marrow examination.
Design/Method: We conducted a retrospective review of the medical records of childhood ALL over a nine-year period (2010-2018) in National Cheng Kung University Hospital.
Results: One hundred and twenty-five children diagnosed with ALL were reviewed. We found 8 patients presented with isolated thrombocytopenia (platelet count less than 120,000/mm3) and an otherwise normal complete blood cell count. Four of them showed liver function impairment and one had concurrent hepatomegaly. Five patients showed hepatosplenomegaly. Three of them revealed no blast in peripheral blood smears and one was treated initially as ITP with intravenous immunoglobulin.
Conclusion: In our series, children with ALL could present with isolated thrombocytopenia. The risk of missing the diagnosis of ALL will happen. A careful physical examination, review of the peripheral blood smear and complete blood count are important to diagnose isolated thrombocytopenia as ITP. Additional liver enzymes levels may provide a clue to physicians to reduce possibility of missed diagnosis of ALL in children presenting as isolated thrombocytopenia.

Poster # 622

VARIATION IN PRACTICE PATTERNS FOR INPATIENT MANAGEMENT OF IMMUNE THROMBOCYTOPENIC PURPURA

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Background: Immune Thrombocytopenic Purpura (ITP) is the most common cause of symptomatic thrombocytopenia in children. In 2011, the American Society of Hematology (ASH) published evidence-based guidelines that recommended observation for patients with no or mild bleeding, irrespective of the platelet count. However, a wide variability exists in the inpatient care of the newly diagnosed ITP patients across the country and limited data exist comparing the patterns across different regions and different sizes of hospitals.
Objectives: In this study, we used the Nationwide Inpatient Sample (NIS) database to examine the patterns of inpatient management of acute ITP patients and to compare the variation in care based on location and hospital size.
Design/Method: Data were extracted from the NIS database for all patients admitted for the first time with acute ITP aged 19 years and under, discharged between year 2001 and 2013. Univariate and bivariate statistics were used to describe the sample. To assess the trends in splenectomies, platelet transfusions and IVIG treatment, we employed a Cochran Armitage test of trends. Logistic regressions was used to examine the trends across region, hospital type and

hospital of different sizes across time.
Results: Overall hospitalizations for ITP decreased by 21% from 2001 to 2013, while the number of IVIG treatments increased by 73% ($p<0.0001$) and splenectomies decreased by 61% ($p<0.001$). When trending by geographical location, the South performed more of all three procedures than other regions. However, Northeast experienced the largest decline in splenectomies from 2001 to 2013, while the number of IVIG treatments roughly doubled in the Midwest (131 to 390). Urban teaching hospitals performed far more of all three procedures than urban non-teaching and rural hospitals. The number of IVIG treatments increased by 72% (987 to 1,700) at urban teaching hospitals and 93% (143 to 275) at urban non-teaching hospitals.
Conclusion: Significant variation in practice patterns and resource utilization exists across different parts of the country. While overall percentage of splenectomies and platelet transfusions decreased which is in conjunction with the recently published evidence based guidelines for ITP management, the use of IVIG dramatically increased across the country during the time period under study. It is possible that 2013 was still too early to see a significant change in practice based on the 2011 ASH guidelines. These data are an excellent starting point to evaluate management trends post-2013 which hopefully will reflect the adoption of an observation-only approach for children who do not have "wet" bleeding.

Poster # 623

SHOULD BASELINE QUANTITATIVE IMMUNOGLOBULIN LEVELS BE PERFORMED ON EVERY NEWLY DIAGNOSED ITP PATIENT

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Background: Immune thrombocytopenia (ITP) is the most common cause of symptomatic thrombocytopenia in children. Approximately 20-22% of patients with Common Variable Immunodeficiency (CVID), a heterogeneous syndrome characterized by hypogammaglobulinemia and recurrent bacterial infections, develop autoimmune disease, among which autoimmune thrombocytopenia is preeminent. In review of literature, over fifty percent of ITP episodes started prior to diagnosis of CVID. Literature also shows that there is a discrepancy as to the utility of measuring baseline quantitative serum immunoglobulin levels in a newly diagnosed ITP patient. This study aims to identify what is currently being practiced at our institution and the incidence of immunodeficiency in patients that were diagnosed with ITP.
Objectives: The primary objective is to determine number of patients who had quantitative immunoglobulins measured at initial diagnosis of ITP, and number of patients who were found to be immunodeficient at the time of diagnosis and during follow up visits.
Design/Method: This is a retrospective chart review looking at newly diagnosed ITP patients ages 0-18 years, from January 1st 2010- December 31, 2017. Data collected through electronic medical records and included age, sex, quantitative serum immunoglobulin levels, and CBC over the course of the study.
Results: A total of thirty five patients were included in the study. Out of thirty-five patients, twenty had their quantitative serum immunoglobulin levels collected at diagnosis and two other patients had their levels checked once they developed chronic ITP. Two patients were found to have immunodefiency. The first patient was found to have IgA deficiency during the initial visit

while the second patient had previous immunodefiency workup and was diagnosed with p110 delta activating mutation (PASLI disease). Twelve patients went on to develop chronic ITP, none of which developed new immunodeficiency.
Conclusion: Literature review shows that there is a discrepancy as to the utility of measuring baseline serum immunoglobulin levels in a newly diagnosed ITP patient. While our study has small population sample and would benefit from further investigation, we conclude that measuring baseline immunoglobulin levels at diagnosis of ITP does not predict or help diagnose immunodeficiency at early stages prior to evolution of symptoms.

Poster # 624

SAFETY AND EFFICACY OF ROMIPLOSTIM IN OVER 200 CHILDREN WITH IMMUNE THROMBOCYTOPENIA (ITP)

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Background: Romiplostim is approved globally for use in adults with ITP and in the EU for children with ITP. More comprehensive data are needed on the use of romiplostim in children with ITP.
Objectives: To examine the safety and efficacy of romiplostim in children with ITP.
Design/Method: Data were combined from 5 romiplostim trials in children with ITP, both placebo-controlled (a phase 1/2 and a phase 3 trial) and open-label (a 3-year trial and 2 extension trials).
Results: Patients (N=286, 24 initially placebo and 262 initially romiplostim) had median (Q1, Q3) age of 10 (6, 13) years, ITP duration of 1.9 (1, 4) years, and baseline platelet count of 14 (8, 23)x10^9/L. All had received prior treatments (23% had received >3) and 7% had prior splenectomy. Of 282 patients exposed to romiplostim (20 initially received placebo), median (min, max) duration of treatment was 65 (8, 471) weeks, with median (min, max) average weekly dose of 6.6 (0.1, 9.7) μg/kg. Twenty-four percent of patients had serious adverse events, most commonly epistaxis (6%), low platelet count (2%), or headache (2%). There were 7 cases of postbaseline neutralizing antibody against romiplostim and no neutralizing antibodies against endogenous thrombopoietin. For patients undergoing bone marrow biopsies in a 3-year open-label trial, there were no findings of collagen or bone marrow abnormalities. One patient had an increase in modified Bauermeister bone marrow grade from 0 to 2, with no associated adverse events. One patient had a platelet count of 1462x10^9/L at week 14 for 1 week, and another had 10 elevated platelet counts between weeks 20 and 172 (max of 872x10^9/L); there were no associated thrombotic events. Median platelet counts rose quickly and were over 50x10^9/L from week 12. Overall, 89% of romiplostim treated patients (vs 8% of placebo-treated patients) had a platelet response (≥50x10^9/L). From the first monthly response (median, 6 weeks), the median (Q1, Q3) percentage of months responding was 92% (75%, 100%). Nineteen romiplostim-treated patients (and no placebo-treated patient) discontinued all ITP therapies including romiplostim for ≥6 months while maintaining platelet counts ≥50x10^9/L. Treatment-free periods lasted a median (Q1, Q3) of 12 (8, 14) months. Grade 3 bleeding was reported for 10% of patients (epistaxis in 5%) and grade 4 bleeding for <1%.

Conclusion: In this comprehensive database of romiplostim ITP trials, romiplostim was well tolerated. Most patients had a platelet response, with some children able to discontinue all ITP treatments for ≥6 months.
This work was supported by Amgen Inc

Poster # 625

JAK2 V617F MUTATION+ ESSENTIAL THROMBOCYTHEMIA WITH ACQUIRED VON WILLEBRAND DISEASE IN AN 8-YEAR-OLD

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Background: Essential Thrombocythemia (ET) is a myeloproliferative disorder most commonly diagnosed in adults, with risk for both thrombotic and hemorrhagic events. ET is a rare cause of thrombocytosis in children and must be considered in the differential diagnosis. Estimated incidence of ET in children under 14 years old is 0.09 case per million. ET can be associated with a JAK2 mutation, (more commonly identified in adult ET patients (50-60%) compared to pediatric patients (20-30%)). Acquired von Willebrand disease (AVWD) is seen in a subset of adult ET patients which leads to increased bleeding symptoms, but has rarely been described in pediatric patients.
Objectives: To describe the presentation and treatment of ET with AVWD in an 8-year-old.
Design/Method: Case Report
Results: An 8-year-old African American female presented for evaluation of 1 year of headaches which were occurring with increasing frequency and severity. Additionally, she reported frequent epistaxis over the past 24 months. Her initial evaluation included an MR brain that was normal and screening labs. Her completed blood count (CBC) revealed: leukocyte count of 13.3 x103/uL, hemoglobin of 15.3 g/dL, and platelet count of 964 x103/uL. Upon medical record review, CBC from 1-year prior revealed: leukocyte count of 15.2 x103/uL, hemoglobin of 13.6 g/dL, and platelet count of 972 x103/uL. Based on persistent thrombocytosis, headaches and epistaxis, workup for a myeloproliferative disorder was completed including bone marrow evaluation and genetic testing. Given her epistaxis, von Willebrand testing was also completed. Bone marrow evaluation revealed increased number of megakaryocytes with complex lobation patterns, with normal morphology of myeloid and erythroid precursors without evidence for Polycythemia Vera. Genetic testing was positive for JAK2 V617F mutation. Von Willebrand testing demonstrated acquired VWD (VW GPIbM activity of 34 U/dL and loss of high molecular weight multimers). Due to her symptoms, the patient was started on Hydroxyurea (HU). With titration of HU, at a dose of 30 mg/kg her platelet count decreased to 270 x103/uL and her VW studies normalized. Improvement in her headaches coincided with her decreased platelet count.
Conclusion: ET should be considered in the differential diagnosis for persistent thrombocytosis in children, despite the low incidence. Concomitant symptoms that should raise the suspicion include persistent headache and bleeding symptoms. Treatment with single agent Hydroxyurea led to resolution of thrombocytosis and normalization of von Willebrand studies. Without clear management guidelines for ET in children, treatment with Hydroxyurea should be considered in symptomatic patients with ET and AVWD.

Poster # 626

ATYPICAL HEMOLYTIC UREMIC SYNDROME (AHUS): AN EMERGING PEDIATRIC HEMATOLOGIC DISEASE

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Background: Atypical hemolytic uremic syndrome (aHUS) is an ultra-rare disease process characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ damage (TMA). Often misdiagnosed as other TMA related diseases, aHUS is considered to arise from genetic mutations predisposing patients to uncontrolled complement dysregulation when triggered by a precipitating event. Once triggered, aHUS manifests as a medically urgent syndrome requiring thoughtful recognition and rapid intervention to prevent long-term, permanent end-organ damage. Though more is now understood about this disease, specific pediatric characteristics are not well documented.
Objectives: To gain a better understanding of the causes, clinical progression, and effective treatments of aHUS especially in pediatric patients.
Design/Method: A clinical review of patients with aHUS (n=7) treated at the UT Health San Antonio division of Pediatric Hematology from 2011 to 2018 was performed. The disease characteristics, treatment, and clinical changes were analyzed to compare the differences in experiences and outcomes.
Results: The most common reasons patients presented to the hospital were nausea/vomiting and fever. Mutations in three patients were identified and the majority were in complement factor H (CFH). 85% of patients presented with elevated BUN and all presented with increased creatinine, indicating impaired kidney function upon presentation. Four patients presented with decreased hemoglobin. Two patients presented with a decreased platelet count including one patient with an extremely critical value of 16 K/uL (reference range 189-403 K/uL). The majority of the patients (57%) had a surgical history significant for renal transplantation due to impaired kidney function and renal damage. More than half of the patients were treated with dialysis, but all were ultimately treated with Eculizumab. Long term follow-up noted that all patients remained on Eculizumab therapy. One was non-compliant but resumed once her kidneys began to fail again. At their most recent analyses, 85% of patients showed an improvement in BUN levels, 43% of patients showed a decrease in creatinine levels, all patients showed improvement in their anemia with increased hemoglobin levels, and 71% of patients were not thrombocytopenic.
Conclusion: Patients with aHUS may present with many different signs and symptoms after an event has triggered uncontrolled complement activation. Though other organ systems may be involved, most patients present with signs of renal injury, thrombocytopenia, and anemia. While other therapeutic modalities may improve lab values, beginning treatment with Eculizumab and performing renal replacement therapy as early as possible can be key to a positive outcome in patients with aHUS.

Poster # 627

COMPLEMENT MONOCLONAL ANTIBODY ECULIZUMAB IN STEC HUS: AN IN-DEPTH REVIEW OF CURRENT EVIDENCE

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Background: Shigatoxin associated HUS (STEC-HUS) remains a leading cause of pediatric acute kidney injury (AKI) in children below 5 years of age. Treatment is mostly supportive. The role of eculizumab in STEC-HUS remains unclear. The best evidence available are derived from case reports, case series and retrospective studies, showing improvement in cases with neurological involvement. Its role in less severe forms of disease has not been reported.
Objectives: We describe a 2 years old girl with STEC HUS without neurological involvement, treated with eculizumab with remarkable clinical improvement, and review current evidence of eculizumab in STEC HUS.
Design/Method: Case report followed by literature review on use of eculizumab in STEC HUS using databases PubMed, Embase, Ovid Medline and Cochrane.
Results: Case: We describe a 2-year-old girl who presented with classic triad of HUS (AKI, microangiopathic hemolytic anemia and thrombocytopenia). In view of worsening clinical picture (persistent anuria, worsening hemolysis and thrombocytopenia), patient was treated with eculizumab on hospital day 5. The administration of eculizumab was followed by rapid improvement in clinical course of disease. Stool test came back positive for STEC by PCR. At 4 months follow up, patient had residual hypertension and proteinuria.Literature review: We identified 16 reports describing use of eculizumab in patients with STEC HUS (5 case reports, 3 case series, 1 retrospective case control study, 6 retrospective and 1 prospective cohort study). All case reports and series described use of eculizumab in severe cases with neurologic or multi-organ involvement. All of those reports described rapid hematologic and neurological improvement after 24-48 hours of eculizumab administration. One case control and 3 cohort studies used historical control groups; none were randomized or blinded. Of those 4 studies with control groups, 2 reported no significant difference between the groups for survival, neurological and renal recovery. The other 2 studies reported rapid neurological and hematologic improvement in treatment group compared to control group. One case of staphylococcal septicemia, one case of severe chickenpox and one death due to gram-negative sepsis in patients treated with eculizumab were reported. Most of the studies reported hypertension and proteinuria as the common long term morbidity.
Conclusion: The role of eculizumab in STEC HUS is unclear. The best available evidence supports the use of complement blockage in severe cases of STEC HUS with neurological involvement. There have been no reports of its use in earlier stages or non- severe forms of disease.

Poster # 628

UNUSUAL PRESENTATION OF ATYPICAL HEMOLYTIC UREMIC SYNDROME IN THE SETTING OF RECURRENT PANCREATITIS

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Background: Atypical Hemolytic Uremic Syndrome (aHUS) is estimated to affect 3 per 1 million children while acquired thrombotic thrombocytopenic purpura (TTP) affects 1 per 10 million children every year. If untreated, studies have shown TTP to have a mortality rate >90%. These life-threatening conditions are classified as microangiopathic hemolytic anemias (MAHA) and present in similar manners with hemolytic anemia, thrombocytopenia, and renal impairment
Objectives: We discuss the case of a 5-year-old male with recurrent pancreatitis who developed aHUS.
Design/Method: A 5-year-old male with two previous episodes of pancreatitis presented to the emergency department with one day of abdominal pain. Initial blood work showed an elevated Amylase and Lipase. An abdominal CT was concerning for pancreatitis that was subsequently confirmed with MRCP; he was treated with fluid resuscitation and pain control. On day two of hospitalization, patient developed fatigue, jaundice and pallor. A non-immune hemolytic anemia process was confirmed with an acute drop in hemoglobin, schistocytes on peripheral smear, an indirect hyperbilirubinemia, elevated lactate dehydrogenase and negative Coombs testing. He developed an acute kidney injury with gross hematuria as well as a significant thrombocytopenia with little improvement following repeated platelet and blood transfusions. With the clinical picture of MAHA and the high mortality rate of TTP, he was empirically treated with serial plasmapheresis and steroids while definitive testing was pending.
Results: His symptoms, hematologic abnormalities, and kidney injury gradually improved during treatment. His ADAMTS13 levels drawn prior to therapy were normal, similar to previous reports of TTP associated with recurrent pancreatitis, but genetic testing revealed a CD46 gene mutation consistent with aHUS.
Conclusion: This case demonstrates an unusual presentation of aHUS in association with pancreatitis. It stresses the importance of a multi-disciplinary approach and initiating potentially life-saving treatment while definitive diagnostic testing is pending. Maintaining a broadened differential and adapting medical therapy based on clinical changes is imperative.

Poster # 629

CHRONIC THROMBOCYTOPENIA AND BONE INFARCTS AS PRESENTING SYMPTOMS FOR TYPE 1 GAUCHER DISEASE

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Background: Gaucher Disease is the most common lysosomal storage disease and results from autosomal recessive inheritance of a GBA1 mutation that compromises function of glucocerebrosidase. Unlike Gaucher disease types 2 and 3, type 1 Gaucher disease (GDT1) has no primary neurologic manifestations. GDT1 is characterized by progressive local toxicity from accumulation of glucosylceramide in the liver, spleen, and marrow. The initial presenting symptoms of GDT1 are often related to thrombocytopenia or splenomegaly and for this reason, Hematologists are the most likely specialist to encounter this disease at presentation. Despite referral to Hematologists, the median time of diagnosis from onset of symptoms is approximately 2 years.
Objectives: To describe a case of GDT1 that presented to Tulane Pediatric Hematology as a second opinion for chronic thrombocytopenia and bone infarcts.

Design/Method: A 14-year-old female with chronic ITP, diagnosed 2 years prior, presents to the ER with acute, debilitating right thigh pain. CT revealed lesions consistent with an acute right femur infarction, but a neoplasm could not be ruled out. MRI revealed acute and chronic bilateral distal femur infarctions and avascular necrosis of the left ischium. Labs for HIV, lupus, and sickle cell disease were negative. Platelets were 101,000(nl 140,000-450,000). Despite Hematology and Orthopedic consultation, an etiology for the infarcts was not discovered. Her pain improved with analgesics and she was discharged home. Five months later she presented to Tulane Pediatric Hematology for a second opinion. Extremity pain recurred and she returned to the ER for evaluation. Physical exam was notable for splenomegaly, confirmed on ultrasound, and her platelet count was 69,000 (nl 140,000-450,000). Peripheral smear showed abnormally shaped erythrocytes and thrombocytopenia, findings associated with evolving myelodysplasia and other bone marrow disorders. A bone marrow biopsy revealed sheets of macrophages with fibrillary and foamy cytoplasm accounting for 70-80% of the marrow space and morphologically consistent with Gaucher cells.
Results: She was referred to Genetics with glucocerebrosidase level of 1.0 (nl >8.7) and glucopsychosine of 1000 (nl< 47), diagnostic of GD. Mutation analysis found one common pathogenic variant (c.1226A>G) and one variant of unknown significance (c.637C>T). She was started on enzyme replacement infusions with the plan to continue until meeting treatment goals (1-2 years) before transitioning to oral treatment.
Conclusion: The presentation of thrombocytopenia, bone infarcts, splenomegaly and absence of neurologic involvement are consistent with classic clinical findings seen in GDT1. Hematologists are often the diagnosing physicians and must maintain a high index of suspicion for this disease.

Poster # 630

IS CETIRIZINE A RISK FACTOR FOR DRUG INDUCED METHEMAGLOBINEMIA?

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Background: Methemoglobinemia (MHB) is characterized by increased serum levels of oxidized heme with iron in ferric form, which due to its increased affinity for oxygen results in reduced O2 release at tissue sites and thereby, tissue hypoxia. Protective enzymes, cytochrome-b5 reductase & NADPH maintain methemoglobin at homeostatic level of about 1%. Cetirizine, commonly used to treat allergies is a selective H1 receptor antagonist. It is metabolized and eliminated via oxidation & conjugation. This process can create powerful reducing agents as by-products that can oxidize heme Fe into ferric form.
Objectives: To report a case of Cetirizine induced MHB.
Design/Method: Single case report.
Results: An 18 year old African American female, with history of anxiety and depression presented to ED with self-reported ingestion of 10-16 tablets of cetirizine (10mg each) for allegedly relief of abdominal pain. In ED the vital signs and arterial blood oxygen saturation (SaO2) on room air were normal. She was anxious and tremulous. Investigations revealed low serum bicarbonate (19 mmol/L), high bilirubin (1.9 mg/dL) and high creatinine (Cr, 1.2 mg/dL) values. Serum acetaminophen, salicylate and lactate levels were normal. Urine tests for illicit

drugs and pregnancy were negative. After 4-5 hours, she developed central cyanosis without respiratory distress. Pulse oximetry was notes to be 85% (forehead) and 75% (left hand) which did not improve with supplementation of 4L/minute of 100% oxygen via nasal cannula. Arterial blood gas, otherwise normal, revealed dark red appearance of blood and methemoglobin level of 38%. Patient responded to methylene blue and vitamin C. Workup for underlying cause of MHB including sulfhemoglobin and methemoglobin reductase was noncontributory. Patient declined for further specific investigations.
Conclusion: Diagnosis: Methemaglobinemia secondary to acute excessive ingestion of cetirizineComments: To our knowledge cetirizine has not been documented to cause methemoglobinemia.The medication may be considered for inclusion in the list of drugs as a risk factor for methemoglinnemia and monitored for this complication espy in conditions of excessive ingestion.

Poster # 701

PEROXIREDOXIN II (PRDX2) IS A NOVEL CANDIDATE GENE FOR CONGENITAL DYSERYTHROPOIETIC ANEMIA

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Background: Congenital Dyserythropoietic Anemias (CDAs) are a group of rare heterogeneous genetic disorders characterized by ineffective erythropoiesis with distinct morphologic abnormalities of bone marrow erythroblasts. Peroxiredoxin II (PRDX2) is an antioxidant enzyme, highly expressed during terminal erythropoiesis, and one of the most abundant proteins after hemoglobin in red blood cells (RBCs). It reduces the reactive oxygen species (ROS) readily produced within the erythroid cells due to the presence of heme iron and oxygen. PRDX2-/- mice were found to have hemolytic anemia with evidence of oxidative damage of the RBC proteins resulting in decreased erythrocyte survival.
Objectives: To determine the pathogenic role of a novel PRDX2 variant identified by Whole Exome Sequencing (WES) in a patient with CDA.
Design/Method: The proband with non-immune hemolytic anemia and suboptimal reticulocytosis was diagnosed with atypical CDA and was enrolled in the CDA Registry (CDAR; ClinicalTrials.gov Identifier: NCT02964494). Bone marrow pathology demonstrated erythroid hyperplasia with dyserythropoiesis, including megaloblastoid changes, nuclear lobation and fragmentation, with less than 10% binucleated erythroblasts. Review of the peripheral blood smear showed significant poikilocytosis, mild polychromasia, and the presence of blister and ghost cells indicating oxidative damage. Her father had a similar clinical presentation and peripheral blood smear. Genetic and further phenotypic work-up was performed following the CDAR protocol.
Results: Next Generation sequencing and deletion/duplication assay for the known CDA-associated genes were negative. WES for the patient and her parents (family-trio design) revealed the PRDX2 missense variant (c.154C>T;p.Pro52Ser) present in heterozygous state in both proband and her father; no mutation in this gene was present in the asymptomatic mother.

This variant is located in the enzymatically-active protein domain, adjacent to the active Cys51, causing a non-conservative substitution of a phylogenetically highly-conserved amino acid, with the potential to cause a conformational change. Flow cytometry confirmed significantly increased ROS in the patient-derived versus control EBV-immortalized lymphocytes as well as in the reticulocytes and mature erythrocytes of the proband and her father. Western blot showed decreased PRDX2 protein in proband's and her father's EBV-immortalized lymphocytes versus similar sample derived from mother and healthy control volunteer. Induced pluripotent stem cells (iPSCs) were generated from the patients' peripheral blood mononuclear cells to allow ongoing in vitro studies of this PRDX2 variant in erythropoiesis.
Conclusion: PRDX2 c.154C>T; p.Pro52Ser appears to be a loss-of-function mutation causing increased oxidative stress in the patient's erythroblasts and RBCs, leading to dyserythropoiesis and decreased RBC survival with a phenotype of autosomal dominant hemolytic anemia with dyserythropoiesis.

Poster # 702

HEREDITARY PYROPOIKILOCYTOSIS DUE TO COMPOUND HETEROZYGOUS NOVEL BETA-SPECTRIN GENE VARIANTS

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Background: Hereditary pyropoikilocytosis (HPP) is most frequently caused by a hereditary elliptocytosis (HE) - causing mutation of the alpha-spectrin gene (SPTA1) in trans to αLELY, a low expression SPTA1 allele. In these cases, significant poikilocytosis and transfusion requirement is noted in early infancy with subsequent improvement to a mild hemolytic anemia. Rarely, more severe HPP with chronic anemia after infancy is caused by pathogenic SPTA1 or SPTB (beta-spectrin gene) mutations in-trans.
Objectives: To present a case of HPP due to compound heterozygous novel SPTB variants.
Design/Method: This is a case report of a child with hemolytic anemia since birth. Next Generation Sequencing (NGS) for hereditary hemolytic anemias (evaluating 32 genes involved in erythrocyte membrane disorders, enzymopathies, and congenital dyserythropoietic anemias), revealed two novel SPTB variants and a novel variant in PIEZO1, a gene known to be associated with hereditary xerocytosis (HX). Parental genetic and phenotypic studies were performed to evaluate the pathogenicity of these variants.
Results: We describe a 3-year-old girl of Burmese descent, born full term, with jaundice and indirect hyperbilirubinemia within the first day of life. She required hospitalization and transfusion support for a severe hemolytic anemia. No known family history of anemia or hemolysis. She had negative direct and indirect Coombs; hemoglobin electrophoresis and globin gene testing normal, G6PD activity not-decreased. Peripheral blood smear revealed spherocytes, irregular pyknocytes, and elliptocytes.NGS revealed two novel SPTB variants and a novel PIEZO1 variant. Follow-up testing on the parents showed that each SPTB variant was inherited from each one parent, confirming that the proband had both SPTB alleles affected. Both mother's (c.6014T > C; p.L2005P) and father's variant (c.6224A>G; p.E2075G) were located at the β-spectrin self-association site. The mother shared the patient's PIEZO1 variant (c.4573C > G; p.L1525V). Ektacytometry on parents' blood revealed HE for both with no evidence of HX

for the mother. RBC cation content was normal for both parents, providing reassurance that this PIEZO1 variant is not pathogenic.The patient has required 10 blood transfusions in her first 3.5 years of life, mostly given in the newborn period or in the setting of viral illnesses. She has persistent leukocytosis, thrombocytosis and splenomegaly.
Conclusion: Biallelic SPTB mutations at the self-association site lead to severe instability of the spectrin tetramer and the red cell cytoskeleton structure as indicated from the patient's ektacytometry, performed >3 months post transfusion. The result is severe HPP with chronic hemolytic anemia persisting after infancy.

Poster # 703

RECURRENT LEG ULCERATION IN PATIENTS WITH HEMOGLOBIN E/BETA THALASSEMIA

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Background: Leg ulcers, often associated with significant morbidity, may complicate the clinical course of thalassemia. Neither the natural history nor the optimal treatment(s) for this complication in patients with thalassemia is clearly defined.
Objectives: To identify the prevalence and therapeutic outcomes of leg ulcers in a common, understudied form of thalassemia, Hemoglobin E/beta thalassemia (HbE thalassemia), in patients in Sri Lanka.
Design/Method: We reviewed records of patients with HbE thalassemia at The National Thalassemia Center (Kurunegala, Sri Lanka) to identify all patients diagnosed with a leg ulcer between 1993 and 2018.
Results: 73 ulcers in 33 HbE thalassemia patients {25 of 202 (12%) of Kurunegala patients and eight additional patients in the Adult Thalassemia Unit, Ragama (61% female)} were diagnosed at (mean±SEM) 21.1±1.5 years; 75% patients developed a first ulcer between age 11 and 30 years. Ulcers commonly developed around the ankle (45%), unspecified areas of the leg (27%), dorsum of the foot, heel, toe, and/or pre-tibial areas (7%), and unrecorded locations (19%); 59% were left-sided, 15% were bilateral, and 14% reportedly developed following trauma. A diagnosis of HbE thalassemia had been confirmed relatively late (at 11.5±1.9 years) in these patients: prior to development of an ulcer, most had been rarely/irregularly transfused (79% with <3 transfusions/year; 8% with 3-8 transfusions/year). At ulcer diagnosis, mean hemoglobin was 6.6±0.1 g/dL. A total of 61% patients were splenectomised, and platelet counts were modestly elevated (565±39 x109). Serum ferritin (1142±193 μg/L) suggested moderate iron overload. Neither therapeutic approaches, nor evolution of healing, were clearly documented, particularly before 2005. Documented treatments included regular transfusions (in 18%), antibiotics (18%), zinc supplementation (4%), and other treatments (12%) including skin grafts, wound toileting, plastic surgery consultation, and topical steroids. No treatment with hydroxyurea was documented. A total of 53% patients experienced ulcer recurrences, following apparent resolution of an ulcer: 40% experienced 2 recurrences, and 21% experienced 3-6 recurrences.

Years lived with a leg ulcer was 8.9 ± 1.8 years (range, 4 months to 27 years).
Conclusion: In HbE thalassemia, leg ulcers are common and, possibly related to inadequate therapy in many patients, chronic. While both transfusions and hydroxyurea are reportedly protective against leg ulcers in non-HbE-thalassemia patients (Blood 2010; 115:1886-92), there is a need for exploration of optimal treatment(s) in HbE thalassemia. The relative benefits of transfusions, hydroxyurea, conservative measures, and other approaches should be evaluated, ideally in a clinical trial, in patients in HbE thalassemia and leg ulcers.

Poster # 704

LINEAR GROWTH IN PATIENTS WITH THALASSEMIA MAJOR IN SRI LANKA

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Background: Prior to 1990, poor growth in thalassemia major was common, and related to multiple factors including inadequately-corrected anemia and uncontrolled body iron burden. A decade following the introduction of deferoxamine, most adults whose body iron had been adequately controlled from childhood achieved mid-parental height (N Eng J Med 1990:323:713). In many thalassemia patients in emerging countries, linear growth remains abnormal.
Objectives: To describe growth patterns in thalassemia patients at Sri Lanka's National Thalassemia Center. We hypothesized that body iron would be more effectively controlled in younger patients treated from early childhood with deferasirox (introduced after 2010) than in older patients whose early care was challenged by a relative unavailability of deferoxamine, and that this may have influenced patterns of growth.
Design/Method: Height percentiles (WHO Child Growth Standards, 2006) were correlated with serum ferritin concentration (SFC), ALT, and baseline hemoglobin recorded from 2015 to 2018; and assessed mid-parental heights (MPH) in 98% patients.
Results: In 232 patients aged (mean±SEM) 15.1±0.4 years, we identified moderate iron loading [SFC 2452±159 ug/L and ALT 44±3 (normal ≤40) U/L], and a low transfusion scheme [pre-transfusion hemoglobin, 8.8±0.1 g/dL]. In 84 patients aged ≥18 years (22.1±0.4 years), 83% had achieved ≥3rd height percentile, and 29% had reached MPH. Neither SFC nor hemoglobin differed significantly between patients who had, and had not, achieved MPH and ≥3rd height percentile; by contrast, serum ALT was significantly different between these groups (88±17 vs 40±5 U/L; P=0.0025). In 148 patients <18 years, MPH was not yet quantifiable (at 10.7±0.3 years), but 51% have achieved ≥3rd height percentile. Encouragingly, in patients <18 years, baseline hemoglobin was significantly higher (9.1 ± 0.1 g/dL) than in patients ≥18 years (8.6 ± 0.1 g/dL; p=0.0066), and SFC was lower (and adequately controlled in most patients at 1961±173 ug/L) than in older patients (3337±317 ug/L; p<0.0001). Improved iron control was reflected in striking differences in the prevalence of diabetes (2.2% in younger, and 13.5% in older, patients; P=0.002) and of hypothyroidism (3.7% and 24%, respectively; P=0.001).
Conclusion: In this (largest) thalassemia center in Sri Lanka, patients prescribed deferasirox

after age 10 years have not achieved the standard of growth usually observed in higher-resource countries. In the treatment of younger children, we have identified improved adherence to transfusion guidelines, and improved iron control, including lower rates of complications. The data will assist in evaluation of the influence of deferasirox, and other factors, on linear growth in children with thalassemia.

Poster # 705

A SURVIVOR OF α(ADANA)α/-- HB H HYDROPS FETALIS: IMPORTANT PRECONCEPTION, ANTE-AND POSTNATAL LESSONS

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Background: Alpha thalassemia-related hydrops fetalis (HF) commonly develop due to defects in all four alpha globin genes, presenting as Hb Barts HF (Barts-HF). Defects of three alpha globin genes usually present as Hb H Disease, a form of thalassemia intermedia, but may uncommonly present as Hb H HF (HbH-HF). Hemoglobin (Hb) Adana (HBA2/HBA1: c.179G>A), a non-deletional alpha globin gene mutation, can reach endemic proportion in some localities. HbH-HF has been reported due to Hb-Adana/alpha-zero thalassemia.
Objectives: To report our experience of a child with Hb-Adana/alpha-zero thalassemia who survived the HbH-HF.
Design/Method: Case report.
Results: Y was conceived naturally to non-consanguineous Filipino parents, as their second pregnancy. Maternal red cell indices (RCI) were normal except for mildly-decreased mean corpuscular hemoglobin; paternal RCI suggest alpha-zero thalassemia. Their first pregnancy at another country was complicated by HF. Despite three intrauterine transfusions (IUT), a hydropic but non-dysmorphic baby was delivered at 35 weeks gestation (/40) and died aged three days. Investigations revealed severe anemia, normal karyotype, and parvovirus negative. Hemoglobinopathy investigations not performed as parental RCI combination not high risk for Barts-HF. Y developed HF at 19/40, with high peak-systolic velocity in the middle cerebral artery, suggestive of anemia. Cordocentesis revealed normal molecular karyotype, Hb 2.9 g/dL, and fetal red cell changes suggestive of severe thalassemia. Hemoglobinopathy screen showed HbF and Hb Barts in equal portions with small amounts of HbA and fast moving Hb, making Barts-HF unlikely, but consistent with HbH-HF. Alpha globin sequencing revealed α(Adana)α / --(SEA), thereby confirming the diagnosis. The HF resolved rapidly after IUT done at 20/40. Four further IUTs were given prior to semi-elective Cesarean section at 37/40 for asymmetrical fetal growth restriction without signs of uteroplacental insufficiency. Hb at birth was 11.9 g/dL. He required brief continuous positive airway pressure, and was discharged aged eight days fully breastfeeding. Following initial monitoring, a regular transfusion regimen was established. Ferritin from birth to age 14 weeks: 1,469–2,963 µg/L (median 2,390).The baby was small for gestational age, had glanular hypospadias, positional talipes and conjugated hyperbilirubinemia. His current neurodevelopment was age-appropriate.Iron chelation and hematopoietic transplantation are actively considered.
Conclusion: HbH-HF can be successfully managed with in-utero and ex-utero transfusions if

diagnosed early. Despite non-suggestive parental RCI, investigation of hemoglobinopathy, including alpha globin sequencing should be considered when there is non-immune hydrops with fetal anemia.The International Registry of Barts-HF Syndrome Survivors (Songdej, Blood, 2017) should consider including HbH-HF survivors due to similar pathophysiology.

Poster # 706

IRON QUANTIFICATION BY MRI IN PATIENTS WITH ALPHA THALASSEMIA

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Background: The Alpha Thalassemias are a group of inherited disorders of hemoglobin synthesis affecting the alpha globin genes. Patients with deletional alpha-thalassemia often remain transfusion independent. Iron overload can occur from chronic hemolysis and intestinal over-absorption. The use of Magnetic Resonance Imaging (MRI) to quantify iron overload in the liver and heart is well established in beta-thalassemia patients, however iron quantification via MRI in deletional alpha-thalassemia has not been as well documented.
Objectives: Evaluate hepatic and cardiac iron burden in our cohort of deletional alpha-thalassemia patients using MRI.
Design/Method: We performed a retrospective chart review of children with deletional alpha-thalassemia, who have undergone cardiac and liver MRI to evaluate iron burden, from January 2012 to June 2018.
Results: Nineteen patients with deletional alpha thalassemia underwent cardiac and liver MRI for iron quantification from January 2012 to June 2018. All patients were identified on newborn screening results and diagnosis was confirmed by genetic testing. The median age of our cohort was 15 years (range 10 to 19 years) and 63.2% were female. 31.5% of the patients were of Vietnamese descent. Median hemoglobin was 10 g/dL (range 8.9 – 11.6 g/dl) and median peak ferritin was 113 ng/mL(range 51 - 273). Median LIC was 1.4 mg/g dry weight of liver (range 0.8 – 3.4). Three patients had LIC >2.5, all of these patients were > 16 years of age. Median T2* level was 37 (range 20.4 – 63). The patient with the highest LIC had a peak ferritin level of 273 and T2* of 20.4. One of the 19 patients had received a single red cell transfusion in her lifetime.
Conclusion: In our small cohort of patients, three patients had LIC > 2.5mg/g dry weight of liver indicative of mild iron overload, there was no evidence of iron overload in the remaining patients. None of our patients required chelation for iron overload. Although this is a small patient cohort, our data suggests that patients with deletional alpha-thalassemia do not develop significant iron overload in the pediatric age range. We found higher LIC values in patients as they aged beyond 16 years. Follow-up studies in these individuals as they progress into adulthood are needed to determine the rate of iron accumulation in these critical target organs and to assess need for iron chelation despite being transfusion independent.

Poster # 707

NEPHROLITHIASIS IN CHRONICALLY TRANSFUSED PATIENTS SECONDARY TO DEFERASIROX USE

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Background: Patients with Beta thalassemia major (TM) and transfusion dependent Thalassemia Intermedia (TI) patients require blood transfusions life-long to replace their defective red blood cells, due to impaired production of beta-globin chains. This life-long requirement results in significant risk for iron overload. Iron chelating agents, including deferasirox, allow excretion of excess iron to prevent potential damage to organ systems. However, these agents carry their own adverse effects and need to be monitored closely. The renal adverse effects include acute kidney injury, Fanconi syndrome, and nephrolithiasis.
Objectives: Report of our institution's experience of increased nephrolithiasis with deferasirox.
Design/Method: Study population included patients that required transfusions every two weeks. Nephrolithiasis was detected by either computerized tomography or renal ultrasound. Seven of 21 patients on chronic chelation with deferasirox (including TM, Diamond-Blackfan anemia, TI) had experienced renal stones by clinical and radiographic criteria. This population included 6 females and 1 male with a total of 9 reported kidney stones. The average age at the time of the kidney stone was 34.72 +/- 8.00 years old. Deferasirox was being taken at an average dose of 1113 mg daily.
Results: The renal stone formation has been seen with the oral suspension as well as the oral pill version of deferasirox. The average length of chelation therapy with deferasirox at the time of the kidney stone formation was 737.9 days. These patients were on Calcium and Vitamin D supplementation as well. Urine electrolytes were not tested in this population however they were found to have hematuria and proteinuria. Serum creatinine was normal.
Conclusion: This is the first case series of nephrolithiasis on deferasirox reported in an institution in the United States. There have been isolated instances reported in other countries treating thalassemia patients. Contributing factors to nephrolithiasis in transfusion dependent patients on deferasirox have been theorized to include abnormal vitamin D homeostasis, renal glomerular, and tubular dysfunction causing hypercalciuria, hyperphosphatemia, proteinuria, and renal hyperfiltration. Nephrolithiasis did not appear to be related to the chelating dosage but most occurred at around two years of chelation therapy. It is unclear what the specific pathophysiology is in this patient population but the role of vitamin D +/- calcium supplementation therapy and contribution of deferasirox needs to be further studied to find how bone heath can be maintained without increasing renal stone risk. Renal function also needs to be monitored closely at baseline and when on chronic chelation.

Poster # 708

PEAK REGISTRY: A GLOBAL LONGITUDINAL OBSERVATIONAL STUDY OF PATIENTS WITH PYRUVATE KINASE DEFICIENCY

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Background: Pyruvate kinase (PK) deficiency is a rare hereditary glycolytic enzymopathy caused by mutations in the PKLR gene, which lead to reduced red blood cell (RBC) PK enzyme activity, resulting in defective RBC glycolysis and hemolytic anemia. Patients may experience symptoms of hemolytic anemia, most commonly fatigue (sometimes extreme), jaundice, dyspnea and weakness. Current treatment is limited to supportive care, including RBC transfusions, splenectomy/cholecystectomy, and iron chelation, which are associated with some risk to the patient. No disease-specific therapy currently exists. The observational PK deficiency Natural History Study (NHS; NCT02053480; N=258) initiated longitudinal analysis (2-year follow-up) and reporting on PK deficiency-related signs, symptoms and treatment outcomes to better understand natural history and clinical burden. The Peak Registry aims to build upon the NHS with additional patients and longer follow-up.
Objectives: To report the Peak Registry design and progress to date.
Design/Method: A global, longitudinal, observational registry for adult and pediatric patients with PK deficiency (NCT03481738). The 9-year study will enroll ~500 patients over 7 years at ~60 study centers in up to 20 countries. Patients will be followed prospectively for ≥2 years, and up to 9 years. Patients of all ages with a diagnosis confirmed by genetic testing are eligible if willing and able to give written informed consent/assent. Patients actively enrolled in any Agios-sponsored trial involving PK activator treatment will be excluded. Demographic, clinical, treatment, and other data relevant to disease management will be collected from participating physicians via electronic case report forms. The primary objective is to develop an understanding of the longitudinal clinical implications of PK deficiency, including natural history, treatment and outcomes, variability in clinical care, and disease burden. Secondary objectives include: understand prevalence, incidence, and severity of complications associated with PK deficiency; examine phenotype-genotype correlation; evaluate pregnancy outcomes; and provide longitudinal data to assist physicians with the clinical management of individual patients. Study conduct, data analyses and reporting will be governed by a steering committee comprised of experts involved in the research, diagnosis, and/or care of patients with PK deficiency in cooperation with the sponsor.
Results: Site and patient recruitment is ongoing; an update will be provided.
Conclusion: This non-interventional study aims to extend the scope of the NHS with additional patients from an expanded geographic distribution and longer follow-up, to further improve the understanding of the complex clinical burden and natural history of PK deficiency, and outcomes of current treatment practice patterns.Supported by Agios Pharmaceuticals, Inc.

Poster # 709

EXTRAVASCULAR HEMOLYSIS DURING TREATMENT WITH ECULIZUMAB FOR PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic anemia wherein erythrocytes lack CD55 and CD59 making them susceptible to complement-mediated intravascular hemolysis. Eculizumab, a monoclonal C5 antibody, abolishes the formation of the membrane attack complex (MAC), thereby preventing terminal complement activation

responsible for intravascular hemolysis. The introduction of eculizumab to treat PNH has drastically changed the management and overall prognosis by reducing the transfusion requirement and risk of thrombosis. However, this therapy can result in extravascular hemolysis (EVH) and persistent anemia.
Objectives: To describe three patients with PNH on eculizumab and evidence of ongoing EVH.
Design/Method: Chart review and analysis of hemolysis markers.
Results: Case 1: Seventeen-year-old biracial female presented two years ago with severe anemia, fatigue, hemoglobinuria, and jaundice. Peripheral flow with flaer was diagnostic for PNH and patient was commenced on eculizumab. She became transfusion-free within weeks and had no evidence of bone marrow (BM) aplasia. Six months into therapy, she remained anemic (hemoglobin ~ 9 g/dL) with normal lactate dehydrogenase and no evidence of hemoglobinuria. Direct antiglobulin test which was previously negative, was positive for C3. Case 2: Nineteen-year-old female of African American origin presented at 12-years-of-age with severe aplastic anemia (SAA), for which she received immunosuppressive therapy (IST). Four years later, she presented with abdominal pain and hemoglobinuria, leading to a diagnosis of PNH. Within a few months of starting eculizumab, she developed EVH contributing to her persistent anemia. Case 3: Twelve-year-old female of African American origin received IST for SAA at 8-years-of-age. Few months after completion of IST, she was noticed to have increasing PNH clones with intravascular hemolysis. She remains on complement blocking therapy, but now with evidence of EVH. These patients have ongoing reticulocytosis and hyperbilirubinemia, with normal CH50, LDH, plasma free hemoglobin and BM cellularity.
Conclusion: Eculizumab blocks complement at C5, resulting in the upstream accumulation of C3 fragments, which can opsonize red blood cells resulting in EVH. A recent study also suggested that high density of C3b opsonization of PNH RBCs can result in a conformational change in C5 that disrupts the steric hindrance induced by eculizumab, causing breakthrough hemolysis. This recognition is vital in eculizumab treated PNH patients, so therapy is not discontinued for lack of response, avoiding unnecessary intervention. EVH is an important cause of anemia in these patients with normal BM exam. Ongoing hemolysis can contribute to increased iron overload as seen in two of our patients.

Poster # 710

CRIZANLIZUMAB DOSE CONFIRMATION IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE: SOLACE-KIDS DESIGN

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Background: Sickle cell disease (SCD) is the most common single-gene disorder in African Americans and can lead to complications, including acute pain and acute/chronic organ damage. P-selectin, an adhesion molecule expressed primarily on endothelial cells and platelets, plays a key role in the initiation of leukocyte rolling along the blood vessel wall (leading to inflammation propagation) and contributes to the pathogenesis of microvascular occlusion in SCD. Although children and adults with SCD have similar P-selectin expression, SCD worsens over time as repeated vascular occlusion results in increasing cumulative endothelial damage.

Crizanlizumab (SEG101), a humanized monoclonal antibody that binds P-selectin and blocks interaction with its ligands (including leukocyte PSGL-1), significantly decreased vaso-occlusive crises (VOCs) leading to healthcare visit vs placebo and was well tolerated in SUSTAIN, a phase 2 study in adults with SCD.
Objectives: To report the design of the first crizanlizumab study in pediatric patients with SCD.
Design/Method: Primary objectives of this phase 2, multicenter, open-label study are to confirm appropriate dosing and safety of crizanlizumab therapy >2yrs in pediatrics, using sequential, descending age groups of pediatric SCD patients with VOC. Secondary objectives include assessing number of VOCs and number/duration of hospitalizations and emergency room visits. Planned enrollment is ≥100 patients with confirmed SCD diagnosis (all genotypes), who experienced ≥1 VOC within the preceding 12mo, in 3 sequential groups: Group 1 (≥26 patients; 12yr-<18yr), Group 2 (≥26 patients; 6yr-<12yr), and Group 3 (≥8 patients; 2yr-<6yr). First, the dose will be confirmed (Part A) by 6-8 patients in Group 1. If not confirmed, the dose will be adjusted based on observed pharmacokinetics/pharmacodynamics and 6-8 additional patients will be enrolled to confirm the new dose. Once the dose is confirmed, Group 1 will be expanded (Part B), and 6-8 patients will be enrolled to Group 2 for dose confirmation. This schema will continue until dose confirmed in Group 3, which will then be expanded for enrollment of an exploratory group of ≥6 patients ages 6mo-<24mo. Patients being treated with hydroxyurea/hydroxycarbamide must have been taking it for ≥6mo prior to study entry with no planned dose adjustments other than accounting for weight changes. Crizanlizumab (5.0 mg/kg intravenously) will be administered on week 1, week 3, and every 4 weeks thereafter.
Results: Trial ongoing (ClinicalTrials.gov: NCT03474965)
Conclusion: This study aims to address the unmet treatment need in pediatric patients with SCD by extrapolating efficacy from SUSTAIN, based on comparable pharmacokinetics/pharmacodynamics. Sponsored by Novartis.

Poster # 711

PHASE 2A STUDY (GBT440-007) OF VOXELOTOR IN ADOLESCENTS WITH SICKLE CELL DISEASE

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This study was performed at 10 institutions in the United States and Lebanon., United States

Background: Sickle cell disease (SCD) is an autosomal recessive disorder caused by a single amino acid substitution that produces sickle hemoglobin (HbS). HbS polymerizes when deoxygenated, causing red blood cell sickling and resulting in anemia, hemolysis, and vaso-occlusion. Injury from SCD begins in infancy and accumulates over a lifetime, causing end-organ damage, reduced quality of life, and decreased life expectancy. Voxelotor is an orally-administered, first-in-class hemoglobin (Hb) oxygen-affinity modulator that interferes with HbS polymerization. GBT440-007 is an ongoing phase 2a study assessing voxelotor in pediatric patients with SCD.
Objectives: To assess the efficacy, safety, and pharmacokinetics (PK) of voxelotor 1500 mg/day in adolescents with SCD.

Design/Method: Adolescents aged 12 to 17 years were treated with voxelotor 1500 mg/day for up to 24 weeks. The primary objective was to assess the effect of voxelotor on anemia. Secondary objectives included the effects on measures of hemolysis, PK, cerebral blood flow as assessed by transcranial doppler ultrasound (TCD), and safety.
Results: Fifteen patients were enrolled and treated with voxelotor 1500 mg/day. Median age was 14 years (range, 12–17 years). All patients were on baseline hydroxyurea (HU). Median baseline TCD flow velocity was 112 cm/s (range, 92–177 cm/s); 14 patients had normal and 1 patient had conditional TCD flow velocity at baseline (177 cm/s). As of October 9, 2018, 11 patients completed 16 weeks of treatment. 55% of patients achieved >1-g/dL increase in Hb at week 16 from baseline, with a median increase in Hb of 1.1 g/dL. Median reductions in percent reticulocytes, indirect bilirubin, and lactate dehydrogenase were 5.8%, 36.9%, and 23.1%, respectively. The adolescent with conditional TCD flow velocity at baseline, who continued on concurrent HU at the maximum tolerated dose, still had a reduction in flow velocity of 20 cm/s, with a concordant increase in Hb of 1.7 g/dL and decrease in reticulocytes from 16.5% at baseline to 10.4% at week 24. Most treatment-related adverse events (AEs) were grade 1 or 2, with the exception of 1 patient with grade 3 rash, and there were no drug discontinuations due to AEs.
Conclusion: Voxelotor 1500 mg/day was well tolerated and demonstrated a robust improvement in hemoglobin and reduced hemolysis. These results are consistent with inhibition of HbS polymerization by voxelotor and support the ongoing clinical evaluation of voxelotor as a potential disease-modifying therapy for adolescents with SCD. Supported by Global Blood Therapeutics.

Poster # 712

VOXELOTOR IN ADOLESCENTS AND ADULTS WITH SICKLE CELL DISEASE: RESULTS OF THE PHASE 3 HOPE TRIAL

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This study was performed at 59 institutions across 12 countries, United States

Background: Sickle cell disease (SCD) is an inherited disorder caused by a single amino acid substitution producing sickle hemoglobin (HbS). Deoxygenation of HbS causes polymer formation and red blood cell sickling, which lead to anemia, hemolysis, and vaso-occlusion. These clinical features contribute to the chronic and acute manifestations of SCD. Voxelotor is a once-daily oral therapy designed to modify HbS, interfere with hemoglobin (Hb) polymerization, and improve anemia and hemolysis. The randomized phase 3 HOPE study (NCT03036813) evaluates the efficacy and safety of voxelotor in patients with SCD aged 12 to 65 years.
Objectives: To present the results of the pre-specified Part A of the HOPE study (first ≈150 randomized patients).
Design/Method: Eligible patients were randomly assigned to receive voxelotor 900 mg/day, 1500 mg/day, or placebo for ≥24 weeks. The primary endpoint was the proportion of patients

with a >1-g/dL increase in Hb from baseline at week 24. Secondary endpoints included change from baseline in measures of hemolysis (eg, reticulocyte counts and unconjugated bilirubin level) and safety.
Results: 154 patients were included in Part A; median age was 25 years (range, 12–59), 14% were adolescents, and 42% were male. Most were HbSS/HbSβ^0: 94% (900 mg), 92% (1500 mg), and 90% (placebo). Hydroxyurea use at study entry was 67% (900 mg), 62% (1500 mg), and 64% (placebo), and median baseline Hb was 8.3 g/dL (900 mg; range, 6.3–10.8), 8.6 g/dL (1500 mg; range, 5.9–10.8), and 8.5 g/dL (placebo; range, 6.1–10.4). At week 24, the proportion of patients with a >1-g/dL increase in Hb from baseline was significantly larger for both voxelotor 900 mg (33%; P=0.0159) and 1500 mg (65%; P<0.0001) compared with placebo (10%). Consistent with improvement in Hb, voxelotor also resulted in concordant improvements in measures of hemolysis. Overall, the treatment-emergent adverse events (TEAEs) were similar across all treatment arms except for diarrhea, which was higher in the voxelotor treatment arms (900 mg, 19%; 1500 mg, 21%; compared to placebo, 10%). The majority of these TEAEs were grade 1 or 2 in severity.
Conclusion: Voxelotor treatment demonstrated a dose-dependent increase in Hb, with a large proportion of patients achieving a >1-g/dL improvement in Hb, and decreases in measures of hemolysis. Voxelotor was generally well tolerated. Voxelotor has the potential to modify the morbidity of chronic organ damage associated with SCD by improving anemia and hemolysis.
Supported by Global Blood Therapeutics.

Poster # 713

EVOLUTION OF THE HGB-206 STUDY DESIGN FOR EVALUATING LENTIGLOBIN GENE THERAPY IN SICKLE CELL DISEASE

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Background: β-globin gene transfer may reduce or eliminate complications in patients with sickle cell disease (SCD) by allowing production of functional adult hemoglobin (HbA). Design of clinical studies is critical, particularly in challenging, heterogeneous diseases like SCD. LentiGlobin gene therapy (GT) contains autologous hematopoietic stem cells (HSCs) encoding β-globin with an anti-sickling T87Q substitution (HbAT87Q). The HGB-206 study (NCT02140554) is evaluating the safety and efficacy of LentiGlobin GT in patients with SCD.
Objectives: To describe changes to the HGB-206 study protocol intended to expand enrollment to adolescents and improve the efficacy of GT for SCD.
Design/Method: HGB-206 was initiated in 2015 as a single-arm, open-label, multi-site, Phase 1 study in approximately 20 adults with severe SCD (history of recurrent VOC, acute chest syndrome, stroke, or tricuspid regurgitant jet velocity of >2.5 m/s). Patients were initially treated with drug product (DP) made from bone marrow harvested (BMH) HSCs (Group A, N=7), however HbAT87Q production was suboptimal. Therefore, investigators explored adjustments to the treatment protocol and DP manufacturing process. These included chronic RBC transfusions

before HSC collection, increased busulfan levels, and DP made from BMH HSCs but incorporating a refined manufacturing process (Group B, N=2). Subsequently, plerixafor mobilization and apheresis for HSC collection was introduced. Between December 2016 and September 2018, 9 patients were treated in Group C (currently enrolling) with DP made from plerixafor-mobilized HSCs.
Results: While the initial primary study endpoint was safety, the protocol was further revised after markedly higher gene therapy-derived HbAT87Q levels were observed in Groups B and C to assess efficacy as a primary endpoint in the later cohort. Enrollment criteria were modified to include adolescents (≥12 years old) and ensure patients had experienced significant vaso-occlusive events (VOEs) in 2 years prior to the study (≥4 events requiring inpatient hospitalization). The primary efficacy endpoint for Group C patients is now a composite of weighted average HbAT87Q ≥30% of total Hb and either weighted average total Hb increase of ≥3 g/dL versus baseline or weighted average total Hb ≥10 g/dL, over a ≥6-month period. The key secondary efficacy endpoint is a ≥75% reduction in severe VOEs.
Conclusion: The revised HGB-206 protocol includes adolescents with SCD and will hopefully better assess efficacy by including younger patients with less chronic disease. The protocol changes needed illustrate the challenges associated with identifying appropriate endpoints for SCD and evaluating autologous GT for SCD. This study is funded by bluebird bio, Inc.

Poster # 714

VERY FEW ADOLESCENT AND YOUNG ADULTS WITH SEVERE DISEASE UNDERGO HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Newborn screening, comprehensive multi-disciplinary care, and disease-modifying therapies have improved outcomes in patients with sickle cell disease (SCD). However, hematopoietic stem cell transplantation (HCT) remains the only treatment with curative intent and produces excellent results in children undergoing BMT from HLA-matched sibling donors. There are over 100,000 patients with SCD in the US, but only 1,200 HCT procedures have been reported to the CIBMTR since 1991, but there are limited data on the proportion of patients with SCD who have severe disease, as defined by current investigational SCD BMT protocols, and the proportion of these patients who undergo HLA typing, donor search, and HCT.
Objectives: To determine the proportion of adolescent and young patients with SCD who have severe disease, receive HLA typing, receive a donor search, or undergo HCT.
Design/Method: Healthcare encounters, including emergency department (ED) visits and inpatient admissions are abstracted and collected within the Children's Healthcare of Atlanta (CHOA) sickle cell clinical database for all patients with a diagnosis of SCD and each encounter is verified by chart review. We screened all healthcare encounters in all patients age > 14 years who met disease severity criteria for eligibility for HCT. This was conducted as a part of the screening for potential subjects for participation in BMTCTN 1503; a study comparing HCT to

standard clinical care. We determined which patients met disease severity criteria, underwent HLA typing, received a sibling or unrelated donor search, or received HCT. The screening process included patients (15-40 yrs) that qualified for one or more of the following criteria: (a) Stroke or other serious brain complication, (b) 2 or more episodes of acute chest syndrome (ACS) in the last 2 years, (c) 3 or more severe pain crises per year in the last 2 years, (d) 8 or more blood transfusions per year to prevent SCD-related problems (e) echocardiographic finding of a heart problem (TRJ $\geq$ 2.7 m/sec).
Results: Between 7/15/2016 and 7/15/2018, of 688 patients (14-28 years), a total of 127 (18.65%) patients met the BMTCTN 1503 disease severity criteria. Of these, 45 (35%) patients had HLA typing performed and 25 (19.7%) had a donor search performed and three patients (2. 4%) underwent HCT.
Conclusion: Conclusion: That only a small proportion of patients with SCD who meet disease severity criteria for HCT proceed to HCT suggest the need for more research to improve the awareness, applicability, and acceptability of HCT for SCD.

Poster # 715

IMPACT OF SICKLE CELL DISEASE ON THE PRESENTATION AND PROGRESSION OF PEDIATRIC HIV

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Background: Sickle cell disease (SCD) and HIV infection are co-endemic in sub-Saharan Africa among pediatric populations, both causing multi-organ damage, immune aberrations, and significant morbidity and mortality. Given their separate roles in immune dysregulation, we hypothesized that SCD would have clinically significant impacts on the presentation and progression of pediatric HIV.
Objectives: Our goals were to determine how SCD affects baseline (i.e. antiretroviral (ART) therapy initiation) characteristics and disease progression of children with HIV.
Design/Method: The study was a retrospective, frequency-matched cohort study (study period 2004-2018). Cases of HIV+ and SCD-afflicted patients (HIV+/SCD+) were obtained via electronic chart review from Baylor College of Medicine Children's Foundation Uganda, a pediatric HIV clinic in Kampala, Uganda, and matched 1:3 with HIV+ patients without SCD (HIV+/SCD-), matching for gender, date of birth, and date of ART initiation. Inclusion criteria included: age at baseline <19 years, ART initiation at Baylor-Uganda. Outcomes included: death/loss to follow-up (LFTU), HIV treatment failure, CD4 count, WHO clinical stage, nutritional status, hemoglobin.
Results: 35 HIV+/SCD+ subjects and 95 HIV+/SCD- controls were analyzed (39% female (51/130), age 3.6 years (SD3.9)). At baseline, WHO stage (64% total cohort Stage III/IV) and nutritional status (9.4% severe acute malnutrition) were similar for both groups, whereas HIV+/SCD+ had higher though non-significant baseline CD4 count (1036 (SD713) vs 849 (SD638) cells/microliter, p=0.20, two-tailed t-test) and lower hemoglobin (7.3 (SD1.7) vs 9.9 (SD2.0) grams/deciliter, p<0.001, two-tailed t-test). There were 19 deaths, 6 (17%) HIV+/SCD+ and 13 (14%) HIV+/SCD-, with unadjusted/adjusted models showing no significant difference.

LTFU (3 (9%) HIV+/SCD+, and 10 (11%) HIV+/SCD-), nutritional progression, and WHO clinical stage progression showed no significant differences between groups. Hemoglobin increased in both groups (HIV+/SCD+ 8.9 (SD2.4) and HIV+/SCD- 11.6 (SD1.8) grams/deciliter at year 3). Kaplan-Meier analysis showed a slower rate of treatment failures in the HIV+/SCD+ cohort, though not meeting statistical significance (p=0.11, log-rank survival test). Trajectory analysis showed that in the time period analyzed, the HIV+/SCD+ cohort showed a more rapid rise and higher total CD4 count (p=0.012, regression analysis).
Conclusion: Our outcomes analysis of the impact of SCD on HIV presentation and progression among pediatric patients revealed no significant differences in death/LTFU between HIV+/SCD+ and HIV+/SCD- patients. Interestingly, HIV+/SCD+ patients showed higher CD4 counts and fewer HIV treatment failures, providing evidence that the immune modulation seen in SCD, including lack of functional spleen and chronic inflammatory environment, might mitigate the morbidity of HIV infection.

Poster # 716

UNSWITCHED MEMORY B CELLS ARE REDUCED IN CHILDREN WITH SICKLE CELL DISEASE DESPITE HYDROXYUREA USE

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Background: The spleen is among the first organs affected by sickle cell disease (SCD). In SCD, the hallmark of impaired splenic function is increased susceptibility to infection due to encapsulated organisms during childhood. The initial response against encapsulated organisms in the spleen is mediated by unswitched memory B cells (uMBCs). uMBCs from the spleen circulate in peripheral blood and have been used as a measure of splenic function in other disorders associated with impaired splenic function. The immune function of the spleen as measured by the uMBC subsets has not previously been assessed in SCD children.
Objectives: To test the hypothesis that the uMBC subset in SCD children is reduced relative to children without SCD and, to determine whether hydroxyurea use is associated with larger uMBC subset.
Design/Method: Children seen at the Texas Children's Cancer and Hematology Centers from March 2018 – December 2018 were recruited for participation in this IRB approved study. Subjects were 18 months-18 years of age. Complete blood counts were measured using an ADVIA hematology analyzer. Whole blood samples were stained with fluorescent-labelled CD45, CD19, IgD, and CD27 and analyzed by flow cytometry.
Results: We evaluated 150 subjects, including 98 (65.3%) Hb SS, 9 (6%) Hb S/beta-0-thalassemia, 14 (9.3%) Hb SC disease, 2 (1.3%) Hb S/beta-+-thalassemia, and 27 (18%) controls without SCD. There was no difference in the mean age at sampling between SCD children and controls (118.3 months vs 103.1 months, p=0.25). The mean uMBC was 6.8% of all B cells for controls, 4.4% for HbSS group, and 5.8% for SCD patients with any other genotype. Controls were significantly greater than HbSS subjects (p<0.01). There was no statistically significant difference between controls and other genotypes (p=0.44) or between HbSS and other genotypes (p=0.11). To determine whether hydroxyurea had an effect of uMBC subset, we grouped subjects

with SCD by current (n=104), past (n=2), or never (n=18) HU use. The mean uMBC was 4.5% for current HU users, 7.9% for past HU users, and 5.5% for never HU users. There was no statistically significant difference between the HU categories (current vs. past, p=0.2; current vs. never, p=0.33, never vs. past, p=0.48).
Conclusion: We have demonstrated that SCD children are deficient in uMBCs. This finding of impaired splenic immune function supports the known clinical observation of increased susceptibility to encapsulated organisms. Ongoing investigations will identify additional clinical correlates to low uMBC, such as risk of infections and response to vaccinations.

Poster # 717

TRANSFORMING GROWTH FACTOR BETA-1 LEVELS AS A BIOMARKER IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Transforming growth factor beta (TGF- β) is a multifunctional cytokine which plays an important role in modulation of the inflammatory response. TGF-β1, a TGF- β isoform, is elevated in patients with sickle cell disease (SCD). However, little is known regarding the relationship between TGF-β1 levels and disease severity and other disease modifiers.
Objectives: To investigate the role of TGF-β1 level as a potential biomarker in individuals with SCD. We compared TGF-β1 levels with disease severity and explored correlations between steady state TGF-β1 levels and various clinical and laboratory parameters.
Design/Method: We conducted a prospective, observational, single institution, IRB approved study. We collected blood samples to measure baseline TGF-β1 levels during regular outpatient visits not associated with an acute illness. Selected demographic and treatment variables were extracted from the medical records. Statistical analyses was performed by using Mann-Whitney U test to test for differences between groups, and Kendall's tau coefficient was used to test for correlations between TGF-β1 levels and various individual laboratory parameters.
Results: 40 patients were enrolled in 6 months with TGF-β1 levels available for 32 patients for interim analysis (25 HbSS, 5 HbSC, 1 HbSS with elevated HbF, 1 HbS βthal+). 75% are females and 25% are males with an age range of 3-20 years. The mean baseline TGF-β1 level (7180 pg/mL) was elevated compared to normal range (344-2382 pg/mL). There was no statistically significant difference (p=0.68) in TGF-β1 levels between the more severe (HbSS and Hb S beta thal 0) and less severe genotypes (HbSC, HbSS with elevated HbF, HbS βthal+). We also did not see a statistically significant difference (p=0.87) in the TGF-β1 levels between patients based on clinical severity (number of vaso-occlusive pain admissions in the preceding years). A potential reason identified for lack of correlation with disease severity is use of disease modifying therapy - hydroxyurea or chronic transfusions for all patients with severe disease. Interestingly, among 19 patients on hydroxyurea, we found a moderately strong negative correlation between TGF-β1 levels and hemoglobin levels (p=0.0006). There was a moderately strong positive correlation between TGF-β1 and platelet levels among patients on hydroxurea (p=0.0071) and also not on hydroxyurea (p=<0.0001), and a moderately strong positive correlation between TGF-β1 and absolute neutrophil counts among patients not on hydroxyurea (p=0.0147).

Conclusion: We found elevated TGF-β1 levels in patients with SCD and also identified associations between TGF-β1 and hematologic markers of disease severity.

Poster # 718

LOW HEMOGLOBIN INCREASES RISK OF CLINICAL COMPLICATIONS IN SICKLE CELL DISEASE: REVIEW/META-ANALYSIS

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Background: Sickle cell disease (SCD) is characterized by deoxygenation-induced polymerization of sickle hemoglobin, leading to altered red blood cell rheology, anemia, hemolysis, and vaso-occlusion. The anemia and hemolysis contribute to multiorgan damage and death.
Objectives: To perform a meta-analysis evaluating the association of hemoglobin and measures of hemolysis with clinical complications in SCD.
Design/Method: Systematic literature searches of Excerpta Medica (EMBASE) and MEDLINE (via PubMed) databases were conducted (1998 to 2017) to identify studies associating hemoglobin with clinical outcomes in SCD. Abstracts from the previous 2 years (2016-2017) of 5 scientific conferences that present studies related to SCD were also evaluated. Citations identified were reviewed in a 2-step process by a single reviewer.For quantitative analyses, findings were separated into categories of outcomes related to hemoglobin. These were then aggregated to assess the overall magnitude of the association. Pooled results were analyzed using random effects models to control for within- and between-study variability. To derive risk ratios associated with hemoglobin change, ratios of means from select studies that reported hazard and odds ratios in meta-analyses by change in hemoglobin between groups for outcomes related to hemoglobin were combined. When studies reported separate values for hemoglobin outcomes, these were combined prior to the meta-analysis.
Results: 45 of 1434 studies were included. Ten studies representing 3043 patients demonstrated an association between lower hemoglobin and a history of stroke, silent cerebral infarct, or increased transcranial Doppler velocity; statistical significance was reached in 7 studies. Eleven studies representing 1868 patients demonstrated an association between lower hemoglobin and albuminuria; statistical significance was reached in 9 studies. Twelve studies representing 1465 patients demonstrated an association between lower hemoglobin and elevated estimated pulmonary artery systolic pressure, defined as elevated tricuspid regurgitant jet velocity (≥2.5 m/s). Five studies representing 2703 patients demonstrated lower hemoglobin across all but one study for deceased versus living patients. Aggregate findings demonstrated hemoglobin was statistically significantly lower by approximately 0.4 to 1 g/dL among those experiencing a negative clinical outcome.At increased levels of hemoglobin ≥1g/dL, the risk for negative clinical outcomes decreased by 41–64%.
Conclusion: Evaluation of peer-reviewed literature demonstrates a significant relationship between the degree of anemia and worse clinical outcomes in SCD. Additionally, modest differences in hemoglobin are important and support hemoglobin increase by >1 g/dL as a

therapeutic target. These results suggest interventions reducing the severity of anemia may confer clinical benefit in SCD. Supported by Global Blood Therapeutics, Inc.

Poster # 719

ADVERSE CHILDHOOD EXPERIENCES ARE LINKED TO INCREASED MORBIDITY IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Adverse Childhood Experiences (ACEs) have a strong graded relationship with poor health across the lifespan. The relationship between ACEs and disease risk is well established; however there is paucity of literature describing the impact of ACEs on chronic disease outcomes, including sickle cell disease (SCD).
Objectives: To evaluate the relationship between ACEs and healthcare utilization for acute chest syndrome (ACS) and pain among children and adolescents with SCD.
Design/Method: This cross-sectional study involved 56 patients with SCD age 2-19 years. We administered Sections 1 (original 10 ACEs) and 2 (expert-recommended) of the Child (≤12y), Teen Self Report (13-19y) and Teen (parent-report) Center for Youth Wellness ACE-Questionnaires (CYW ACE-Q) during routine clinical encounters. Subjects were grouped by age (child: ≤12y and teen: 13-19y) and further categorized as having low ACEs (0-1) or high ACEs (≥2) based on the original 10 ACEs. We performed a Mann Whitney U, Chi square, Fisher's exact and linear regression analyses.
Results: The mean age for the 56 subjects was 10.6 years (±4.1), with 52% male and 37 in the child group. There was no difference in SCD phenotypes, asthma prevalence or disease modifying therapies between groups. Of the 56 patients, 30.3% had ≥ 2 ACEs. For the Child Section 1 analysis, the average number of ED pain visits was higher in the high ACE group (3.63, 1.9, p = 0.01). There was no difference in pain (1.09, 1.07, p=0.19) or ACS (2.36, 1.92, p=0.197) hospitalizations between groups or correlations between ACEs and pain or ACS. For the Teen Section 1 analysis, the average number of ACS hospitalizations was higher in the high ACE group (5.16, 2.23, p=0.04). There was no difference in ED (5, 2.15, p=0.20) or hospital (3.5, 2.23, p=0.31) pain encounters. ACEs were significantly associated with hospital admissions for ACS (p=0.02) and pain (p=0.03) and approached significance for ED pain visits (p=0.052). Section 2 ACEs alone were not associated with pain or ACS in either age group. Section 1 and 2 ACEs combined were significantly associated with ED and hospital visits for pain and ACS in the teen group but not in the child group.
Conclusion: These preliminary results demonstrate that ACEs are associated with increased SCD morbidity in children and adolescents. Larger studies are needed to truly understand their impact. This research will be instrumental in the delivery of biopsychosocial models of care for SCD and other chronic disease populations.

Poster # 720

PRE-SURGICAL HEMOGLOBIN AND POST-OPERATIVE COMPLICATIONS IN PATIENTS WITH SICKLE CELL DISEASE (SCD)

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Background: Presurgical (PreS) blood transfusions are given to patients with SCD to prevent perioperative complications. Randomized controlled trials (Vichinsky et Al 1995 & 1999) showed that raising a patient's preS hemoglobin (Hb) level to 10 g/dL was just as effective as lowering PreS Hb S to 30%.
Objectives: The aims of this investigation were (1) to learn proportion of surgeries performed under general anesthesia with preS Hb≥ 10 at our Institution, an urban community hospital (2) to test a hypothesis that there would be more post-operative complications in patients with preoperative Hb < 10 compared to those preS Hb ≥ 10
Design/Method: This is a retrospective chart review. Using ICD 9 codes, CM 282.60 and 282.61(Hb SS, SC and S-β Thal), general anesthesia and surgical procedure codes, all medical records were identified. Study period was from 04/2012 to 03/2018. We developed data extraction sheet containing 52 items. Hurley IRB exempted this study from requiring the consent form.Definitions of postoperative complications: fever [temperature≥ 100.4°F (38.0°C)], Pain (requiring IV narcotic use unrelated to surgery), hemolysis or postoperative hemorrhage (a drop in Hb≥1 g/dl) or postoperative readmission within 30 days after index surgery.
Results: A total of 43 patients (16 female) undergoing 60 procedures met the above criteria. Age ranged from 2 to 56 years. Common procedures were cholecystectomy (7), insertion/removal of central venous catheter (6).32 procedures(53%) were performed with preS Hb of ≥10 with mean of 11.0, median 10.8. 28 (47%) had preS Hb <10 with mean 8.7, median 9.0. There was no statistically significant difference (chi square) in any complication categories between Hb≥10 and Hb<10 group, however, there was a trend that showed more pain complications in Hb<10 group. Shorter anesthesia duration was associated with more pain complications (not statistically significant).
Conclusion: There were no differences in the postoperative complication rates, as defined above, between presurgical Hb≥10 and <10 group, though there was a trend that the latter had more pain complications than the former. Lack of statistical significance between the 2 groups may be due to (1) small number of subjects, (2) confounding variables such as different sickle cell genotypes, hydroxyurea use, different surgical procedures, presurgical conditions of patients, etc, or (3) both. On the other hand, presurgical Hb difference at this level may not have had significant impact on the complications. This conclusion is tentative and needs a study with a larger number of subjects.

Poster # 721

DOES VIRAL ILLNESS AFFECT RECURRENCE OF SPLENIC SEQUESTRATION IN CHILDREN WITH SICKLE CELL DISEASE?

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Background: Splenic sequestration crisis (SSC) is a potentially life-threatening complication that occurs in infants and young children with sickle cell disease (SCD) and has a high risk of recurrence. We do not know the effect of an inciting event such as viral infection (VI) on the rate of recurrence. We hypothesized that a first SSC in the setting of a VI would be less likely to recur.
Objectives: Recurrence of splenic sequestration.
Design/Method: We performed a retrospective review of children admitted to our institution with SCD and SSC between 2008 and 2018. All genotypes and ages were included. Respiratory viral panels (RVP) were used to assess the presence of a VI at their index episode. Recurrent events within 6 months of the index episode were included in the analysis. Exact conditional logistic regression and Fisher's exact tests were performed to assess presence of VI and other factors as possible predictors of recurrence risk.
Results: We identified 48 children with SCD who presented with an initial episode of SSC during this time period. The median age was 3.1 years (IQR: 1.4-6.1). Thirty (63%) were male. Twenty-nine had HbSS, 10 had HbSC, 7 had HbSB°thalassemia and 2 had HbSB+thalassemia. Twenty children (45.8%) exhibited recurrence within 6 months. Results show that a higher hemoglobin level at initial SSC decreased the risk of recurrence (p=0.0152). Higher reticulocyte count at the initial SSC increased the risk of recurrence (p=0.0094) while having HbSC genotype decreased this risk (p=0.0348). Twenty-seven children (56%) were febrile and 13 of 35 (37%) had an RVP performed during the index SSC and tested positive, with the most commonly identified virus being rhino-entero virus. The recurrence rate was 30% (4/13) among those with a positive RVP and 50% (11/22) among those who tested negative. Assuming those not tested were negative for VI, having a positive RVP was not found be a significant predictor of recurrence (p=0.34).
Conclusion: This contemporary cohort of children with SCD exhibited 45.8% recurrence of SSC, similar to the literature. Higher reticulocyte count at the initial episode increased while HbSC genotype decreased the recurrence risk. We did not observe a significant decrease in the risk of recurrence when the initial episode occurred in the setting of a VI. The lack of significance may be due to limited power to detect small differences in this small sample. Future prospective studies may help delineate the relationship between VI and SSC recurrence.

Poster # 722

SPLENECTOMY OUTCOMES IN CHILDREN YOUNGER THAN 2 YEARS WITH SICKLE CELL DISEASE

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Background: Splenectomy is usually recommended for individuals with sickle cell disease (SCD) after acute splenic sequestration crises. Current literature recommends splenectomy after 2 years of age, to theoretically allow time for sufficient vaccination response. Older studies

recommended deferring splenectomy until age 5 because of previously documented high rates of overwhelming post-splenectomy infection (OPSI). While recent studies have demonstrated a decreased risk of OPSI since the advent of newer vaccinations, few patients studied were under age 2. Our group published data in 2009 examining patients with SCD who had undergone splenectomy before the age of 4. However, as many experience their first sequestration prior to age 2 and often recur, we sought to review our experience with outcomes of splenectomy in children under 2.
Objectives: We studied the outcomes of splenectomy in SCD patients under the age of 2 years with long-term follow-up.
Design/Method: The study involved a retrospective chart review of all patients with SCD who underwent splenectomy before two years of age at the Medical University of South Carolina, between 1993 and 2017. After IRB approval we performed data collection and descriptive analysis.
Results: From 1993 to 2017, 27 children with SCD (17 males, 10 females), < 2 years, had splenectomy after one or more episodes of splenic sequestration. Nine patients (33 %) were younger than 18 months of age at surgery time with the youngest being 12.7 months. For splenectomy, LOS for patients averaged 3 days (2- 7 days) including both pre-admission and post-surgical care. Mean postoperative follow up duration was 13.5 years (0.3-23.3 years). All patients had hemoglobin SS phenotype. All the patients remained on prophylactic antibiotics following splenectomy. During this follow up period, 5 patients (18.5%) had 5 documented sepsis episodes (identified by a positive blood culture requiring treatment). Two of those 5 had central lines as risk factors. Only 1 of them had pneumococcal sepsis. One patient died (3.7% of all patients), at 3 years of age at home, reason unknown, within the 24-year study period.
Conclusion: The life-threatening nature of acute splenic sequestration, the inherent complications of blood transfusion, and the frequency of recurrent sequestration may justify aggressive treatment in young patients. The results of our study support the practice of performing splenectomy when needed in patients with SCD < two years of age. The morbidity and mortality rates of OPSI is less than historical reports. Prior to widespread adoption, further long-term follow-up is needed in more patients.

Poster # 723

THE EFFECT OF SPLENECTOMY ON TRICUSPID JET VELOCITY IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Background: Background: Pulmonary arterial hypertension (PHTN) is a common complication in adults with Sickle Cell Disease (SCD) and is being increasingly recognized in pediatric patients. In adult patients with SCD, PHTN has been reported to be associated with 40-month mortality rate of approximately 40%. The age of onset of PHTN and its predisposing SCD are not well understood. High reticulocyte count, low oxygen saturation, high platelet count and increased markers of hemolysis have been previously reported in association with higher risk of developing PHTN. Additionally, it has been reported that patients with other disorders, who underwent splenectomy are at higher risk. Considering that surgical splenectomy is often used in

treatment of splenic complications in pediatric patients with SCD it is important to evaluate its role in development of PHTN. Diagnosis of PHTN is established by cardiac catheterization. Measuring Tricuspid Regurgitant Jet Velocity (TRV) with echocardiography is a noninvasive way to access for risk of PHTN.
Objectives: Objective: To evaluate if pediatric patients with SCD who have undergone splenectomy are at an increased risk of having elevated TRV compared to those with SCD.
Design/Method: Methods: Retrospective chart review of splenectomized patients with HbSS and HbSbeta thalassemia followed at the Marian Anderson Center at St. Christopher's Hospital for Children, Philadelphia between 1999 and 2018. A total of 31 patients with and 62 without a history of splenectomy were matched by age at echocardiogram in a 1:2 ratio, with a mean age at echocardiogram of 15 years.
Results: Results: Statistical analysis, conducted with SPSS, found that having had a splenectomy does not increase the risk of developing PHTN for pediatric patients with SCD. Results of a two-tailed t-test show a p-value of 0.882 when comparing the mean TRV for those with a history of splenectomy to those without. Additionally, when the groups were separated based on normal versus elevated TRV a Pearson Chi Squared test showed no significant difference for those with splenectomy and those without splenectomy with a p-value of 0.695.
Conclusion: Conclusion: Based on preliminary data splenectomy in pediatric patients with SCD does not increase risk of developing PAH during childhood. However, additional studies including more patients with and without splenectomy and evaluation of markers of hemolysis and co-morbid conditions may help to shed additional light on what differences, if any, exist between these groups two of patients with SCD.

Poster # 724

SPLENIC VEIN THROMBOSIS IN THE SETTING OF SPLENIC INFARCTION IN AN ADOLESCENT WITH SICKLE CELL TRAIT

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Background: Sickle cell trait occurs in 8-10% of African Americans, and at lower rates in other groups such as the Hispanic population. The complications of sickle cell trait are relatively uncommon but include increased risk of exertional rhabdomyolysis, renal disease, venous thromboembolism, and potentially exercised-induced sudden death. Altitude-associated splenic infarction has been documented in patients with sickle cell trait and is seen not infrequently at our center given our geographic location. However, there are only two prior case reports in English of splenic infarction complicated by splenic vein thrombosis, and no cases with portal vein thrombosis could be identified.
Objectives: We report three cases of altitude-associated splenic infarction in a family of patients with sickle cell trait including one case complicated by splenic vein and portal vein thromboses.
Design/Method: Case report and review of the literature.
Results: A 17 year-old male with history of sickle cell trait and epilepsy presented with left upper quadrant abdominal pain, nausea, fever, and breakthrough seizures two days after traveling from his home at sea-level to high altitude in Frisco, CO (elevation 9100 feet). Computed tomography scans demonstrated splenic infarct, 3 cm splenic vein thrombosis near the hilum, as

well as thrombus in the anterior branch of the right portal vein. Labs were notable for leukocytosis (WBC 27.5 x103/uL), very mild anemia (hemoglobin 11.5 g/dL) with reticulocytosis (6.5%), hyperbilirubinemia (1.5 mg/dL), and positive sickle solubility testing consistent with his known sickle cell trait. He was treated by descent from high altitude to moderate altitude in Denver, CO (elevation 5280 feet) and admitted for pain control. Therapeutic low molecular weight heparin therapy was initiated for his thromboses with a planned duration of 3 months of therapy. The patient's mother and 13 year-old brother, both with sickle cell trait, were also admitted for splenic infarction but did not have evidence of thrombosis.
Conclusion: This case demonstrates a case of altitude-associated splenic infarction in an adolescent with sickle cell trait, complicated by splenic vein and portal vein thrombosis. Splenic vein thrombosis in this setting has only been documented in individual case reports previously, and portal vein thrombosis has not been reported. The portal vein thrombosis is concerning for clot extension, which would support a need for therapeutic anticoagulation in patients with splenic infarct and venous clot detected on imaging. Patients without thrombus may be treated with supportive care for pain, hydration and descent from high altitude.

Poster # 725

THE ASSOCIATION BETWEEN RESPIRATORY ILLNESSES AND HYDROXYUREA USE IN SICKLE CELL DISEASE

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Background: The association between respiratory illnesses (RIs) and increased morbidity and mortality in sickle cell disease (SCD) is well established. Asthma has been reported to increase incidence of acute chest syndrome (ACS), vaso-occlusive crises and early mortality. Attenuation of airway hyperresponsiveness has been credited to hydroxyurea use (HDU) in SCD, however, its implication in reducing acute asthma exacerbation (AAE) is yet to be proved.
Objectives: To determine the morbidity of RIs [i.e. ACS, pneumonia, AAE, bronchiolitis, and influenza] and to determine the association between HDU and development of asthma in children with SCD.
Design/Method: We conducted a retrospective chart review of children 0-21 years followed at Bronx-Care Health System for SCD from 2001 to 2018. Sociodemographic variables, SCD type and HDU were collected. Patients were followed for development of RIs, including all visits for each patient. ED and inpatient visits, length of stay, PICU and oxygen requirement were considered. Descriptive analyses and chi-squared test were used to determine the association between HDU and development of asthma, with statistical significance set at 2-sided p-value<0.05.
Results: There were a total of 94 patients with SCD in the study; 35 had both ED visits and inpatient admissions for RIs, 13 had only ED visits and 46 had only inpatient admissions. There were 62 ED visits and 129 documented inpatient admissions in total. The median age at admission was 5.3 years, 48.2% patients were on hydroxyurea and HbSS (58%) was the most common type. ACS (49.6%) and pneumonia (33.3%) were the most common diagnoses with longer hospital stays (5 days and 4 days, respectively) and increased need for oxygen

supplementation (95.3% and 46.5%, respectively). Asthma was present in 42% of SCD patients with RIs. There was no association between HDU and development of asthma (OR 0.96, p 0.92), or with asthma severity (OR 0.84, p 0.74). There also was no difference between HDU and development of asthma and asthma severity in the subgroups of HbSS and HbSC.
Conclusion: The morbidity of RIs among children with SCD was found to be high. Although there was no association between HDU and development of asthma or asthma severity in our study, assessment of clinical significance for associations cannot be definitively evaluated with limited data on HDU compliance and changing trends of initiating HDU, not necessarily based on severity of SCD. Further studies, possibly using fetal hemoglobin levels as a marker for compliance with hydroxyurea effectiveness are needed to document an association.

Poster # 726

CARDIOVASCULAR ABNORMALITIES AND DETERMINANT FACTORS IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Introduction: Sickle cell disease (SCD) is one of the most commonly inherited hemoglobinopathies: roughly 72,000 Americans have SCD. With the significant improvement in the care of patients with SCD and subsequent aging, various cardiovascular sequelae have been noted. In particular, left ventricular (LV) diastolic dysfunction, LV hypertrophy (LVH), pulmonary hypertension, and coronary artery dilatation (CAD) have been reported. As such, screening transthoracic echocardiograghy (TTE) has been recommended for all school-age children with SCD.
Objectives: This study aims to characterize the prevalence of echocardiographic abnormalities in pediatric patients with SCD and identify contributing factors for these abnormalities.
Design/Method: Methods: A single-center retrospective chart review of all pediatric patients with sickle cell disease who had undergone screening TTE from 2010-2016 was performed. For patients with multiple TTEs, the most recent TTE was reviewed. Exclusion criteria included age older than 18 or younger than 5. TTEs were excluded if performed during or within a month of admission for sickle cell crisis, acute chest syndrome, or stroke. Abnormal TTE findings of interest include LV remodeling (determined by elevated LVMI, LV dilatation [from LVIDd and LVEDD], and LVH [measured by LVISd, and LVPWd]), elevated right ventricular pressure (RVP > 25 mmHg) and CAD.
Results: Results: Of 129 patients, abnormalities were noted for 51% (n=66) of patients. In our SCD population, the prevalence of elevated LVMI, LV dilatation, LVH, elevated RVP, and CAD were 33% (n=43), 22% (n=29), 16% (n=20), 15% (n=19), and 5% (n=6), respectively. Compared to patients with normal TTEs, patients with abnormal TTE findings were older (12.9 vs. 11.3 years, p = 0.013), more likely to have lower mean hemoglobin (8.59 vs. 9.89, p<0.001); higher mean reticulocyte count (12.81 vs. 8.33, p<0.001) or lower mean oxygen saturation (96.8% vs. 99.1%, p<0.001), and have history of hypoxia (38% vs. 14%, p=0.002).
Conclusion: Conclusion: In this single-center retrospective chart review of pediatric patients with SCD, the prevalence of TTE abnormalities was consistent with previous studies. Our data suggests a correlation with severity of SCD and hypoxemia with abnormal TTE.

Poster # 727

LIPID PANEL ABNORMALITIES AND PULMONARY HYPERTENSION IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Pulmonary Hypertension (PH) is identified as a major complication of sickle cell disease (SCD). Tricuspid regurgitant velocity (TRV) and brain natriuretic peptide (BNP) have been used to estimate right ventricular and pulmonary artery systolic pressures as markers for PH. In adults, elevated triglyceride levels have been shown to independently correlate with elevated TRV. It is unclear whether an association exists between elevated lipid panel markers and markers of PH in the pediatric population. We hypothesize that elevated BNP and lipid panel markers would be associated with elevated TRV and subsequently lead to a higher risk for developing PH.
Objectives: In this study, we evaluate the relationship between lipid panel markers and elevated TRV in children with SCD.
Design/Method: A retrospective study was performed of patients with SCD followed at our institution who were > 10 years of age with an echocardiogram performed within the last 5 years. Data obtained included gender, SCD genotype, lipid panel, BNP, TRV, markers of hemolysis (Hemoglobin, Hematocrit, Reticulocyte count, LDH), inflammation (Ferritin, CRP) and those within a comprehensive metabolic panel (CMP). Analysis of variance tests were performed to assess for statistically significant differences in lipid panel markers, BNP, and other listed markers between patients with normal versus elevated (>/= 2.5 m/sec) TRV.
Results: Of the 83 patients that met inclusion criteria, 18 (22%) were considered to have elevated TRV. Ferritin, LDH, and reticulocyte counts were significantly higher in patients with elevated TRV compared to patients with normal TRV (p=0.001, 0.051, and 0.017 respectively). Hematocrit levels were significantly lower in patients with elevated TRV compared to those with normal TRV (p=0.057). Low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) levels were statistically significant between groups, with higher mean values seen in patients with normal TRV compared to patients with elevated TRV (p=0.034 and 0.012 respectively). No associations were found between BNP or other studied biomarkers and TRV.
Conclusion: Higher levels of ferritin, LDH, and reticulocyte counts were associated with elevated TRV. These results suggest that pediatric SCD patients with higher disease severity and thus elevated hemolytic markers are at higher risk for developing PH. Lower levels of LDL-C and TC were associated with elevated TRV. Prospective studies with larger sample sizes are needed to elucidate the relationship between lipid panel markers and PH. Early identification of risk factors for PH in SCD pediatric patients will aid in decreasing morbidity and mortality for this population.

Poster # 728

EFFECT OF HYDROXYUREA AND CHRONIC TRANSFUSIONS ON LEFT VENTRICULAR REMODELING IN SICKLE CELL DISEASE

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Background: In the treatment of sickle cell disease (SCD) both Hydroxyurea therapy and chronic transfusions have known efficacy in improving anemia and decreasing acute and chronic complications of SCD. The chronic anemia of SCD leads to cardiovascular disease including left ventricular (LV) remodeling and impaired diastolic function. The effects that Hydroxyurea therapy and chronic transfusions may have on cardiac structure and function remain relatively unknown. Given the known improvement in anemia and reduced red blood cell sickling, we hypothesized that both Hydroxyurea therapy and chronic transfusions would result in decreased LV remodeling and improved cardiac function compared to patients not receiving either therapy.
Objectives: We aimed to compare the associations of therapy with Hydroxyurea, chronic transfusions, or neither with LV remodeling and cardiac function in children with SCD.
Design/Method: A retrospective study of patients 10 to 22 years old with SCD SS or SBeta0 thalassemia and followed at St. Christopher's Hospital for Children with an echocardiogram obtained within the past 18 months was completed. Data collected included gender, Hydroxyurea use, chronic transfusion use, hemolysis and inflammatory laboratory parameters, and 2D and Doppler echocardiographic parameters. Cardiac parameters included evaluation of structure, geometry, systolic function, and diastolic function. Analysis of variance (ANOVA) tests were used to assess for statistical significance of differences in laboratory and cardiac parameters between therapy groups and Analysis of Covariance (ANCOVA) tests were used to control for age.
Results: Demographic, laboratory, and echocardiogram data was collected on all 61 patients who met inclusion criteria. Patients were separated into therapy groups, which included those on Hydroxyurea, those on chronic transfusions, and those without either therapy. Of the 61 patients included, 27 (44%) were on Hydroxyurea therapy, 17 (28%) were on chronic transfusion therapy, and 17 (28%) were not on either therapy. Hemoglobin, ANC, WBC, and ferritin were significantly different between the three groups ($p = 0.014, 0.002, 0.003, 0.000$ respectively), with highest mean values being seen in the chronic transfusion group. There were no statistically significant differences between therapy groups and cardiac parameters.
Conclusion: Despite higher mean hemoglobin levels in patients receiving Hydroxyurea therapy or chronic transfusions, there were no significant differences between the therapy groups and cardiac parameters for structure, geometry, systolic function, and diastolic function. Additional studies with larger sample size are needed to confirm these findings and assess cardiovascular benefit of these therapies.

Poster # 729

EXPERIENCE OF CHRONIC TRANSFUSION THERAPY IN SICKLE CELL DISEASE: A QUALITATIVE STUDY

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Background: Chronic transfusion therapy (CTT) is a disease-modifying therapy used for primary or secondary prevention of sickle cell disease (SCD) complications. The Silent Cerebral Infarct Transfusion (SIT) trial also reported improved health-related quality of life in patients on CTT. While the efficacy of CTT in prevention of SCD complications is well established, there is a limited understanding on the patient and family experience of CTT.
Objectives: The objective of this study was to obtain insight into the patient and family experience of CTT using qualitative methods.
Design/Method: Study participants included parents of children < 18 with SCD (Group 1) and children age 12-18 with SCD (Group 2) who received CTT for >1 year. A semi-structured interview format was used. The interview script focused on the patient and family experience of CTT, their understanding of risks and benefits, and expectations from CTT. Transcribed interviews were analyzed using open coding methods.
Results: Fifteen parents of patients with HbSS/HbS-Beta thalassemia age 2-16 (Group 1) and 9 patients age 12-18 (Group 2) were interviewed. These represented 18 unique patients including 6 parent-patient dyads. The median age of parents in Group 1 was 41 years (IQR 37-46), and of their children was 10 years (IQR 6-11). The median age of Group 2 was 14 years (IQR 14-16). 6 (66.7%) of Group 1 patients were female, and 5 (55.6%) of Group 2 participants were female. Three emergent themes were: 1) Burden of CTT, 2) Coping with CTT, and 3) Perceived benefits, risks, and decision-making about CTT. Participants reported substantial burden of CTT including difficulties in coordinating family roles, school, and work. In addition to the difficulties with frequent venous access, there were concerns about potentially experiencing complications with CTT, and challenges with taking iron chelation medications. Participants generally reported coping well with CTT and integrated into their routine. Parents and patients also highlighted the importance of support from clinic providers, family and school systems. Participants associated CTT with increased energy, decreased pain, fewer hospitalizations and recognized its role in stroke prevention, while also recognizing the risks of iron overload. Parents described the process of decision-making with their providers about CTT, but only a few patients were involved in the decision making process.
Conclusion: While CTT is an effective therapy in prevention of SCD complications, patients and families experience significant burdens of CTT.

Poster # 730

STAKEHOLDER PERSPECTIVES ON HEALTH-RELATED QUALITY OF LIFE IN FUNCTION OF BLOOD TRANSFUSION TYPE

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Background: As an increasing amount of Sickle Cell Disease (SCD) patients requires chronic blood transfusion. Depending on the applied transfusion mechanism, different disease complications may occur and perspectives on quality of life as experience by the patients may be different.
Objectives: The objectives covered within the scope of this study are: to quantify Health-Related Quality of Life (HRQoL) as experienced by individuals with SCD treated with

automated red blood cell exchange (aRBCX) versus simple blood transfusion. Moreover, the study intends to identify the drivers for quality of life amongst SCD patients that require blood transfusion. Lastly the objective of this study was to assess whether physicians and patients have a similar view on the impact of aRBCx on HRQoL amongst SCD patients. Lastly the study aims to understand the patient experiences as a consequence of aRBCX versus simple blood transfusion.
Design/Method: A cross-sectional study was performed amongst 40 SCD patients, 20 from the USA, 10 from France and 10 from the UK as well as amongst 40 SCD treating physicians with experience in both simple transfusion as well as aRBCX. The physicians had the same regional distribution as the patients.
Results: SCD patients undergoing aRBCX reported an HRQoL that was 25% higher compared to the period where they were treated with simple transfusion (0.70 vs. 0.55; $p<0.01$). The main drivers of HRQoL identified were (correlation efficient): pain reduction (0.57), improved social live (0.49), autonomy in terms of all day living activities and being independent from others (0.56), feeling energetic and physical functioning (0.57) and lastly emotional worry and mental health (0.56), all with p-values < 0.01.80% of the patients preferred aRBCx over simple transfusion. 87% of the participating physicians believed that switching patients from simple transfusion to aRBCX positively affected the SCD patients' quality of life. 80% of SCD patients reported benefits of aRBCX versus simple blood transfusion. In specific, 55% of patients reported benefits related to the overall wellbeing 40% of patients reported superior clinical effectiveness, 38% of patients reported benefits related to the treatment procedure, 33% of patients reported less acute complications and events, 25% of patients reported an improvement in the SCD symptoms they experience and 5% of patients reported and improved cognitive functioning.
Conclusion: In our study SCD patients that require blood transfusion experience better HRQol when they are treated with automated red blood cell exchange versus simple transfusion. This observation is supported by the opinion of their treating physicians.

Poster # 731

DELAYED HEMOLYTIC TRANSFUSION REACTION: EX VIVO INHIBITION OF HEMOLYSIS WITH PIC1

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Background: A 14 year old female with sickle cell disease received a pRBC transfusion for vaso-occlusive disease and acute chest syndrome. Eight days after transfusion she suffered acute onset of severe extremity pain that was followed by new onset of fever, hypertension and respiratory decompensation. Her hemoglobin decreased from 7.6 to 5.0 g/dL overnight consistent with a delayed hemolytic transfusion reaction. The diagnosis was supported by down-trending Hemoglobin A percentage when compared to a post-transfusion sample. She subsequently survived an 8 day ICU stay requiring multiple pRBC transfusions due to hypoxemia and received multiple immunomodulators including methylprednisolone, IVIg, eculizumab, rituximab and tocilizumab. To investigate her disease pathology the patient's erythrocytes and plasma were

analyzed in hemolytic assays in the presence or absence of a classical complement pathway inhibitor, PIC1.
Objectives: To evaluate the ability of a classical complement pathway inhibitor, PIC1, to block complement-mediated hemolysis of the patient's erythrocytes by her own plasma.
Design/Method: Discarded de-identified blood from routine medical management blood draws were obtained from prior to treatment with eculizumab. Hemolytic complement assays utilizing the patient's plasma and erythrocytes in complement permissive buffers in the presence of increasing concentrations of PIC1 were performed. Erythrocytes were sedimented and hemolysis was measured by quantitation of free hemoglobin on a spectrophotometer at 412nm.
Results: The patient's plasma caused hemolysis of her erythrocytes in complement permissive buffers demonstrating complement-mediated hemolysis. Addition of PIC1 showed a statistically significant and dose-dependent decrease of hemolysis. At higher doses PIC1 inhibited hemolysis to the background signal.
Conclusion: For this patient with sickle cell disease and delayed hemolytic transfusion reaction, complement-mediated hemolysis of her erythrocytes by her plasma was demonstrated ex vivo. The complement-mediated hemolysis was completely blocked with a classical complement pathway inhibitor, PIC1. These results suggest that a classical complement pathway inhibitor could be used to halt active hemolysis in a patient suffering a delayed hemolytic transfusion reaction.

Poster # 732

IRON OVERLOAD AND DISSEMINATED MAC IN A PEDIATRIC PATIENT WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is an inherited red blood cell disorder caused by the production of abnormal hemoglobin due to a beta globin gene mutation. Complications in SCD arise due to a complex interplay of processes leading to increased hemolysis and organ dysfunction due to tissue ischemia from small vessel vaso-occlusion. Repeated vaso-occlusive events to the spleen lead to functional asplenia, increasing the risk of infection with encapsulated organisms. Iron overload as a result of repeated blood transfusions is another risk factor for infection that is often under-recognized. Case reports in adult literature and studies in mice have demonstrated the risk of disseminated mycobacterium avium complex (MAC) infection in states of iron overload. MAC species are able to produce molecules called siderophores that have a high affinity for iron and are able to obtain iron from the host's innate iron binding proteins. Patients with SCD and iron overload therefore have a distinct risk for disseminated MAC.
Objectives: The patient presented is a 15-year-old male with SCD and severe iron overload who initially presented with weight loss, fatigue and fever. His course was complicated by cytopenias and progressive respiratory failure for which he underwent extensive work up. After a prolonged incubation period of 18 days, MAC was detected on blood culture. He ultimately died as a result of disseminated MAC and hemophagocytic lymphohistiocytosis (HLH). This case highlights the adverse effects of iron overload in relation to infectious complications in a pediatric patient with SCD.

Design/Method: A comprehensive literature review was completed.
Conclusion: Although chronic transfusion therapy can ameliorate some of the negative effects of SCD, long term exposure leads to iron overload. Practitioners are well-versed in resultant complications such as hepatic and dysfunction. However, infectious complications as a result of iron overload are often overlooked. With increased recognition of the association between iron overload and MAC, earlier diagnosis and treatment of these infections may decrease poor outcomes. Otherwise, diagnosis will continue to be delayed due to the extended time to detection of mycobacterium on cultures. If HLH develops in conjunction with disseminated MAC, the combination can be fatal given the competing treatments for these diseases. We hope this case increases awareness of disseminated MAC in the pediatric sickle cell population so that physicians may consider this diagnosis earlier in the disease process.

Poster # 733

RETROSPECTIVE ANALYSIS OF COMPLIANCE AND EFFICACY OF A NOVEL FORMULATION OF DEFERASIROX (JADENU)

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Background: Transfusion-related iron overload is a complication of chronic transfusion therapy in patients with sickle cell disease. Several medications are available to chelate iron, and adherence to chelation medication is critical to prevent the iron related damage. Jadenu®, a novel film-coated tablet formulation of deferasirox, was introduced in 2015.
Objectives: To see if Jadenu®, the novel formulation of Deferasirox was more compatible for adherence compared to the previous formulations on the market via adherence, iron control, and patient/parent reported preferences and quality of life in our chronically transfused patients with sickle cell disease.
Design/Method: Patients with sickle cell disease receiving chronic transfusion therapy and chelation were invited to participate in this single-institution trial. Subjects and parents were administered a survey on medication preference and self-reported adherence. Subjects and parents then completed the PedsQL™ Sickle Cell Disease Module 3.0 (acute and one month), as well as the PedsQL™ Quality of Life Short Form 4.0 (acute and one month). Retrospective measures of iron burden including laboratory values and imaging was abstracted from the electronic medical record. In subjects who transitioned to tablet deferasirox, iron measures were compared during the time period on their prior chelation and while they were taking tablet deferasirox. Unparied and paired t-tests were used to compare continuous variables as appropriate. Fisher's exact testing was used to compare categorical data.
Results: 21 subjects were enrolled in the study. Average age was 15yo (range 8-22yo). 15 subjects were prescribed tablet deferasirox, and six were prescribed deferasirox for oral-suspension (dissolvable). Of those on tablet deferasirox, 92% reported missing more doses with the dissolvable formulation than with the tablet, with 50% reporting missing 3-4 doses per week of the dissolvable formulation. Participants reported barriers to taking the dissolvable formulation included: side effects, administration, taste, forgetfulness, and general dislike. 64% reported no side effects from either formulation. There were no statistically significant differences in quality of life measures between subjects taking the two formulations of

deferasirox, except patient-reported psychosocial quality of life was higher in 8-13y cohort of subjects taking tablet deferasirox (70.0 vs 86.6, p=0.05). In general, parent-reports of quality of life measures were lower than patient-reports for both groups. There was a trend towards improved LIC on the tablet formulation (15.6mg/g dry weight vs 14.9mg/g dry weight, p>0.05) but average ferritin stayed consistent between the two subjects..
Conclusion: Film-coated tablets were the patient preferred formulation of deferasirox and subjects reported improved adherence with this formulation.

Poster # 734

ENCEPHALOPATHY SECONDARY TO DEFERASIROX-INDUCED HYPERAMMONEMIA IN A PATIENT WITH SICKLE CELL DISEASE

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Background: Deferasirox, an effective oral iron chelator, reduces morbidity and mortality related to chronic iron overload. Adverse effects range from common mild gastrointestinal disturbances and transient elevations of serum creatinine and transaminases to rare renal and hepatic failure. Increased incidences of mild adverse effects were demonstrated in patients with low total body iron irrespective of deferasirox dose. We report a case of hyperammonemia and metabolic encephalopathy in a sickle cell disease (SCD) patient on deferasirox for transfusion-induced hemosiderosis.
Objectives: To demonstrate the insidious onset and risk of deferasirox-induced hyperammonemia and metabolic encephalopathy in a SCD patient with over-chelation of iron.
Design/Method: A 19-year-old male with SCD (SS-type), on exchange transfusions for history of transient ischemic attacks and taking deferasirox (15 mg/kg/d) despite instructions to discontinue for low ferritin, was admitted for dehydration management. He maintained normal vitals but developed abdominal pain, emesis, and rising creatinine. By day three he had progressive somnolence followed by sudden altered mental status (AMS). He was transferred to PICU and deferasirox was discontinued immediately.
Results: Labs demonstrated hyperammonemia (368 μmol/L), metabolic acidosis (CO2 14 mmol/L, pH 7.28), thrombocytosis (1098 x 109/L) and acute kidney injury (AKI) (creatinine 1.61 mg/dL); hemoglobin S 31%, serum ferritin 21 μg/L, total iron binding capacity 606 mg/dL, and transferrin saturation 4%. Hemoglobin, WBC count, total/direct bilirubin, and transaminases were all relatively normal/at baseline. Head CT/Brain MRI demonstrated no intracranial pathology. Abdominal sonogram and portal venous Doppler were unremarkable. A comprehensive workup for possible causes – including infection, seizure disorder, encephalitis, hepatic veno-occlusive disease/failure, autoimmune disorders, vitamin B/zinc/copper deficiencies, urea cycle defects, and inborn errors of metabolism – were all negative. Management included hemodialysis and supportive care; following full recovery, he was discharged home without deferasirox.
Conclusion: Hyperammonemia and metabolic encephalopathy are rare but serious adverse effects of deferasirox, presenting as sudden AMS following progressive somnolence, and with hyperammonemia that may present without evidence of hepatic dysfunction. Cessation of deferasirox with supportive management facilitates reversal of clinical changes. Warning signs

and symptoms are evident prior to fulminant presentation with non-specific gastrointestinal complaints and AKI, both well-known side effects of deferasirox. It remains unclear if the degree of hyperammonemia caused by deferasirox is exacerbated by over chelation of iron, SCD, or both.

Poster # 735

SICKLE CELL DISEASE EMERGENCY ROOM PEDIATRIC PAIN PROTOCOL

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Background: Sickle cell disease (SCD) is an inherited red blood cell disorder with a myriad of complications. Vaso-occlusive pain crisis (VOC) is the most common complication seen in SCD, accounting for 79-91% of emergency room (ER) visits and a significant number of hospitalizations. Children with SCD represent a vulnerable population and pain is often underestimated.
Objectives: To determine if SCD pain management at our institution aligns with national and institutional pain management guidelines prior to the implementation of a SCD-specific protocol.
Design/Method: We retrospectively analyzed electronic medical record (EMR) data at Riley Hospital for Children between June 2015 and May 2018 for all pediatric patients (0-21 yo) with a confirmed diagnosis of SCD who presented to the ER with uncomplicated VOC. This data included pain scores as well as timing, type, and dose of analgesia. Univariate analyses were used to compare data between encounters.
Results: One hundred and eighty-six patients were seen for a total of 504 encounters, the majority of whom were male (59%, $p<0.001$) and had Hb SS disease (67%, $p<0.001$). The mean length of an ER visit was approximately 5 hours (+/-113 minutes). The median pain score at presentation was 9 (0-10 scale), with an average of 23 minutes from check in to first documented pain score. However, 19% of patients had no initial pain score documented, which occurred more often if the patient's initial analgesic was given orally ($p<0.001$). The mean time from ED check in to first dose of analgesia (PO, IV, IN) was 76 minutes. The mean time between pain scores and medication administration increased between subsequent doses. IV/IN analgesia was used initially in 67% of encounters, morphine being the preferred analgesic (29%), followed by hydromorphone (15%) ($p<0.001$). There was no association between initial pain score and IV analgesia choice ($p=0.9$), or likelihood to be discharged ($p=0.63$), but patients who received PO analgesia had a lower average initial pain score (4.32, $p<0.001$), though statistically were not more likely to be discharged ($p=0.06$). 70% of these encounters resulted in hospitalization, with an average LOS of 4.1 days.
Conclusion: The acute nature of many sickle cell complications makes the ER a common setting where management of SCD occurs. Despite education regarding current evidence, our study illustrated inconsistent initial analgesia choice and prolonged time to medication administration and reassessment. Future studies will look at the use of collaborative, standardized, SCD-specific clinical guidelines to improve SCD patient outcomes in the ER.

Poster # 736

KETAMINE & LIDOCAINE DECREASE OPIOID CONSUMPTION DURING VASO-OCCLUSIVE CRISIS IN SICKLE CELL DISEASE

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Background: Recurrent exposure to opioids in sickle cell disease (SCD) can lead to opioid tolerance (OT) and opioid induced hyperalgesia (OIH) through activation of N-methyl-D-aspartate (NMDA) receptors. NMDA receptor antagonists like ketamine and lidocaine can modulate OT and OIH.
Objectives: The objective of this study was to evaluate the utility of ketamine and lidocaine in decreasing opioid consumption during vaso-occlusive crisis (VOC).
Design/Method: This was a single institution retrospective review of admissions for VOC in patients with SCD. We reviewed admissions during which patients were treated with lidocaine and/or ketamine infusions in addition to standard opioid therapy ("active therapy" admissions, ATA) and a control admission during which opioid was used without any adjunct therapy ("standard therapy" admission, STA). Main outcome was daily opioid consumption as morphine equivalent (MED, mg/kg/day), for each admission of interest which was compared between each ATA and STA. The decision for adding ketamine and/or lidocaine infusions to the standard therapy was based on the collaboration between hematology and pain management services.
Results: We identified 4 patients (13 to 17 years of age, 3 with HbSS and one with HbS/ Beta Thalassemia variant) who received ketamine and/or lidocaine infusions during 7 ATA for treatment of acute VOC. The 7 ATA during which patients were treated with ketamine and/or lidocaine infusions in addition to opioid were represented by 4 admissions for a single patient (patient #1) and one admission each for rest of the 3 patients (patients #2-4). Patient #1 showed reduced daily opioid consumption (MED, mg/kg/day) (0.37, 0.35, 0.44, 0.44) during all four ATA compared to an STA (0.48). Similar MED results were noted with patients #2 (0.89 - STA versus 0.23 - ATA) and #3 (0.73 - STA versus 0.60 - ATA). Two patients were treated with systemic lidocaine infusions (patients #1 and #2) during the study timeframe and demonstrated reduced MED during ATA compared with their respective control STA. Patient #4 did not illicit decreased opioid consumption during the ATA (6.68 versus STA - 1.72). This could be due to a 4 years' time gap and possible disease progression between ATA and STA. For the other 3 patients, time between STA and ATA was no more than 17 months, thus having minimal disease progression and pain sensitization.
Conclusion: Our findings suggest that ketamine and lidocaine infusions may be useful in reducing opioid exposure during acute SCD pain, although prospective controlled trials are needed.

Poster # 737

PATIENTS' AND CAREGIVERS' EXPERIENCES WITH PAIN MANAGEMENT IN CHILDREN WITH SICKLE CELL DISEASE

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Background: The quality of life of children with sickle cell disease (SCD) depends on the severity and number of vaso-occlusive crises (VOC) and their need for medical treatment and hospitalizations.
Objectives: The objective of this study was to explore the experiences of pediatric patients and their families during VOC.
Design/Method: This qualitative study used semi-structured interviews designed in partnership with two patients and one parent, in a single center, tertiary care pediatric university-affiliated hospital. Two groups of participants were interviewed independently: (1) adolescent patients hospitalised within the last 2 years for VOC, (2) parents of pediatric patients with SCD hospitalised within the last 2 years for VOC. Data was transcribed in full and analysed using NVivo12. Descriptive thematic content analysis was performed by coding themes emerging from data. After validating codes through interjudge assessment by consensus, themes from teenagers' and parent's discourses were compared for the final analysis.
Results: Between June and August 2018, eight interviews were conducted; half of them were focus groups, half were individual interviews. Ten parents and five adolescents (aged 14 to 16) participated. Teenagers' and parents' answers mirrored each other's. Prompt, adequate pain relief was crucial for all, although the side effects of pain medications were an added source of suffering. Recent quality improvement initiatives were noteworthy improvements to achieve timely pain relief, though personalizing care was also important to participants. Given the unpredictability and severity of VOC, their impact on both patients' and families' lives were substantial (school, work, other children/siblings), as was the long term emotional burden of the painful illness. Parents felt guilty given the hereditary nature of the disease, they encouraged neonatal and prenatal testing, and they sought definitive treatments for both VOC and SCD. Tensions within parent-teenager relationships were described centered on developing autonomy – particularly in the context of upcoming transitions to adult medicine –and protecting the child to improve adherence to treatments.
Conclusion: Participants emphasized the need to provide timely adequate analgesia, through both standardised quality improvement initiatives and a personalised approach to analgesia. Understanding the impact of VOC on patients' lives and their socio-familial context is important to tailor clinical interventions.

Poster # 738

COMPARING SICKLE CELL DISEASE ACUTE PAIN MANAGEMENT IN THE PEDIATRIC AND ADULT EMERGENCY DEPARTMENT

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Background: Vasoocclusive pain leading to frequent emergency department visits and hospital admissions are the hallmark of sickle cell disease (SCD). Adolescents with SCD are known to have higher rates of emergency department (ED) visits and transition to adult care are associated with significant challenges. Adults with SCD have reported higher rates of stigmatization and

perception of neglect when receiving care.
Objectives: Assess if there is a difference in the number of visits, admission rate, analgesia choice, and time to analgesia between pediatric and adult ED visits for patients aged 10-30.
Design/Method: Retrospective chart review of emergency department visits of 10-30-year-old patients with sickle cell disease between Jan 2015 to Jun 2018 at one institution. Visits for vasoocclusive pain were selected based on encounter location, chief complaint and chart review audit. We excluded two adult patients that had significantly more visits than anyone else. Differences between the pediatric and adult ED care were compared via t-test. Pain management was evaluated based on 2014 National, Heart, Lung, and Blood Institute guidelines which recommend opiate analgesia within 60 minutes as first line therapy.
Results: There were 43 pediatric ED visits by 21 unique patients resulting in 21 inpatient admissions. There were 177 adult ED visits by 67 unique patients resulting in 77 inpatient admissions. From the 27 pediatric ED encounters that utilized opiates, 52% (14) received opiates within 60 minutes of arrival. From the 148 adult ED encounters that utilized opiates, 47% (70) received opiates within 60 minutes of arrival. Median time to opiate analgesia was 70 minutes in the adult ED versus 56 minutes in the pediatric ED. 33% of pediatric ED encounters used nonopiate therapy an hour prior to opiate therapy compared to only 16% of adult ED encounters.
Conclusion: Despite shorter median time to opiate analgesia, pediatric ED encounters were significantly more likely to utilize nonopiate analgesia prior to opiate analgesia. However, approximately half of patients in both EDs did not receive analgesia within the 60 minutes recommended by guidelines. While there is some practice variation, this study does not demonstrate significant difference in time to analgesia between adult and pediatric EDs as previous studies have demonstrated.
Poster # 739

PROVIDER UNDERSTANDING OF EMERGENCY ROOM SICKLE CELL DISEASE PAIN PROTOCOL

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Background: Sickle cell disease (SCD) has many potentially devastating complications that occur secondary to vaso-occlusion. Current clinical guidelines are largely based on expert opinion, resulting in large variation of management in this vulnerable population. Physician awareness regarding the current clinical emergency room (ER) pain guidelines for vaso-occlusive crisis (VOC) remains unknown at our institution.
Objectives: To evaluate current awareness and proper identification of VOC management recommendations amongst ER providers.
Design/Method: A 23-question multiple choice baseline assessment of SCD pain management practice was administered to all eligible ER providers at Riley Hospital for Children between September and November 2018. Univariate analyses were performed to evaluate responses between groups.
Results: There were a total of 52 eligible survey respondents comprised of ER staff (27%), trainees (58%), and nurses (15%). The majority of respondents (75%) were not aware of SCD pain management recommendations being available. Approximately 54% of providers endorsed

a high comfort level ("very good" or "excellent") in managing acute VOC, with staff and nurses more likely to report this than trainees (p=002). From this same subset, 75% were able to correctly identify the standard triage level for a patient with VOC, which was greater than those who reported lower levels of comfort but not statistically significant (50%, p=0.057). Less than 10% of all providers knew the recommended timeframe from triage to initial medication administration. Prolonged time between pain assessments (>50 minutes) was reported by 25% of providers with a high comfort level in managing VOC, which was similar to providers with a lower comfort level (13%, p=0.217). 77% of total respondents reported using vital signs as an indication of a patient's pain level and 88% utilized patient reported pain scores. This was not significantly different between provider comfort levels (p=0.285 and 0.412, relatively). Providers with a high level of comfort in managing VOC were more likely to report a pain score of 4 or less being necessary for discharge home (p=0.042), while those with a lower comfort level were more likely to report administering 5 or more doses of medication in the ER prior to determining disposition (p=0.008).
Conclusion: ER management of VOC is crucial for improving clinical outcomes in pediatric SCD. Our results suggest previous education regarding recommended practices was unsuccessful regardless of reported provider comfort. Development of standardized SCD ER pain management guidelines, as well as further physician education may serve as potential areas for improvement in SCD care.

Poster # 740

OPIOID PRESCRIBING HABITS IN SICKLE CELL DISEASE: AN INTERNATIONAL SURVEY OF PROVIDERS

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Background: Vaso-occlusive pain crises (VOC) are the hallmark of sickle cell disease (SCD) and the primary reason for healthcare utilization. Both national and international guidelines recommend aggressive intravenous opioids, intravenous fluids and anti-inflammatory therapy as the mainstay of treatment for acute SCD pain. However, many VOC's are managed at home with oral medication and supportive care. There are no guidelines on home medications management of VOC, likely due to lack of well-defined endpoints and lack of funding for already approved pain medications. Amplifying this is the growing concern for opioid abuse and misuse in the US and internationally.
Objectives: This study aimed to describe the opioid prescribing habits among providers treating SCD in the United States (US) and internationally.
Design/Method: A thirty-question REDcap survey was disseminated electronically. Recruitment techniques included a combination purposeful and snowball sampling strategy.
Results: There were 127 responses and 17 countries represented. Over half of the respondents were from the US (59%). Most of the respondents were Hematologist/Oncologists both pediatric (43%) and adult (34%). Evaluation of the responses from pediatric providers showed that US providers were more likely to prescribe opioids than non-US physicians (100% vs 67%, p<0.004) and were more likely to be "very comfortable" prescribing opioids than non-US physicians (90% vs 29%, p<0.001). Of all physicians who prescribe opioids, most (79%)

prescribed 30 doses or less at a time. However, non-US physicians were more likely to prescribe less than 10 doses at a time (50%vs 13%, p <.05). Overall, the five most commonly prescribed medications for home pain management were; acetaminophen (96%), ibuprofen (76%), short acting morphine (52%), oxycodone (46%) and combination products (41%). However, US physicians were more likely to prescribe oxycodone (70% vs 10%, p< 0.001), dilaudid (52% vs 10%, p<0.05), long acting morphine (51% vs 19%, p<0.05), combination products (61% vs 10%, p<0.001). Non US physicians were more likely to prescribe non-opioids. Non US physicians were more likely to report never being concerned that patients were misusing opioids (48% vs 12%, p<0.05).
Conclusion: Many physicians prescribe opioids for outpatient VOC management. Non-US physicians are more likely to prescribe less potent opioids in lower quantities. As concerns have increased for opioid-induced hyperalgesia and other complications of long term opioid use, alternative disease-modifying agents for the prevention of SCD related pain remain an unmet need. However, it is remains important to identify optimal home pain management strategies to improve care in SCD.

Poster # 741

FEASIBILITY STUDY OF VIRTUAL REALITY, MEDITATION, & MINDFULNESS FOR PAIN IN SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a hematologic disorder resulting in many complications throughout a patient's life. The most common complication is pain, usually in the form of unpredictable acute pain crises. Due to the subjective nature of pain, patients and providers have difficulty treating pain. Furthermore, many sickle cell patients experience both anxiety and depressive symptoms complicating pain treatment and increasing their morbidity. In the face of the continued opioid crisis, many providers are looking for non-pharmacologic modalities to assist in management of pain and a variety of other symptoms including anxiety and depression.
Objectives: Our aim is to complete a feasibility study utilizing a one-time session including mindfulness, meditation, and virtual reality (VR) in patients with SCD who were experiencing acute pain and anxiety or depressive symptoms.
Design/Method: We recruited twenty patients with SCD who were experiencing pain as well as symptoms of anxiety or depression to participate in a one-time mindfulness/meditation and VR session. Their pain score via visual-analog scale (VAS) and symptoms of anxiety and depression were recorded before and after the intervention. Patients participated in a 10 minute audio-only mindfulness session, followed by a 10 minute audio-guided VR session. Their heart rate (HR) was also tracked before, during, and after the intervention with a wearable device.
Results: Twelve patients completed a feasibility questionnaire, with 75% of patients 'somewhat or very satisfied' with participation, and 92% felt VR was helpful. Pain scores decreased by an average of 0.88 (-1.41, -0.35) on VAS. Anxiety symptoms decreased in 12/20 patients with average Generalized Anxiety Disorder-7 (GAD-7) score decrease of 1.80 points (-3.42, -0.18) and depressive symptoms decreased in 11/20 patients with average Patient Health Questionnaire-

9 (PHQ-9) score decrease of 1.85 points (-3.42, 0.28). The majority of patients (75%) had an impression of improvement given scores of three or greater using the 'Patient's Global Assessment of Change' questionnaire. Heart rate data is still being analyzed.
Conclusion: Our study shows feasibility of a one-time mindfulness, meditation, and VR session in SCD patients as well as statistically significant decreases in pain, anxiety, and depressive symptoms. Larger studies, both inpatient and outpatient, are needed to expand our understanding of using VR for the treatment of pain, anxiety, and depression in SCD.

Poster # 742

IMPLEMENTATION OF PAIN ALGORITHM AND PROVIDER EDUCATION IMPROVES OUTCOMES IN SICKLE CELL DISEASE

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Background: Vaso-occlusive painful episodes (VOE) are the most common reason for emergency department (ED) visits and hospitalizations for individuals living with sickle cell disease (SCD). The 2014 National Heart Lung & Blood Institute (NHLBI) guidelines for acute management of VOE recommended rapid evaluation and prompt initiation of treatment, including administration of a parenteral opioid within 60 minutes of registration followed by pain reassessment and opioid re-administration until pain is under control. Time to opioid administration is also recognized as a quality of care measure for VOE outcomes.
Objectives: The broad objective of our quality improvement (QI) project is to optimize VOE pain management in the pediatric ED. The specific aims were to decrease time to administration of first opioid to less than 60 minutes after registration in the ED, increase opioid administration rate within 60 minutes from 50% to 100% of patients, and encourage more frequent pain assessments and repeat opioid administration if needed for improved VOE outcomes.
Design/Method: The QI project was implemented at the Children's Hospital, OU Medical Center, a tertiary academic Children's hospital. Baseline data for HbSS variants presenting to the ED for a VOE was collected for 2015 and 2016. In October 2017, a multi-disciplinary team was identified which included pediatric hematologists, ED physicians and members of the nursing, pharmacy and QI teams. Key drivers were identified and interventions included development of a standardized pain management algorithm, identification of ED champions and education of pediatric ED staff, improving reassessment rate using standardized documentation of reassessments and interventions, and use of intranasal fentanyl when appropriate to provide rapid pain relief.
Results: From January to July 2018, 75 out of 92 encounters (81%) received first dose of opioids within 60 minutes, a substantial improvement compared to 88 out of 166 encounters (53%) in 2015 and 25 out of 162 encounters (15%) in 2016. We also noted a decrease in hospitalizations for VOE with admission rates of 42% in 2018, compared to 53% in 2016 and 81% in 2015.
Conclusion: Development and initiation of a pain algorithm and efforts focused on increasing awareness and education of key providers led to a substantial overall improvement in the time to administration of opioid pain medications in the ED, increased adherence to NHLBI guidelines and a reduction in hospitalization rates. The next steps of the ongoing QI project include

development of individualized pain plans to further advance care of patients with sickle cell disease.

Poster # 743

IMPROVING THE CARE OF PATIENTS WITH SICKLE CELL DISEASE THROUGH THE USE OF INDIVIDUALIZED PAIN PLANS

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Background: Despite advances in the treatment of sickle cell disease, effective management of sickle cell pain remains challenging. Upon presentation to the emergency department (ED), opioid-tolerant patients often receive inappropriate doses of pain medications, leading to delays in appropriate pain management and prolonged hospital stays. We are standardizing the approach to pain management by systematically creating and updating individualized electronic pain plans for each patient with sickle cell disease at our institution. It is expected that variations in treatment in the ED will decrease, time to first dose of pain medication will decrease, admission orders to the hematology service will reflect a more appropriate analgesic dose for each patient, and hospital length of stay will decrease.
Objectives: This project seeks to increase the percent of patients with sickle cell disease discharged from the hematology service following admissions for pain crisis with updated pain plans from 0% to 90% by June 30, 2019.
Design/Method: A new pain plan template was created within the electronic health record (EHR) by a multidisciplinary team. It includes all analgesic, disease-modifying, and adjuvant therapies for patients with sickle cell disease classified by outpatient, ED, and inpatient management. Multiple PDSA cycles were conducted to embed the creation and regular updating of pain plans into the institutional culture and to increase utilization of pain plans for patients with sickle cell disease. Data on eligible hospital discharges and the presence of updated pain plans were abstracted from the EHR. The percent of patients discharged with updated pain plans was captured monthly and tracked using run charts.
Results: Preliminary data demonstrate the percentage of eligible patients discharged with pain plans has increased markedly since project inception and continues to trend upward toward our goal. The median percentage of patients discharged with an up-to-date pain plan has increased from 0% to 82%. More than a third of these plans have been created or updated during admissions for vaso-occlusive crises.
Conclusion: Preliminary data from this project support the systematic creation of electronic patient-specific treatment plans for individuals with chronic disease to streamline patient care and validate that this endeavor is feasible within our clinical workflow. Once the majority of patients with sickle cell disease at our institution have updated pain plans in place, further analysis will be necessary to determine if the pain plans are associated with fewer delays in care and shorter lengths of stay.

Poster # 744

PREVALENCE OF LOW VELOCITIES ON TRANSCRANIAL DOPPLER IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Transcranial doppler (TCD) ultrasound is an effective screening technique to identify increased stroke risk in children with sickle cell disease (SCD) who have elevated cerebral artery velocities, however less is known about interpretation of low velocities. Children with SCD and past stroke have been shown to have a high frequency of either low or non-visualized TCD velocities. However, the prevalence of low velocities on TCD in children with SCD who are not known to have stroke or cerebrovascular disease is unknown.
Objectives: To determine the prevalence of low velocity TCDs in children with HbSS or Sβ0 thalassemia; to describe the clinical characteristics of patients with low velocity TCDs.
Design/Method: The SCD clinical database of Children's Healthcare of Atlanta was reviewed to identify all children with SCD with genotypes HbSS or Sβ0 thalassemia who were ages 2 – 15.99 years during 01/01/2010 – 12/31/2015. Treatment start and stop dates for hydroxyurea, chronic transfusions, or bone marrow transplant were recorded. Electronic medical records were reviewed retrospectively to record all TCD results in the 6-year study period. The time average maximum mean velocities (TAMV) were reviewed to categorize TCD results as follows: a) normal in all vessels; b) high (>200 cm/sec) in ≥1 vessel; c) conditional (170 – 199 cm/s) in ≥1 vessel; d) low velocity (<70 cm/s) in the anterior cerebral artery (ACA), middle cerebral artery (MCA), ACA-MCA bifurcation, or distal internal carotid artery; e) non-visualized (NV) in ≥1 vessel.
Results: Of 1,274 eligible patients, 973 had ≥1 TCD exam in the study period (median 3 TCDs per patient, range 0-10). There were 630 (65%) patients with ≥1 low TCD. There were additional abnormal findings (high, conditional, non-visualized) in other arteries in 171 (27%) of the low TCD exams. At the time of the low TCD, 291 (46%) of patients were on hydroxyurea and 56 (9%) were on chronic transfusion therapy (CTT). Additionally, 66 patients began hydroxyurea and 5 patients began CTT before their next TCD. After the first low TCD, a subsequent TCD was obtained in 458 (73%) patients during the study period. Of these 266 (58%) had normalization of all TCD velocities after the first low TCD.
Conclusion: TCDs with low velocities are common in children with SCD undergoing routine surveillance for stroke risk and may normalize without intervention. Ongoing investigation will examine the relationship of low velocity TCD to future stroke and brain imaging.

Poster # 745

SCREENING CHILDREN WITH SICKLE CELL DISEASE FOR NEUROCOGNITIVE DEFICITS WITH A BRIEF QUESTIONNAIRE

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Background: Children with sickle cell disease (SCD) are known to be at risk for neurocognitive deficits, which can lead to significant effects on academic performance and later job attainment. Studies have demonstrated impairments on achievement tests of full scale, verbal, and performance intelligence (IQ) compared to age-related unaffected controls. However, screening for school problems in children at high risk for poor academic performance (PAP) in a clinic setting has been limited.
Objectives: To identify early elementary school-aged children with SCD at high risk for PAP via administration of a standardized screening tool at their yearly comprehensive sickle cell visit. Also, to determine the role of demographic, clinical, and laboratory factors in PAP risk.
Design/Method: In this pilot study, parents of twenty patients followed in the Cohen Children's Medical Center sickle cell clinic were asked to complete the Behavior Assessment System for Children, 3rd edition (BASC-3) Parent Rating Scale in areas previously identified to be affected in SCD. Children ages 6-9 years and all SCD genotypes were included. Children with a history of clinically overt stroke and abnormal transcranial doppler velocities were excluded. Patients who scored at least 1 standard deviation (SD) below the mean were considered high risk. Fisher's exact tests and exact Wilcoxon rank sum tests were conducted, as appropriate, to assess associations of demographic, academic and laboratory data with risk status (RS).
Results: Four of 20 patients (20%) were found to be at risk by the BASC-3. There was a significant association between those with a history of PAP and RS (p=0.001). Although not statistically significant, there was a trend to suggest possible associations between baseline hemoglobin, reticulocyte count and RS. Children who were not considered at risk had a higher mean hemoglobin level (9.7±1.3 vs 8.8±1.8g/dL) and lower reticulocyte count (6.1±3.9 vs 9.6±5.7%; p=0.37 and p=0.20, respectively). Those on hydroxyurea were significantly less likely to score as at risk (p=0.014).
Conclusion: A parent-directed screening tool is a feasible option to incorporate into the comprehensive sickle cell visit as a means to identify those at risk for neurocognitive deficits and may identify children in the SCD population in need of additional school support. Further prospective studies are necessary to confirm the effects of hemoglobin, reticulocyte count and hydroxyurea treatment.

Poster # 746

NUTRITIONAL AND GROWTH PARAMETER ANALYSIS OF PATIENTS WITH SICKLE CELL DISEASE IN AN URBAN HOSPITAL

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Background: Patients with sickle cell disease (SCD), an inherited disorder of red blood cells, suffer from many chronic complications including significant growth failure and poor nutrition. Higher metabolic needs and increased energy expenditure due to the severity of the disease has been thought to contribute to patients' growth and nutritional complications.
Objectives: These prior findings prompted us to reevaluate our patients with SCD at Harbor-UCLA Medical Center (HUMC), an urban county facility in South Los Angeles. The goal of this study was to gather data on patients' growth parameters including height, weight, BMI, and nutritional intake. We hypothesized that we would see similar values to historical controls where

patients with SCD have stunted growth parameters regardless of their caloric intake, but may be enhanced with the use of Hydroxyurea (HU).
Design/Method: We assessed our cohort of 48 pediatric patients with SCD, including all genotypes, HgbSS, HgbS/C, HgbS/B0 and HgbS/B+. We gathered Z scores of the anthropometric indices, including height, weight, and BMI. Through a nutritional questionnaire, we collected nutritional data for 40 patients and quantified their average caloric intake using the Free Calorie Counter on MyFitnessPal.com. Finally, we compared our patients' intake to their estimated caloric need based on age according to the Dietary Reference Intake: The Essential Guide to Nutritional Requirements (2006).
Results: We determined that more than a quarter of our patients are one or more standard deviations below the average weight and height, 26% and 30%, respectively. With 6.5% malnourished and 11% growth stunted, according to the World Health Organization criteria. There was no statistical difference between the patients taking HU or not. Our nutritional intake analysis demonstrated that 50% of our patients took in at least 100% of their needed calorie intake for age and ate 3 meals/day. Only 5% took less than 50% of their required caloric intake. On average, our patients' liquid intake is 64 oz/day and less than 25% take multivitamins daily.
Conclusion: This baseline analysis of the nutritional status and growth of our patients with SCD at HUMC gives us a better understanding of their caloric requirements. By noting that a significant percentage of patients have low height and weight despite adequate caloric intake we emphasize the need for better disease control and consideration of other methods of enhancing nutritional intake. We hope to be able to use this data to tailor their treatment plan according to their specific health parameters and nutritional needs.

Poster # 747

SCREENING FOR FOOD INSECURITY IN A PEDIATRIC SICKLE CELL DISEASE CLINIC

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Background: Food insecurity (FI), defined as unreliable access to affordable and nutritious food, is a critical social determinant of health that affects 18% of children in the United States. FI is associated with adverse health outcomes, including increased acute care utilization and hospitalization, non-adherence to prescription medications, and decreased access to ambulatory care services. The impact of FI is well-recognized in the primary care literature; however, less is known about the effects of FI in children with chronic medical conditions, such as sickle cell disease (SCD).
Objectives: Our goals were to measure the prevalence of food insecurity in our pediatric SCD clinic, and to identify differences in certain health outcomes between food-secure and food-insecure patients with SCD.
Design/Method: We used a 2-item validated FI screening tool developed by Hager et al. during hematology clinic visits. Patients screened were less than 18 years old with a diagnosis of SCD in clinic for a routine SCD visit between October 2016 and October 2017. We subsequently

reviewed the electronic health record of those patients to assess for health outcomes of interest, including use of hydroxyurea, antibiotic prophylaxis, or an active opioid prescription; history of splenectomy, stroke, acute chest syndrome (ACS), or PICU admission; and history of an ED visit, hospitalization, or missed SCD clinic visit in the last year. Data were analyzed using Fisher's exact test and the Wilcoxon two-sample test.
Results: Of the 100 patients who completed FI screening, 34% reported living in a food-insecure household. There was a significantly higher prevalence of ACS (62% vs 30%, $p = 0.0049$), missed clinic visits (47% vs 24%, $p = 0.025$), and use of an active opioid prescription (79% vs 35%, $p < 0.0001$) in food-insecure versus food-secure patients. Hydroxyurea use, antibiotic prophylaxis, history of splenectomy, PICU admission, and history of an ED visit or hospitalization in the past year were higher in the food-insecure group, but were not statistically significant.
Conclusion: The prevalence of FI in children with SCD in our hematology clinic is nearly twice the national average (34% vs 18%) and more than twice the rate for our local county (16%). FI may predispose patients with SCD to higher rates of adverse health outcomes. It is important recognize the prevalence and impact of FI outside of the primary care setting, particularly in patients with SCD who require routine healthcare access, prescription medications, and for whom their subspecialist may act as the primary care provider.

Poster # 748

SOCIAL DETERMINANTS OF HEALTH AND EMERGENCY DEPARTMENT USE AMONG CHILDREN WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is associated with high use of health care for acute and chronic complications. Although clinical factors associated with acute care utilization in SCD are well documented, the effects of social determinants of health (SDH) are not well described.
Objectives: We aimed to identify SDH correlated with emergency department (ED) visits and hospital admission from the ED among children with SCD using nationally representative survey data.
Design/Method: We analyzed de-identified data from the 2011-2017 National Health Interview Survey (NHIS). The NHIS is an annual cross-sectional in-person health survey administered to households in the United States, including a detailed health questionnaire completed for one randomly selected child from each household. Our analysis included African American children age 0-17 with caregiver-reported diagnosis of SCD. Available SDH variables included household structure, poverty level, insurance type, and maternal education. We also examined differences in ED used according to age, sex, caregiver-rated general health status, region of residence, and presence of comorbid asthma. Weighted means or proportions were compared according to ED use in the past 12 months using Wald tests.
Results: The analysis included a sample of 96 children (mean age 8±5 years; 52% female), representing approximately 81,000 children with SCD residing in the US during the study period. Forty-four children (weighted percentage, 50%; 95% confidence interval: 35%, 64%) visited the ED within the last 12 months; among this group, 20 (44%) were admitted to the

hospital after their most recent ED visit. Children who visited the ED were more likely to be living in a single-mother household, compared to children who did not require any ED visits (73% vs. 46%, p=0.034). Additionally, children who visited the ED tended to be younger than children without ED use in the last 12 months (mean age 6 vs. 9 years, p=0.022). Other variables were not significantly associated with ED use, and no patient characteristics were associated with hospital admission from the ED.
Conclusion: Despite dramatic advances in preventive pharmacologic treatments for SCD, ED use remains high in this population. In a nationally representative sample of children with SCD, household structure was the only SDH characteristic associated with ED use in the past 12 months. The lack of association between ED use and either poverty or insurance type may be related to the overall high level of social disadvantage among children with SCD.

Poster # 749

IMMUNIZATION RATES IN PATIENTS WITH SICKLE CELL DISEASE: A SINGLE INSTITUTION EXPERIENCE

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Background: Sickle cell disease (SCD) is a chronic condition associated with high levels of health care utilization. Thirty six percent of deaths among patients with SCD younger than two years of age are attributed to infections. Penicillin prophylaxis and immunizations have proven to have a positive impact on morbidity and mortality among patients with SCD. Although vaccination guidelines that are specific for patients with SCD are available, there are limited data regarding implementation of these guidelines.
Objectives: To determine the adherence rate for pneumococcal, meningococcal and influenza immunizations among children with sickle cell disease seen at the St. John Pediatric Hematology Clinic, as well as association between adherence rates and different variables.
Design/Method: This was a retrospective chart review study. Patients with SCD were identified from St. John Hematology Clinic records. Immunization adherence and timeliness of pneumococcal, meningococcal and influenza vaccines of identified patients were examined in reference to published guidelines. We examined the association between immunization adherence and demographic and clinical factors; age, sex, type of SCD, and compliance with follow up.
Results: A total of 31 children with SCD were studied, with a mean age of 8.6 ± 3.1 years; 61.3% were male. Vaccination adherence for the pneumococcal polysaccharide (73.3%) and meningococcal (60%) vaccines was significantly lower than adherence for pneumococcal conjugate (96.8%) vaccine. Children who follow up in our hematology clinic had significantly lower vaccination adherence for both pneumococcal polysaccharide and meningococcal vaccine than patients who follow up elsewhere.
Conclusion: There is a gap between current guidelines and clinical practice regarding vaccinations recommended for children with SCD. Fractionation of care between hematologists and pediatricians tends to increase this gap. Further research and interventions are warranted to decrease risk of infection among this large and high-risk population.

Poster # 750

TEXT-MESSAGE REMINDERS TO IMPROVE INFLUENZA IMMUNIZATION COMPLIANCE IN SICKLE CELL DISEASE PATIENTS

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Background: Influenza (flu) vaccinations are an important indicator for quality of care in children with sickle cell disease (SCD). Vaccination rates are low nationally in pediatric patients with SCD. Given that over 90% of people in the United States on cellular phones, text-message reminders for vaccines are utilized in general pediatric settings to improve vaccine compliance. Our aim is to determine whether a text-message reminder platform can improve flu vaccine compliance for SCD patients enrolled in the University of Illinois (UIC) Pediatric Hematology Clinic.
Objectives: To improve overall flu vaccine compliance and on-time receipt of the flu vaccine utilizing a text-message reminder platform.
Design/Method: This study was approved by the UIC Institutional Review Board (IRB). 301 SCD patients ages 6 months to 21 years are followed in the UIC Pediatric Hematology Clinic. A retrospective chart review was performed to ascertain flu vaccine compliance for the 2016-2017 and 2017-2018 flu seasons (defined as September 1-April 30). A prospective pilot study utilizing a text-message platform was launched in September 2018, and is currently in progress. This platform delivers once weekly text message reminders to the patient cohort.
Results: 100 patients in the 2016-2017 flu season received the flu vaccine, of which 64 patients received the vaccine on time (defined by the Centers for Disease Control and Prevention as receiving the flu vaccine before November 30 of the flu season). In the 2017-2018 flu season, 82 patients received the flu vaccine, of which 63 patients received the vaccine on time. In this current flu season, 93 patients have received the flu vaccine. Of these 93 patients, 67 patients received the text message reminder and 64 patients from this subgroup received the flu vaccine on time.
Conclusion: The preliminary data revealed that approximately 30% of the patient cohort received the flu vaccine during the 2016 and 2017 seasons. During this current season where the text message reminder platform was initiated, a similar number of patients received the flu vaccine on time compared to previous seasons, but more patients have received the vaccine when compared to this timepoint in previous flu seasons. These rates may be influenced by several factors including appointment attendance, loss to follow up, change in patient contact information, and negative patient/family perceptions toward receipt of the flu vaccine. A text message platform can be a useful modality in improving access to healthcare and further investigation is needed to improve the efficacy of this delivery system.

Poster # 751

IMPROVING CONTINUITY OF CARE IN PATIENTS WITH SICKLE CELL DISEASE IN MIREBALAIS, HAITI

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Background: The pediatric non-communicable disease (NCD) program at Hôpital Universitaire de Mirebalais (HUM), Haiti aims to provide longitudinal specialized care coordinated by an NCD team. Sickle cell disease (SCD) has a high prevalence among these pediatric NCDs. However, many patients were not being seen regularly and although hydroxyurea, a medication shown to improve outcomes, has been available since 2016 at HUM, it was not being used. An assessment of the barriers to care revealed poor patient follow-up at the patient level due to knowledge gaps and transportation costs, clinician level due to provider comfort and knowledge of SCD protocols as well as systems level due to an outdated registry, inaccurate diagnoses and no clear clinic schedule.
Objectives: We aimed to increase the number of patients receiving appropriate follow up by 10% by addressing patient, clinician and system level barriers from 2017-2018. Appropriate follow up was defined as a visit at least every 3 months for children ≤ 5 years old and every 6 months if ≥ 6 years old. Secondary aims included increasing hydroxyurea use and improving outcomes.
Design/Method: Interventions addressed knowledge gaps through patient group education sessions semiannually with transportation covered and formal physician education to increase diagnosis, referral and awareness of protocols. System interventions included a regular clinic schedule, updated registry, confirmation testing and medical summaries in patient charts.
Results: The number of patients in the program was 33 in 2017 and 30 in 2018. Appropriate follow up improved from 75% to 84%. Loss to follow up remained stable. Patient recruitment doubled. Patients on penicillin prophylaxis increased from 43% to 70%. Seven patients were started on hydroxyurea. The number of hospitalizations and transfusions each decreased by 50%. The number of patients requiring hospitalization for vaso-occlusive crises decreased by 75%. Two patients received surgery, cholecystectomy and splenectomy, facilitated by the team. Further obstacles to the program were found including nurse turnover, inaccurate patient contact information and limited transportation particularly during protests. Barriers to the initiation of hydroxyurea included the inability to obtain screening laboratories as well as medication stock outs due to increased use.
Conclusion: Designated clinics with patient summaries in charts paired with education sessions and covered transport costs improved patient follow-up. Better follow-up and both patient and provider education improved outcomes, decreasing hospitalizations and number of transfusions. More complications have been identified and patients have been connected to the care they need earlier. Future goals include targeting barriers to hydroxyurea use.

Poster # 752

IMPROVING TIME-TO-ANTIBIOTICS FOR FEBRILE PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Background: Pediatric patients with sickle cell disease (SCD) develop splenic dysfunction as early as 3 months of age, rendering them immunocompromised and at high risk for rapidly progressing and life-threatening bacterial infections. Despite the introduction of vaccines and prophylactic antibiotic therapy, infection remains a major cause of preventable morbidity and mortality. Fever in pediatric patients with SCD may be the only sign of infection, and should therefore be treated as an emergency. Current practice guidelines emphasize prompt administration of empiric antibiotics, with some expert consensus guidelines advising that the time-to-antibiotics (TTA) is within sixty minutes of identifying a febrile patient with SCD.
Objectives: This study aims to use a quality improvement model to examine the current time to delivery of antibiotics and implement an intervention for febrile patients with SCD who present to the Emergency Department (ED) at our institution.
Design/Method: We have identified and implemented an intervention using the Plan-Do-Study-Act model for quality improvement. A one-year retrospective chart review was conducted to evaluate the current practice at our academic tertiary-care center. Subjects included in the study were pediatric patients who presented to the ED with SCD and fever. Data points collected included time of ED arrival, initial temperature (either recorded or self-reported), time to first vitals, and time of blood culture collection. Specific antibiotic information including time ordered, time administered, and type of antibiotic given were also obtained.
Results: The pre-intervention cohort was comprised of 48 encounters with a mean time to antibiotic delivery of 181 minutes. Only two patients received antibiotics within 60 minutes of triage. Delays in antibiotic administration were identified to be in ordering and administering antibiotics. Post-intervention data collection is currently underway.
Conclusion: To address these delays, we have implemented a triage algorithm to be used by the ED triage staff. This algorithm identifies patients with sickle cell disease who present with fever or concern for infection. Once identified, a Sepsis Huddle is initiated with a provider and nursing staff. If the sepsis criteria are met, a Code Sepsis will be called to mobilize resources and prompt use of a sepsis order set in the electronic ordering system. Post-intervention data collection is underway and will be compared with pre-intervention data. Our aim is to rapidly identify febrile patients with SCD as high risk for sepsis and to standardize their care. We hypothesize an improvement in time-to-antibiotics from pre-intervention to post-intervention.

Poster # 753

IMPLEMENTATION OF A HEMOGLOBINOPATHY NEWBORN SCREENING PROGRAM AS A QUALITY IMPROVEMENT INITIATIVE

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Background: Background: Hemoglobinopathies are one the most common diseases and approximately 270million individuals worldwide are carriers for abnormal hemoglobin genes. This heterogeneousgroup of disorders encompasses changes in the alpha-globin and beta-globin genes. Increasedincidence of these mutations is found in the Middle East, Mediterranean region, and parts of Asiaand Africa, however, demographic shifts of high-risk populations has led to increased carrierrates in North American and Europe. The implementation of prenatal and

newborn screeningprograms is necessary to address these complex populations and provide appropriate counselingfor those at risk.
Objectives: Objectives: The primary purpose of the Pediatric Hemoglobinopathy Newborn Screening qualityimprovement initiative is to improve notification and education for parents of newborn infantsidentified as carriers of abnormal hemoglobin traits on routine newborn screening.
Design/Method: Design/Method: Through Plan-Do-Study-Act (PDSA) cycles, a quality improvement processwas initiated to address lack of notification for abnormal hemoglobin traits discovered onnewborn screening and appropriate management and counseling. Before the implementation ofour hemoglobinopathy newborn screening program in January 2018, initiation of parentalnotification and counseling in the electronic medical record was absent in many cases. Thequality improvement process notifies parents of abnormal hemoglobin carrier states by letter, andprovided educational material and offered an opportunity for counseling sessions. The diagnosisof an abnormal hemoglobin trait is documented in the patient's electronic medical record for theprimary care provider. Education sessions regarding the new process and available resourceswere performed at outlying clinics. Telephone surveys were conducted with parents to assesseffectiveness and satisfaction with the Pediatric Hemoglobinopathy Newborn ScreeningProgram. Data analysis was performed comparing the rate of missed notification and counselingfor hemoglobin carriers on newborn screening pre- and post-implementation. Data collectionfrom telephone surveys and identification of hemoglobinpathy errors were analyzed using a chi-square.
Results: Results: The rate of hemoglobin newborn screen errors was 32% pre-implementation versus5.7% post-implementation ($p = 0.003$). Data collection and analysis of phone surveys arecurrently in process.
Conclusion: Conclusion: Newborn screening programs have improved early diagnosis and initiation ofcomprehensive care of hemoglobinopathies. However, there exists a gap in identification andcounseling for hemoglobin trait carriers. This quality improvement initiative outlines theeffectiveness of implementing a hemoglobinopathy newborn screening program to identifycarriers and offer prompt diagnosis, counseling, and coordination of care.

Poster # 754

IMPLEMENTING NEWBORN SCREENING FOR SICKLE CELL DISEASE IN ACCRA, GHANA: RESULTS AND CHALLENGES

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Background: Early diagnosis of sickle cell disease (SCD) through newborn screening (NBS) is a cost-effective intervention shown to reduce morbidity and mortality. In sub-Saharan Africa, where disease burden is greatest, there are no universal NBS programs and few institutions have the capacity to conduct NBS.
Objectives: To identify barriers and challenges in implementing universal NBS for SCD at Korle Bu Teaching Hospital (KBTH), Ghana's largest public hospital.
Design/Method: The SCD NBS program at KBTH is a multi-phase partnership between the hospital and the SickKids Centre for Global Child Health, Toronto. The goal of the 6-month pilot

phase (June to December 2017) was to screen 4,000 babies born in KBTH and enrol babies with possible SCD (P-SCD) into the pediatric SCD clinic for follow up care. A dedicated NBS program coordinator was hired and public health nurses and midwives were trained on dried blood spot sampling (DBS) techniques. Testing of blood samples using isoelectric focusing was performed at an off-site, national research laboratory. A stakeholder dissemination meeting was held in August 2018 following completion of the pilot phase.
Results: Although planned for 6 months, the pilot phase was completed in 13 months (June 2017 to July 2018). One hundred and five public health nurses and midwives acquired competency in DBS. Out of 10,211 live births, only 4,527 babies (44.3%) were screened. Of these, 79 (1.8%) were identified with P-SCD and 70 (88.6%) were successfully contacted. Eighteen dedicated newborn clinics were held and babies with P-SCD commenced penicillin prophylaxis. Four major challenges were identified: 1) Inadequate nursing staff to perform screening, 2) Intermittent shortage of screening supplies, 3) Delays in receiving screening results, and 4) Lack of clinic space and nurses to accommodate the increased patient enrolment. Strategies to overcome these challenges were discussed at the dissemination meeting and lessons learned will be incorporated into the next phase. These include the launch of an innovative, integrated hospital discharge process for all newborns, advocating for increased staffing on the maternity wards, improved supply chain management, use of a novel digital mobile application for receiving laboratory results, and hiring dedicated newborn clinic nurses.
Conclusion: The pilot phase of NBS for SCD in KBTH presented challenges which have implications on achieving and sustaining universal screening for babies born in the hospital. In the next phase of the program, these challenges will be addressed to build on the modest initial gains.*Supported by a grant from Pfizer Inc.

Poster # 755

EPIDEMIOLOGY AND OUTCOME OF ACUTE KIDNEY INJURY IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Renal manifestations are among the most common complications of sickle cell disease (SCD), with abnormal function present even in early infancy. Recurrent episodes of microinfarction and glomerular injury lead to long-term damage. Episodes of acute kidney injury (AKI) can contribute to the progression of sickle cell nephropathy. However, little is known about the risk factors contributing to AKI development in this population and the impact of AKI on morbidity.
Objectives: To describe the incidence of AKI in SCD pediatric patients, the risk factors which contribute to its development and the impact of AKI on health outcomes.
Design/Method: We queried the PHIS database for inpatient encounters of children with SCD admitted for vaso-occlusive pain crisis (VOC) or acute chest syndrome (ACS) between 2005 and 2017. Information collected included demographic data and clinical variables considered risk factors for AKI development or potential consequences of AKI. Logistic regression model with a random hospital effect was used to identify the greatest risk factors for AKI development.
Results: There were 72,202 encounters in 13,753 patients that met inclusion criteria. 1.4% of all

patients experienced at least one episode of AKI. Patients with at least one hospital encounter complicated by AKI were older at the time of their first VOC admission ($p<.001$) and had a greater median number of discharges per patient (4 vs. 2, $p<.001$). Discharges in which AKI was documented as a complication were associated with increased ICU admissions, cost of hospitalization and length of stay (all $p<0.001$). Patients were also documented as having higher rates of hypertension, pulmonary hypertension, stroke, chronic kidney disease (CKD), proteinuria and hematuria. In addition, patients who had a history of AKI at any time point were more likely to experience the same complications and comorbidities described above in any encounter, as well as having an increased risk of readmission within seven days (14.2 vs. 7.1, $p<0.001$). Modelling results found that each one-year increase in age predicted a 9% increase in the risk of AKI. Male sex (OR 1.36), history of proteinuria (OR 3.4) and history of CKD (OR 43.61) predicted increased odds of developing AKI. History of hydroxyurea use was protective (OR 0.6).
Conclusion: The risk of AKI during admissions for VOC and/or ACS is relatively low in this cohort. However, episodes of AKI and history of AKI are associated with increased morbidity and resource utilization. Increasing the use of hydroxyurea may decrease the likelihood of this complication.

Poster # 756

HOSPITALIZATIONS FOR INVASIVE PNEUMOCOCCAL DISEASE AFTER PCV13 IN CHILDREN WITH AND WITHOUT SCD

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Background: Although the incidence of pediatric invasive pneumococcal disease (IPD) decreased since the introduction of the pneumococcal conjugate vaccine, PCV7 (1), patients with sickle cell disease (SCD) continued to have a higher rate of IPD compared with the general population (2).
Objectives: We sought to examine rates of hospitalization for IPD before and after the introduction of PCV13 among children with SCD and to examine associated changes in resource utilization.
Design/Method: This cross-sectional study used data from the Pediatric Health Information Systems (PHIS) database. Children and adolescents who were discharged with a diagnosis of IPD from 2004-2009 (Pre-PCV13) or 2012-2017 (Post-PCV13) were included. Data from 2010-2011 were excluded, as this was considered a transitional period. Incidence data, baseline characteristics, and healthcare utilization were compared between time periods for cohorts with and without SCD using Mann-Whitney U and Chi-squared tests.
Results: A total of 9160 IPD discharges were identified from 36 children's hospitals. Of these, 231 IPD discharges were identified in patients with SCD. The mean annual rate of IPD hospitalization among patients with SCD was 21.0 cases/year in the pre-PCV13 period and 17.5 cases/year in the post-PCV13 period, whereas in the general pediatric population, the mean annual rates of IPD hospitalization were 814.0 cases/year and 712.7 cases/year in these time periods. The proportion of hospitalizations for IPD per 100 total SCD hospitalizations decreased

by 17% (0.217 to 0.180) over this time frame. In the general population, the IPD rate pre-PCV13 was lower than that of the SCD cohort (0.185 per 100 hospitalizations), but the decrease over time was similar at 18%. The decrease in IPD rates after the introduction of PCV13 was not statistically significant in either cohort. There was no significant change in mortality, length of stay, ICU admission, or mechanical ventilation rates for IPD discharges with SCD in the post-PCV13 period. In contrast, there was a significant increase in resource use, including ICU days and mechanical ventilation, among the general population.
Conclusion: The introduction of PCV13 was associated with a decreased rate of hospitalization for IPD both in the general pediatric population and among those with SCD. While IPD admissions after PCV13 were associated with increased resource use in the general population, this was not true for patients with sickle cell disease. References:1. McCavit, Pediatr Blood Cancer, 2012.2. Payne, Pediatr Infect Dis J, 2013.

Poster # 757

ROLE OF STEROIDS IN MANAGEMENT OF HEMATURIA IN SICKLE CELL TRAIT

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Background: There are 3 million individuals in the US with sickle cell trait (SCT), a known risk factor for renal papillary necrosis (RPN), renal medullary carcinoma, chronic kidney disease and venous thromboembolism, with hematuria secondary to RPN as the most common. Proposed pathophysiology suggests the renal medullary environment predisposes hemoglobin S to sickle due to dehydration, acidosis, hypoxia and high osmolarity. Sickling leads to microthrombi in the vasa recta resulting in ischemia presenting with painless gross hematuria. There is no standard treatment and the approach is conservative with alkalization of the urine with intravenous fluids. Severe or refractory blood loss, however, may warrant use of other agents.
Objectives: To highlight the use of steroids for management of hematuria in SCT.
Design/Method: A 13-year-old female presented to the ER with a 3-week history of painless gross hematuria. She denied menorrhagia, hematochezia, dysuria, preceding injury, or flank pain. A week prior she was given Bactrim for a presumed UTI but urine culture remained negative and hematuria persisted. In the ER she was found to have Hgb of 7.2 and retic of 2.8. Hgb electrophoresis confirmed SCT. She was admitted for a workup that included a renal ultrasound, which was notable for a bladder mass concerning for blood clot, CT angiogram that ruled out AV malformation but noted non-enhancing areas of superior left renal cortex, and renal MRI read as normal. Cystoscopy showed left lateralizing hematuria and left retrograde pyelogram with mild hydronephrosis and a filling defect in the renal pelvis consistent with RPN. Serum studies were overall negative including ANA panel, streptozyme, EBV, adenovirus, CMV, and hepatitis panel; inflammatory markers were normal. Despite aggressive alkalization of her urine, hematuria persisted and she was discharged home with active hematuria and outpatient follow-up. Shortly after discharge she was admitted to our institution for a second opinion and evaluated by Pediatric Hematology and Nephrology.
Results: Diagnosis was consistent with RPN secondary to SCT. Given the lack of standardized treatment she was treated with a pulse steroid regimen of solumedrol 250 mg daily for three days. Her hematuria resolved within 36 hours. Based on our literature search, steroids have not

been previously reported in the management of RPN. We hypothesize that inflammation plays a role in pathophysiology of RPN in SCT, similar to acute chest syndrome in sickle cell disease, and hence the reason steroids are effective.
Conclusion: Steroids should be considered for refractory hematuria secondary to RPN in SCT.

Poster # 758

CLINICAL DESCRIPTION AND MEDICAL MANAGEMENT OF NECROTIZING LYMPHADENITIS IN A SICKLE CELL CHILD

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Background: Kikuchi-Fujimoto Disease (KFD), or histiocytic necrotizing lymphadenitis, is a self-limiting disorder of unknown etiology that often occurs in young adult females in association with autoimmune disorders. Few cases have been reported in association with sickle cell disease (SCD), with only one known case in a pediatric SCD patient.
Objectives: To review the clinical presentation and differential of a child with SCD presenting with fever and lymphadenopathy.
Design/Method: Case report
Results: A 9 year-old girl with HgbSS SCD presented with fevers, neutropenia, and submandibular pain for 1 week. Her physical exam was remarkable for tender submandibular lymphadenopathy. An ultrasound showed 1-2 cm lymph nodes with no concerning features. ID and rheumatology work ups were non-confirmatory; she was negative for HIV, EBV, HHV6, toxoplasma gondii, parvovirus, adenovirus, enterovirus, bartonella henselae, CMV, mycoplasma pneumoniae, hepatitis, blood cultures, quantiferon, and next generation microbial DNA sequencing (Karius test). Negative autoimmune labs included dsDNA, ANA, complements, SSA, SSB, and Jo1. She was discharged after resolution of symptoms with empiric antibiotics. She was re-admitted 1 week later due to the recurrence of fevers and submandibular pain with worsening pancytopenia. She was treated for febrile neutropenia with IV antibiotics, and repeat blood cultures were negative in setting of persistent fevers, totaling 14 days. A bone marrow aspirate showed mild hypocellularity with no malignant process. Whole body PET scan was negative for occult malignancy. HLH was considered due to elevated ferritin levels of 1094, but she only met 3 criteria. A lymph node biopsy was finally performed and pathology revealed a reactive lymph node with focal paracortical expansion due to a heterogenous population of mononuclear cells, strongly suggesting an early proliferative phase of Kikuchi-Fujimoto lymphadenitis. The patient was started on steroids; her symptoms and pancytopenia resolved.
Conclusion: We present a rare case of KFD in a pediatric SCD patient in order to increase awareness of this diagnosis. KFD should be considered in patients presenting with prolonged fevers, cervical lymphadenopathy, and leukopenia. Early diagnosis via lymph node histology is crucial as the clinical and laboratory presentation mimics diseases requiring costly, invasive diagnostic and therapeutic interventions such as malignancy and systemic lupus erythematosus. Although the disease is benign and self-limiting, glucocorticoids are commonly used to improve symptoms in KFD. However, steroid treatment in SCD patients can cause immunosuppresion,

infection, vaso-occlusive crises, and worsen the disease process, so SCD patients with KFD represent a unique population that requires individualized care.

Poster # 801

THROMBIN GENERATION IN CHILDREN WITH SICKLE CELL ANEMIA IS HIGHER IN THE PRESENCE OF PLATELETS

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Background: In sickle cell anemia (SCA), complex cellular and plasma interactions lead to hyper-coagulability that can be measured by thrombin generation (TG) assay. The total amount of TG or endogenous thrombin potential (ETP) in healthy adults is similar in plasma samples with and without platelets, but in SCA, it is expected to be higher in platelet-rich plasma (PRP) due to chronically activated platelets. Previous studies in SCA using platelet-poor plasma (PPP) show conflicting and variable results. There are no studies in SCA simultaneously comparing TG using PRP and PPP. TG in PPP can be studied with addition of thrombomodulin (TM) as well. Activation of the protein C/protein S (PC/PS) pathway by TM causes a reduction of ETP in healthy individuals but not in hyper-coagulable states where this pathway is impaired. This is relevant in SCA where PC and PS levels are decreased.
Objectives: Our primary objective was to compare ETP in children with SCA, at steady state, in PPP versus PRP. We also investigated the association of pertinent clinical variables with PRP ETP and evaluated the PC/PS pathway using TM.
Design/Method: Plasma samples from SCA patients aged 2-15 years were tested for TG by calibrated automated thrombography. The platelet count was calibrated uniformly for platelet-rich samples. Relevant clinical and laboratory information was collected. Sample size was calculated for a primary outcome of the difference between PPP and PRP ETP for each subject.
Results: In 43 children with HbSS, ETP in the presence of platelets was 5.9% higher [1239 nmol/(min*L) (Standard Deviation or SD 224.1) vs. 1151 nmol/(min*L) (SD 223.3); p= 0.026]. The difference was highest in the 6-10 year age group (9.5%; SD 14.1) followed by the 2-5 year age group (5.4%; SD 21.4). In a multivariate linear regression model, age, gender, current use of hydroxyurea, degree of hemolysis (measured by hemoglobin and reticulocyte count) and severity of pain crises (measured by the number of admissions in the previous year for vaso-occlusive crises) were not predictive of this difference. In PPP, ETP reduction after TM addition was 7.4% (SD 16.8) while a 50% reduction was expected based on the experimental method used.
Conclusion: To conclude, TG in children with SCA is higher in the presence of platelets. Furthermore, minimal reduction of ETP after TM addition highlights the role of an impaired PC/PS pathway. Future studies of TG in PRP with and without TM may help to describe the entire process of hyper-coagulability in SCA.

Poster # 802

SURVIVORS OF CHILDHOOD CANCER THROMBIN GENERATION

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Background: Survival for childhood cancers can exceed 85%. Despite this increase, one third develop a life-threatening health problem. As they age into adulthood, survivors of childhood cancer are at high risk for thromboembolism leading to heart attack or stroke. Studies document that induction chemotherapy in children increase their hypercoaguable state. However, few studies establish if children remain hypercoagulable after treatment is completed. Coagulation studies document that increased endogenous thrombin potential (ETP) increases the risk of a thromboembolism. We hypothesize that pediatric cancer survivors have an increased thrombin generation many years after treatment compared to healthy controls.
Objectives: We hypothesize that pediatric cancer survivors have an increased thrombin generation many years after treatment compared to healthy controls.
Design/Method: We performed a case-control study of childhood cancer survivors compared with age and sex matched healthy controls. We assessed differences in complete blood counts, routine coagulation, thromboelastography (TEG), and thrombin generation measured by calibrated automated thrombogram and ELISA for thrombin-anti-thrombin levels.
Results: We enrolled approximately fifty pediatric cancer survivors consisting of 27 leukemias and lymphomas, and 23 solid tumors. Platelet count significantly decreased in cancer survivors compared to healthy controls with an average decrease of -65.28 ($p < 0.0001$). Clot strength also decreased for cancer survivors with a median of 24.9 (Ref Range:). In contrast survivors of childhood cancer increased their ETP an average of 124 nM compared to healthy controls, $p = 0.0003$. Anthracycline treated survivors increased ETP on average 234.4 nM compared to those who did not, $p < 0.0001$.
Conclusion: Survivors of childhood cancer have decreased platelet counts and low clot strength suggestive of a more hypocoagulable state. In contrast, pediatric cancer survivors, especially if previously treated with anthracyclines, had significantly elevated endogenous thrombin potential, a sensitive marker of increased thromboembolism risk. Further evaluation of the childhood cancer survivor's pro-thrombotic cells and extracellular vesicles may identify a therapeutic target to decrease unwanted thromboembolism.

Poster # 803

COAGULATION PROFILES OF NEWLY DIAGNOSED PEDIATRIC LEUKEMIA PATIENTS

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Background: Newly diagnosed pediatric leukemia patients (NDPLP) can present with anemia and thrombocytopenia along with coagulopathy noted by prolonged prothrombin (PT)/international normalized ratio (INR) and/or activated partial thromboplastin time (aPTT). They can also have bleeding symptoms such as bruising and epistaxis. The PT/INR and aPTT are used as non-specific measures of possible bleeding, leading to the administration of blood products such as fresh frozen plasma (FFP) prior to procedures. This can be unnecessary as

PT/INR and aPTT are crude markers and do not necessarily predict risk of bleeding.
Objectives: To obtain laboratory values and bleeding symptoms of NDPLP and to further characterize these profiles.
Design/Method: Retrospective chart review of NDPLP patients aged 1 to 18 years with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and acute promyelocytic leukemia (APML) initially diagnosed at Cohen Children's Medical Center between July 2015 and June 2018. Exact Wilcoxon tests and Fisher's Exact tests were performed, as appropriate, to compare lab values and bleeding symptoms with prolonged PT/INR and aPTT status.
Results: Sixty NDPLP patients were identified, 78% having ALL (85% Pre-B cell), 17% AML and 5% APML. None had a personal or family history of bleeding, 36% of patients had bleeding symptoms within a month of diagnosis. The median white blood cell (WBC) was 15 K/uL, absolute neutrophil count (ANC) 730 per uL, hemoglobin (Hb) 8.7 g/dL, platelets (Plt) 77 k/uL. Fifty-three percent (N=32) had prolonged PT/INR and 7% had prolonged aPTT; 56% of NDPLP had a mixing study with 3% of these not correcting with mixing. Factor levels were obtained in 25% of NDLP (due to the majority of subjects missing these data, statistics not reported). All patients underwent procedures and blood products were administered in 62%: 47% received Plts, 40% packed red blood cells, 5% factor VII, 3% FFP. No patients had bleeding symptoms peri-operatively. The initial WBC was associated with PT/INR (P value <0.001) but bleeding symptoms were not significantly associated with prolonged PT/INR or aPTT.
Conclusion: In NDPLP, we failed to have enough evidence to suggest that bleeding symptoms upon presentation are associated with a prolongation in either PT/INR or aPTT. Of initial laboratory values, WBC may correlate with possible prolongation in PT/INR. Many patients received blood products without further characterization of their coagulopathy. Future studies with the use of more advanced technology such as rotational thromboelastometry (ROTEM) can help tailor care for patients based on appropriate characterization of bleeding.

Poster # 804

INTRAPULMONARY ADMINISTRATION OF RECOMBINANT ACTIVATED FACTOR VII FOR DIFFUSE ALVEOLAR HEMORRHAGE

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Background: Diffuse alveolar hemorrhage (DAH) is a devastating disease process with 70-100% mortality in the literature. High concentrations of tissue factor have been demonstrated in the alveolar wall in acute respiratory distress syndrome (ARDS), pneumonia and DAH. Furthermore, tissue factor pathway inhibitor (TFPI) expression increases twenty-fold. Factor VIIa activates the tissue factor (extrinsic) pathway and successfully overcomes the TFPI inhibition of activation of factor X. Pulmonary administration of activated recombinant factor VII (rFVIIa) in DAH has been described in case reports and small case series with successful hemostasis and minimal complications. We recently began using this medication in our DAH patients at St. Jude Children's Research Hospital.
Objectives: To assess the safety and efficacy of intrapulmonary rFVIIa for DAH in oncology and hematopoietic cell transplant (HCT) patients.
Design/Method: Retrospective descriptive study of treatment strategies and outcomes in

pediatric oncology and HCT patients with DAH at St. Jude Children's Research Hospital, Memphis, TN, USA between August 2011 and June 2018.
Results: We treated 32 patients with 103 episodes of DAH. Twenty-seven of 32 were HCT patients, 4 had an oncology diagnosis and 1 had post-transplant lymphoproliferative disease after heart transplant. The most commonly used medications for DAH were corticosteroids (93%), rFVIIa (78%), aminocaproic acid (28%) and etanercept (9%). A total of 112 doses of rFVIIa were given to 25/32 patients; 54 intravenously and 58 by intrapulmonary instillation. Mortality in patients receiving intrapulmonary rFVIIa was 58% (7/12) versus 75% (15/20) in those not receiving intrapulmonary rFVIIa. Mortality in oncology patients was 100% (4/4) versus 59% (16/27) in HCT patients. We observed no adverse events related to intrapulmonary rFVIIa. Platelet counts at the time of the bleeding episode were < 50,000 in 4/103 episodes, 50-100,000 in 44/103 episodes and > 100,000 in 55/103 episodes.
Conclusion: The mortality rate observed in HCT patients with DAH at St. Jude is better than that in the literature; however, our patient numbers are too small to demonstrate statistical significance. The practice of maintaining a platelet count >50,000 was not sufficient for hemostasis as 97% of bleeding episodes occurred with a platelet count >50,000. Novel methods of achieving hemostasis that limit the pulmonary toxicity due to alveolar exposure to blood products are needed. Our study demonstrates favorable safety of intrapulmonary rFVIIa but larger studies are warranted to evaluate efficacy.

Poster # 805

PROPHYLACTIC USE OF RECOMBINANT FVIIa IN PATIENTS WITH GLANZMANN THROMBASTHENIA

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Background: Glanzmann's thrombasthenia (GT) is rare autosomal recessive disorder, consisting of a platelet surface receptor disorder of glycoprotein (GP) IIb/IIIa (integrin αIIbβ3), resulting in faulty platelet aggregation and diminished clot retraction. GT may be classified by flow cytometry using monoclonal antibodies for αIIb and β3. Bleeding phenotype most commonly presents with menorrhagia, purpura, epistaxis, gingival and gastrointestinal (GI) bleeding. Epistaxis is particularly common in children, and may respond to compression, topical thrombin, anti-fibrinolytics and nasal packing. Further treatment with platelet transfusion, rFVIIa and/or nasal cautery has shown success in controlling nasal hemorrhage.
Objectives: We present a boy with Glanzmann's thrombasthenia with multiple pediatric intensive care admissions (PICU) for hemorrhagic shock secondary to severe epistaxis and GI bleeding, refractory to platelet transfusions and local control, treated with prophylactic rFVIIa. He does not qualify for bone marrow transplant.
Design/Method: A 12 yo male with GT presented in hemorrhagic shock following one day of epistaxis. Intravenous aminocaproic acid, normal saline boluses, packed red blood cell transfusions (pRBC) and platelets were administered. The patient was admitted to the PICU. Bleeding was controlled with intravenous aminocaproic acid every 6 hours, one dose of intravenous rFVIIa and nasal packing. Bilateral internal maxillary artery ligation followed. During the next 4 years, he was admitted 29 times, 10 of which were to the PICU due to

hemorrhagic shock. His various bleeding presentations included combinations of epistaxis, hematemesis, melena/hematochezia and telangiectasias. Two central lines were required for management of resuscitation. As a last-ditch effort to control severe acute bleeding, we initiated prophylactic intravenous rFVIIa at 65µg/kg per day 3 times a week.
Results: Since the start of prophylactic rFVIIa, he has been admitted once in a 7-month period for an elective procedure. His severe bleeding episodes are controlled. He has not required pRBC or platelet transfusional support. There has been no thrombosis formation.
Conclusion: rFVIIa has been reported to be effective with a good safety profile in patients with GT. Unlike platelet transfusions, rFVIIa poses no infectious risk nor does it cause antibodies production to HLA and/or αIIbβ3. Despite the short half-life of rVIIIa, we show significant improvement in the quality of life of our patient, supporting our prophylactic use. Our hope is data from the GT registry will contribute toward continued development of clinical "recommendations" for the management of GT using rFVIIa until a higher level of evidence may become available from randomized clinical trials.

Poster # 806

ACQUIRED VON WILLEBRAND SYNDROME IN CHILDREN WITH CARDIAC DISEASE: A RETROSPECTIVE ANALYSIS

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Background: Acquired von Willebrand Syndrome (AVWS) is an under-recognized bleeding disorder resulting from an acquired deficiency or dysfunction of von Willebrand factor (VWF). Pediatric AVWS is most frequently encountered in association with acquired or congenital heart defects with high-shear conditions that lead to accelerated proteolysis of VWF and deficient high molecular weight multimers (HMWM).
Objectives: To describe characteristics, laboratory evaluation, and management of AVWS in children with cardiac disease followed at our center.
Design/Method: We performed a retrospective review of consecutive patients with cardiac disease who were diagnosed with AVWS at our center since 2009. Pertinent data were extracted from the electronic medical records and summarized using descriptive statistics [median (interquartile range)]. Laboratory data were compared using the Mann-Whitney U test. Two-tailed p-value <0.05 was considered statistically significant.
Results: Twenty-one patients (median age 3 years, 10 females) were diagnosed with AVWS at our center since 2009. Of the 21 patients, 8 patients (38%) were on extracorporeal membrane oxygenation (ECMO), 6 patients (29%) were on ventricular-assist devices, and 7 (33%) were patients with congenital heart disease not receiving mechanical circulatory support (MCS). Thirteen patients (71%) were receiving single or combined antithrombotic therapy. All patients experienced clinically-significant bleeding events [postoperative bleeding (15), GI bleeding (3), severe epistaxis (3)]. Baseline VWF Ristocetin Cofactor (RCo) activity, VWF Antigen, and Factor VIII (FVIII) activity were 99% (81-178), 127% (92-201), and 177% (102-200), respectively. Baseline ratios of VWF RCo/Antigen and FVIII/VWF Antigen were 0.74 (0.67-0.92) and 1.32 (0.78-1.62), respectively. Quantitative VWF multimer analysis revealed decreased

HMWM (<18%) in all patients [median 11.5% (8.0-14.0)] except 1 who had a qualitative multimer analysis that was reported to be normal. An abnormal VWF RCo/Antigen ratio (<0.7) was demonstrated in 6 patients (29%) and only 1 patient had a low VWF RCo (<50%). Baseline values for VWF RCo activity, VWF RCo/Antigen ratio and HMWM were not significantly different in patients on ECMO compared to other patients. Management varied and included blood product support, lowering the intensity or temporarily withholding antithrombotic therapy, and surgical interventions to secure hemostasis. Nine patients (43%) received treatment with VWF concentrate for refractory severe bleeding.
Conclusion: Our study suggests that AVWS is an important cause of bleeding in pediatric patients with cardiac disease, especially those receiving MCS. Quantitative VWF multimer analysis was the only test that exhibited optimal diagnostic utility in our cohort. Optimal management is unclear. Prospective studies are required to improve the diagnosis and treatment in this population.

Poster # 807

NOVEL ADAMTS13 MUTATION IN A PATIENT WITH HEREDITARY TTP TREATED WITH PLASMA-DERIVED FACTOR VIII

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Background: Hereditary thrombotic thrombocytopenic purpura (TTP) is caused by deficiency in ADAMTS13. There are no FDA-approved treatments for hereditary TTP, though the use of recombinant ADAMTS13 is being assessed in a phase III study. Patients requiring treatment are usually administered fresh frozen plasma (FFP), which replenishes the deficient ADAMTS13 factor.
Objectives: To describe a novel mutation of the ADAMTS13 gene that is likely pathogenic and to discuss an alternative treatment for hereditary TTP.
Design/Method: Case report and literature review. Analysis of intolerance to functional variation within ADAMTS13's exons and domains was performed using subRVIS. Predictions of missense mutation pathogenicity were made using four in silico programs (PolyPhen2 HumVar, Mutation Assessor, AGVGD, and SIFT).
Results: A 12-month-old female presented with anemia, thrombocytopenia, and schistocytes on peripheral blood smear. ADAMTS13 activity was undetectable and no inhibitor was detected. Genetic testing revealed three mutations in ADAMTS13: paternally-inherited c1787C>T (p.Ala596Val) and c.1392C>T (p.Gly464=) in cis, and maternally-inherited c.548T>A (p.Leu183Gln). The paternally-inherited c1787C>T mutation was classified as pathogenic and previously reported in patients with disease onset in the neonatal period. The maternally-inherited mutation in exon 6, not previously described in association with hereditary TTP, is classified as likely pathogenic by American College of Medical Genetics and Genomics (ACMG) guidelines. The variant occurs in an amino acid surrounded by calcium-binding sites within the Peptidase M12B domain. Previous reports demonstrate that disruption of the domain reduces calcium binding, thereby interfering with ADAMTS13 activity. She was enrolled in the international TTP registry (ttpregistry.net).After initial treatment with on-demand FFP, the

patient required infusions at least monthly due to acute exacerbations with minor viral illnesses. Due to these frequent exacerbations, the patient was transitioned to prophylactic infusions with plasma-derived factor VIII concentrate Koate-DVI which contains modest levels of ADAMTS13 compared to other plasma-derived products and has reported benefit in at least eight other individuals with TTP. Furthermore, viral inactivation during manufacturing and the ability to infuse relatively low-volume doses at home supported its use over FFP. Treatment was initiated with infusions every 14 days at 25 units/kg. She experienced exacerbations, so the prophylactic dosing was increased to 50 units/kg. She has subsequently experienced one exacerbation in over 2 months, but the frequency of exacerbations has improved with this prophylactic approach.
Conclusion: We present a novel mutation in ADAMTS13 that is likely pathogenic by ACMG guidelines. Our patient demonstrated a response to prophylactic Koate-DVI infusions, which offers several benefits over the administration of FFP.

Poster # 808

CONGENITAL TTP WITH LARGE AND SMALL VESSEL DISEASE, AN ATYPICAL PRESENTATION

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Background: Congenital thrombotic thrombocytopenic purpura (cTTP) is an autosomal recessive disorder in which mutations in at least two alleles of the ADAMST13 gene result in disruption of von Willebrand factor multimer degradation, leading to thrombocytopenia and microangiopathic hemolytic anemia due to the dysregulated deposition of platelet rich thrombi in small vessels.
Objectives: To report a case of cTTP with large right MCA infarction and cerebral vascular findings initially suggestive of CNS vasculitis.
Design/Method: Case report
Results: A 16-year-old female with multiple emergency department presentations over 4 years for recurrent, self-limited, episodes of weakness, numbness, dizziness, and headache, was found to be thrombocytopenic and diagnosed with ITP. An MRI performed due to her neurologic history was significant for multiple old infarcts. She re-presented with acute leg numbness and repeat MRI showed new infarcts in the left frontoparietal area. Cerebral angiogram was performed, showing diffuse vasculitis versus vasculopathy involving the left parietal, right MCA, and right frontal regions. She was diagnosed with CNS vasculitis and treated with pulse steroids and cyclophosphamide. A month later she was readmitted with new left sided weakness, treated with pulse steroids, rituximab, infliximab, for presumed refractory CNS vasculitis. Labs were significant for platelet count nadir of 28,000, borderline haptoglobin, elevated LDH, and schistocytes on peripheral smear. ADAMTS13 was 6%, negative for inhibitors (BU), and with elevated von Willebrand factor antigen/activity. She was treated with daily FFP and platelet count improved to 142,000, ADAMTS13 rose to 45%. However, she then developed a large MCA infarction with left sided hemiparesis and aphasia. She received plasmapheresis for 5 days, and ADAMTS13 improved to 59%. ADAMTS13 gene sequencing was notable for Exon 17 c.2074C>T p.Arg692Cys, a known mutation in cTTP as well as Exon 26 c.3656G>A

p.Arg1219Gln mutation, a variant of uncertain significance, which has been reported in one other patient with a hereditary TTP and is highly suggestive of cTTP (Scully, Blood 2014).
Conclusion: Our patient presented with a 4-year history of self-limiting episodes of headaches, numbness, dizziness, and weakness, and developed a large, right sided MCA territory infarction. Her cerebral angiogram was suggestive of vasculitis and she underwent treatment for presumed refractory CNS vasculitis. Her ADAMTS13 sequencing analysis, however, is ostensibly indicative of a hereditary TTP. While cTTP is better known to cause microvascular thrombosis with small vessel involvement, our experience suggests that cTTP may also present with vasculitis/vasculopathy type findings on angiography, and even large vessel disease, which may confound the diagnosis.

Poster # 809

ALLERGIC REACTION AND LACK OF RESPONSE TO FIBRINOGEN REPLACEMENT THERAPY IN AFIBRINOGENEMIA

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Background: Congenital afibrinogenemia is a life-threatening disorder with an estimated prevalence of one per million. Current treatments include fibrinogen concentrate or fibrinogen-containing blood products for acute bleeding. Patients who don't respond to replacement therapy may have fatal outcomes. Severe allergic reactions and development of neutralizing antibodies, though recognized complications in hemophilia therapy, are rarely reported in afibrinogenemia.
Objectives: We describe the strategy used to treat a 6-year-old girl with congenital afibrinogenemia who developed severe allergic reactions to fibrinogen products and diminished response to factor replacement.
Design/Method: Case report
Results: At 21 months old, our patient presented with a cheek hematoma and prolonged prothrombin time, partial thromboplastin time, thrombin time, and reptilase time with undetectable levels of functional and antigenic fibrinogen, consistent with afibrinogenemia. She initially responded to cryoprecipitate and RiaSTAP® infusions; however, after her third dose of RiaSTAP®, she developed an allergic reaction which progressed in severity despite premedication. A RiaSTAP® desensitization plan was formulated with the Allergy and Immunology service, which included utilizing 3 different solutions of increasing concentrations used in a stepwise fashion while slowly increasing the infusion rates. This plan led to improvement in her symptoms and an appropriate increase in fibrinogen activity. However, at 6 years old, with left tibial fracture, her fibrinogen levels remained undetectable after desensitization to RiaSTAP®. This raised concern for development of an inhibitor; however, mixing studies could not confirm the presence of a neutralizing antibody. After one week of empiric replacement therapy with no detectable response, the patient developed severe headache and hypertension with MRI showing findings of Posterior Reversible Encephalopathy Syndrome with subsequent seizure development from acute subarachnoid hemorrhage seen on CT. She was treated with continuous cryoprecipitate infusion in addition to tranexamic acid. One hour later, fibrinogen levels became detectable and continued to rise to above the normal range. She then transitioned to an alternative fibrinogen concentrate, Fibryga®, in order to maintain normal

fibrinogen levels. This response could be explained by repeated exposure to fibrinogen inducing immune tolerance and suppression of antibody formation, similar to immune tolerance induction utilized in hemophilia management. Her subarachnoid hemorrhage stabilized and she underwent incision and drainage of her tibial osteomyelitis.
Conclusion: The management of bleeding in congenital afibrinogenemia may be complicated by severe allergic reactions and lack of response to fibrinogen-containing therapies. Our patient successfully underwent surgical intervention and stabilization of an intracranial hemorrhage using an extensive desensitization protocol followed by frequent/continuous exposure to fibrinogen replacement products.

Poster # 810

HYPOFIBRINOGENEMIA DUE TO A NOVEL FGG MISSENSE MUTATION PRESENTING IN A FAMILY

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Background: Fibrinogen disorders may be acquired or inherited, and comprise two classes of plasma fibrinogen defects: type I deficiencies (afibrinogenemia and hypofibrinogenemia) with absent or low fibrinogen levels and type II deficiencies (dysfibrinogenemia) with reduced functioning of fibrinogen. Hypofibrinogenemia is often caused by heterozygosity in fibrinogen gene mutations.
Objectives: To present a novel missense mutation of the FGG gene resulting in hypofibrinogenemia in a family.
Design/Method: A 4 year-old female presented to the pediatric hematology/oncology clinic for a history of easy bruising and prolonged bleeding. She was found to have a low fibrinogen level of 46 mg/dL and a low fibrinogen antigen level of 113 mg/dL. Her family history was significant for hypofibrinogenemia in her mother, sister and one brother, who all had fibrinogen levels < 50 mg/dL and low fibrinogen antigen levels < 130 mg/dL. The family history was also significant for a number of shared phenotypic features including cutis aplasia, limb malformations and growth and developmental abnormalities, among others, thought to be related to an underlying genetic disorder. Due to her complex medical and family history, Whole Exome Sequencing (WES) was done to determine if there was an underlying genetic etiology responsible.
Results: Results of WES indicated that our patient is heterozygous for the c.1030G>A (p.D344N) alteration in the FGG gene located in coding exon 8 resulting in Aspartic acid being replaced by Asapargine. Co-segregation analysis revealed that the FGG c.1030G>A (p.D344N) alteration was also present in heterozygous state in the patient's mother, sister, and affected brother. The alteration was not present in the patients father or brother with normal fibrinogen levels. The shared morphological features presenting in this family were found to be due to a frameshift mutation in the loss of function of UBA2, however this mutation is not known to be associated with hematologic abnormalities.
Conclusion: We found a novel FGG gene missense mutation in a family presenting with prolonged bleeding found to have hypofibrinogenemia. The D344 amino acid is located in a functionally important protein domain responsible for the binding of calcium to the fibrinogen

gamma chain, which is necessary for proper function. Different alterations in the same amino acid have been observed in individuals with varying degrees of hypofibrinogenemia.

Poster # 811

ACQUIRED HEMOPHILIA: A RARE COMPLICATION OF PEDIATRIC IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE

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Background: Acquired hemophilia complicating idiopathic multicentric Castleman disease (iMCD), a lymphoproliferative disease, has not been previously described in the pediatric population. Acquired hemophilia A is a disorder that can result in severe or life threatening bleeding caused by autoantibodies against FVIII. This has been previously described in patients with autoimmune disorders, malignancies, and lymphoproliferative disorders, but is rare in children. Early recognition, control of bleeding diathesis, and eradication of the inhibitor are critical to successful treatment of acquired hemophilia A.
Objectives: Describe the novel finding of acquired hemophilia A in a pediatric patient with iMCD and resolution of the inhibitor with treatment.
Design/Method: Chart and literature review.
Results: A 14-year-old female, recently diagnosed with EBV mononucleosis, presented with fever, severe diarrhea and acute kidney injury. She was also found to have mild hemolytic anemia, thrombocytopenia, pleural effusion and mild but diffuse lymphadenopathy. Complete diagnostic work-up, including bone marrow biopsies and lymph node biopsy, was found to be compatible with TAFRO subtype (thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, organomegaly) of iMCD.She subsequently developed protracted bleeding from operative and venous access sites, along with excessive cutaneous bruising. Her bleeding was refractory to platelets, fresh frozen plasma, and cryoprecipitate transfusion, requiring multiple pRBC transfusions for support. Although her initial aPTT was normal and there was no previous personal or family history of bleeding disorders, her aPTT increased to 60 seconds and failed to correct with mixing. Further investigation showed <1% FVIII activity with an inhibitor titer at nearly 35 BU/ml. Her bleeding responded to management with recombinant factor VIIa and FEIBA.She was treated for iMCD with high dose steroids and weekly tocilizumab with improvement in fever and inflammatory markers, but had persistent EBV viremia, bleeding symptoms, and only marginal improvement in inhibitor titer. Following the addition of rituximab at week 3 of therapy, the factor VIII inhibitor resolved to undetectable levels by week 6 of treatment, with normal PTT and factor VIII activity. She has had no further episodes of significant bleeding or abnormal bruising. Although autoantibodies are common in iMCD, acquired hemophilia A has been reported only once previously, in a 71 year-old male, who similarly responded to rFVIIa and anti-CD20 therapy. It is not reported in children.
Conclusion: Acquired hemophilia A is a rare complication of iMCD in children and adults; rituximab, often recommended as second-line therapy for iMCD, offers a salutary side effect in control of the inhibitor clone.

Poster # 812

HIGH ESTIMATED SUCCESS RATE FOR EVERY-5-DAY PROPHYLAXIS WITH BAY 94-9027: DATA FROM PROTECT VIII

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Background: Efficacy and safety of BAY 94-9027 as prophylactic and on-demand therapy for patients with severe haemophilia A were shown in the phase II/III PROTECT VIII trial (NCT01580293) and its extension. In PROTECT VIII, patients with 0 or 1 breakthrough bleeds on BAY 94-9027 2×/week at 25 IU/kg for 10 weeks were eligible for treatment with extended-interval dosing. To investigate the clinical benefits of extended intervals, we conducted a post-hoc analysis of bleeding outcomes.
Objectives: Calculate the success rate of every-5-day (E5D) BAY 94-9027 prophylaxis.
Design/Method: PROTECT VIII was a part-randomised, open-label trial of 13 males aged < 18 years and 121 males aged ≥ 18 years with severe haemophilia A (FVIII <1%) and ≥150 FVIII exposure days. In prophylaxis groups, patients with >1 breakthrough bleed in a 10-week run-in period received 30–40 IU/kg 2×/week; patients with ≤1 breakthrough bleed were eligible for randomisation and received 30–40 IU/kg 2×/week, 45–60 IU/kg E5D or 60 IU/kg every 7 days (E7D) for the main 26-week study period. Patients completing the main study could enter an extension. A negative binomial model compared annualised bleeding rates (ABRs) pairwise between groups in the full study period; success rate of E5D treatment across all prophylaxis groups was estimated for the period from randomisation to the end of year 1 of the extension.
Results: Using data from the full study period and a negative binomial model, mean ABRs (95% CI) were comparable between patients on 2×/week (eligible for randomisation, n=8) and E5D dosing (n=30): 2.90 (1.16, 7.28) vs 3.73 (2.32, 6.01), respectively (p=0.6335). The success rate of E5D prophylaxis was estimated for the 104 on-study patients at the end of extension year 1 (n=21, 2×/week; n=41, E5D; n=42, E7D). A patient moved to 2×/week dosing during this period. Assuming this group was representative of the whole cohort (and excluding 11 patients who had >1 breakthrough bleed in the run-in), a success-rate estimate suggests that 87.2% of patients receiving BAY 94-9027 as prophylaxis in both main and extension periods would remain on E5D dosing.
Conclusion: Negative binomial analysis suggests the ABRs of patients treated with BAY 94-9027 twice weekly or E5D are comparable. The majority (87.5%) of prophylaxis patients are predicted to succeed on E5D dosing using a success-rate estimation. These analyses support the use of E5D dosing in most patients on BAY 94-9027 prophylaxis.This abstract was previously presented at EAHAD 2019, Prague.Research supported by Bayer (NCT01580293)

Poster # 813

BAY 94-9027 EFFICACY/SAFETY SUSTAINED FOR 5 YEARS: DATA FROM 33 PATIENTS (PROTECT VIII EXTENSION)

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Background: BAY 94-9027 is a B-domain-deleted recombinant factor VIII (FVIII), site-specifically PEGylated with a 60-kDa polyethylene glycol (PEG) to extend half-life. The efficacy and safety of BAY 94-9027 as prophylactic and on-demand therapy for patients with severe hemophilia A were demonstrated in the phase II/III PROTECT VIII trial and its extension.
Objectives: Analyze outcomes in patients from PROTECT VIII who completed ≥5 years of treatment.
Design/Method: PROTECT VIII was a partially randomized, open-label trial of 134 males aged 12–65 years with severe hemophilia A. Prophylaxis patients initially received BAY 94-9027 25 IU/kg twice weekly for 10 weeks. Patients with ≤1 spontaneous, joint or muscle bleed during this period were randomized to 45–60 IU/kg every 5 days or 60 IU/kg every 7 days for the main 26-week study period; patients not eligible for randomization or with ≥2 bleeds in the 10-week period, received 30–40 IU/kg twice-weekly. Twenty patients received BAY 94-9027 on demand as they had done prior to study. 121 patients entered the extension and 107 were in the prophylactic arm. Prophylaxis patients who switched regimen after the first 7 days of the extension were analyzed in a combined variable frequency group. Annualized bleeding rate (ABR), joint ABR, and safety outcomes were analyzed.
Results: 33 patients completed ≥5 years of treatment with BAY 94-9027 (median age at data cut-off, years [range] = 44.0 [18.0–65.0]). Median number of infusions (range) was 363 (272–546), and median (range) annual factor consumption was 3385 (2732–5053) IU/kg. Median (range) ABR was 2 (0–15) in the full study period, and 1 (0–12) for the final year. Corresponding joint ABRs were 1 and 0, respectively. Over the study period, study drug-related adverse events (AE)s occurred in 6 patients (18.2%); no patients had a study drug-related serious AE. There were no discontinuations for AEs. No patients had confirmed FVIII inhibitors.
Conclusion: Thirty-three patients received BAY 94-9027 prophylaxis for ≥5 years. The demonstrated efficacy of BAY 94-9027 was maintained across this period; in the last year of the extension, median ABR = 1 and a third of patients were free from bleeds. No new study-drug-related AEs and no evidence of long term toxicity of PEGylated product exposure were identified. These data support the use of BAY 94-9027 as a long-term treatment option for patients with hemophilia A.This abstract was previously presented at ASH 2018, San Diego.Research supported by Bayer.

Poster # 814

HEMOPHILIA EDUCATION: A QUALITY IMPROVEMENT AND OUTREACH INITIATIVE FOR SOUTH TEXAS

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Background: Patients and carriers with hemophilia A and B, an X-linked recessive bleeding disorder, do not understand disease inheritance and the importance of early diagnosis and treatment, leading to affected offspring, late diagnoses in at-risk individuals and increasing

morbidity. Hemophilia Treatment Centers (HTCs) were developed to meet the educational, financial, psychosocial, and medical needs of patients living with hemophilia. South Texas is a relative HTC desert, where families rely on outreach capabilities of regional HTCs, and access to genetic services is limited.
Objectives: To increase patient, caregiver, carrier and community knowledge regarding the genetics of hemophilia and management strategies while delivering high quality care among South Texas families affected by hemophilia.
Design/Method: A pre- and post- intervention survey study was performed in outreach clinics operated by the UTHealth South Texas HTC at Valley Baptist Medical Center in Harlingen, TX. The intervention consisted of genetic counseling and hemophilia education using toolkits to reinforce learning. Knowledge was assessed using a 5-point Likert-scale pre/post-test administered during the clinic visit on the day of the intervention and 3 months later to assess retention. Genetic testing was offered to patients and possible carriers. Patient satisfaction of genetic counseling was assessed using a validated survey. Community education regarding the genetics and management of hemophilia, impact of long-term morbidity, and availability of our HTC services was provided through community events.
Results: Three education and genetic counseling sessions were performed with 23 families. Those under the age of 18 years had a survey filled out by a parent/guardian, with 13 patients and 11 caregivers participating. A caregiver only filled out a survey once, regardless of number of children under the age of 18 years. Median age range of patient with hemophilia was 13-19 years. Pre-tests were completed by 24, post-tests by 22, and genetic satisfaction survey by 21 participants. Three month post-testing is ongoing. Survey results found improved knowledge in the following topics after the intervention: genetics/inheritance ($p=0.019$), types of bleeding ($p=0.04$), inhibitors ($p=0.006$), differences among recombinants ($p=0.013$), and how new products compare to traditional factor products ($p=0.013$). The genetic satisfaction survey yielded consistently high results, with averages above 4.7/5 for six questions with standard deviations ranging from 0 to 0.62.
Conclusion: This project demonstrates educational interventions are effective for increasing patient and caregiver disease-specific knowledge, and genetic counseling is well-accepted in this population.

Poster # 815

A QUALITY IMPROVEMENT INITIATIVE TO INCREASE PEDIATRIC EDUCATION IN VENOUS THROMBOEMBOLISM RISK

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Background: Pediatric venous thromboembolism (VTE) incidence has risen over the last decade. Despite this, there continues to be a lack of medical education and training for pediatric residents in VTE risk assessment. In comparison to adult medicine, VTE risk screening guidelines are not instituted at many hospitals for pediatric trainees to reference.
Objectives: This study aims to assess and increase pediatric resident knowledge and education in pediatric VTE risk assessment while implementing a hospital-wide clinical care guideline at the University of Illinois-Chicago Hospital in Chicago, Illinois.

Design/Method: Several plan-do-study-act (PDSA) cycles were completed throughout this study. The initial PDSA cycle consisted of pediatric admitting residents being surveyed to assess baseline VTE practices and knowledge. From this, we developed current and ideal process maps and key driver diagrams to guide our interventions. Over a twelve month period following the results of the baseline survey, multi-faceted interventions were continuously implemented following several PDSA cycles. These interventions mainly focused on 1) resident education, 2) implementation of a clinical decision-support tool, and 3) implementation of an electronic reminder system. Surveys were distributed throughout the entire intervention period to pediatric residents to assess pediatric admission VTE screening completion and practices. Surveys were determined to be successful if VTE screening and risk stratification were completed.
Results: Baseline survey data revealed themes of pediatric resident discomfort with VTE screening and minimal, if any, screening processes occurring. When risk screening was completed, it typically was vague or inappropriate. After interventions and at the end of the twelve month study period, there were a total of 49 completed surveys. We observed an improvement of pediatric resident understanding and VTE screening compliance went from 0% to 29% over the course of the 12 months. Medicine-pediatric residents had more successes than general pediatric residents (63% vs 22%, p=0.02), and fourth-year residents had more successes than first-year residents (12% vs 80%, p=0.06).
Conclusion: As pediatric VTE incidence rises, pediatric residents should be educated and trained in VTE risk assessment. By combining education, implementation of a decision-support tool, and electronic reminders, this may be achieved.

Poster # 816

A PHASE II DOSE-FINDING STUDY OF DALTEPARIN IN CHILDREN WITH VTE WITH OR WITHOUT CANCER

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Background: Venous thromboembolism (VTE) is an important clinical concern in children with cancer. Experience with dalteparin, a low molecular weight heparin, in the treatment of VTE in adults with cancer has been extensively published, but data in children are limited.
Objectives: We sought to determine the twice-daily dalteparin dose required to achieve target Anti-Xa levels of 0.5–1.0 IU/mL, as well as its pharmacodynamics (PD), efficacy, and safety in the treatment of VTE in children <19 years old, with or without cancer.
Design/Method: This prospective, multi-center, Phase 2, open-label study consisted of 3 phases: 1) Dose Adjustment Phase of up to 7 days, in which Anti-Xa levels were measured following the first, second or third dose of dalteparin, until achievement of the target level; 2) PD Phase of up to 7 days, to obtain 2 randomized PD plasma samples for Anti-Xa determination; and 3) Follow-Up Phase, to complete up to 90 days of anticoagulant therapy. Patients were assessed for symptomatic new or progressive (i.e., recurrent) VTE as well as clinically relevant bleeding during treatment. Surveillance VTE imaging was performed at 90±14 days.
Results: The safety population consisted of 38 patients who received at least 1 dose of dalteparin (<2 years: n=3; ≥2 to <8 years: n=8; ≥8 to <12 years, n=7; ≥12 to <19 years: n=20). Twenty-six

patients (68%) had a diagnosis of cancer at baseline, of which 23 (88%) were haematological malignancies. The median [range] dalteparin dose required to achieve target Anti-Xa levels decreased with age (<2 years: 207.5 IU/kg [201.5–213.5 IU/kg]; ≥2 to <8 years: 128.15 IU/kg [123.9–180.3 IU/kg]; ≥8 to <12 years: 125 IU/kg [124.5–152.6 IU/kg]; ≥12 to <19 years: 116.7 IU/kg [99.1–159 IU/kg]). Therapeutic Anti-Xa levels were achieved in 90% of patients within a mean (SD) of 2.6 days (1.54 days); the mean (SD) number of dose adjustments per patient was 0.7 (0.98). One patient (3%) developed symptomatic recurrent VTE. No patients reported clinically-relevant bleeding. Four patients (11%) had treatment-related serious adverse events. 62% of patients had complete resolution of their VTE at the end of the 90-day reporting period.
Conclusion: Twice-daily dalteparin dosing achieved therapeutic levels in 90% of children with or without cancer, with a satisfactory tolerability profile. The median therapeutic doses of dalteparin were higher for the two youngest age cohort groups (<2 years and 2 to <8 years).
NCT00952380Sources of Research Support: This study was sponsored by Pfizer Ltd.

Poster # 817

EVALUATION OF THERAPEUTIC ENOXAPARIN DOSING IN OBESE AND OVERWEIGHT ADOLESCENTS AND YOUNG ADULTS

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Background: The recommended treatment dosing of enoxaparin is based on actual body weight with no dosing limitation. Given the pharmacokinetics of enoxaparin, standard treatment doses given to overweight and obese patients could lead to over-anticoagulation. However, there is limited data to guide enoxaparin dosing recommendations in this population.
Objectives: To evaluate therapeutic enoxaparin dosing requirements in overweight and obese adolescent and young adult (AYA) patients treated at our institution.
Design/Method: We performed a retrospective analysis of a prospectively maintained institutional thrombosis database. We identified all AYA patients (≥12 years old) who were considered overweight or obese based on the definitions of the Centers for Disease Control and Prevention and who received weight-based twice daily therapeutic enoxaparin adjusted to achieve target peak anti-Factor Xa (anti-FXa) level of 0.5-1 U/mL according to our standard institutional protocol. Relevant data were extracted and summarized using descriptive statistics [median (interquartile range) or frequency (%)]. Data comparisons were performed using Mann-Whitney U test or Fisher exact test, as appropriate. Two-tailed p-value less than 0.05 was considered statistically significant.
Results: A total of 43 overweight and obese AYA patients were included in the analysis. The median age was 17.5 years (15.7-18.2) and 27 patients (63%) were females. The median body mass index (BMI) and weight were 37.2 kg/m2 (32.1-63.2) and 89.8 kg (78-102.7), respectively. Of the 43 patients, 29 (67%) were considered obese [median BMI 36.2 kg/m2 (31.9-39-8)] while 14 (33%) were considered overweight [median BMI 27.4 kg/m2 (26.3-28.6)]. The initial enoxaparin dose and the enoxaparin dose that achieved therapeutic anti-FXa levels were 1 mg/kg and 0.8 mg/kg (P-value=0.0004), respectively. Twenty-three patients (53%) required subsequent dose reduction while only 2 patients (5%) required dose increase. The median time to achieve

therapeutic anti-FXa level was 1 day (0.5-1). The initial and the highest peak anti-FXa levels were 0.86 U/mL (0.52-1.06) and 1.1 U/mL (0.84-1.3) (P<0.0001), respectively. There were no significant differences in enoxaparin dose requirement to achieve therapeutic anti-FXa level, initial or highest anti-FXa levels, frequency of dose reduction or time to achieve therapeutic anticoagulation in overweight patients compared to obese patients. One obese patient (2%) experienced thrombosis recurrence while receiving enoxaparin. There were no enoxaparin-related major or clinically relevant non-major bleeding complications.
Conclusion: Our study suggests that overweight and obese AYA patients require less than the recommended enoxaparin dose to achieve target therapeutic anti-FXa levels. Further, larger prospective studies are required to define optimal dosing strategy in this population.

Poster # 818

PEDIATRIC NEPHROTIC SYNDROME-RELATED THROMBOEMBOLISM: ROLE OF ANTICOAGULANT THROMBOPROPHYLAXIS

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Background: Thromboembolic events (TEEs) are a significant complication in pediatric nephrotic syndrome (NS). Important risk factors for development of TEEs include age, NS severity and central venous catheters (CVC). Despite the established risk of TEEs in pediatric NS, the role of anticoagulant thromboprophylaxis (AT) remains unclear.
Objectives: To describe the characteristics and treatment outcomes of NS-related TEEs and report our center's experience with targeted AT in patients with NS.
Design/Method: In 2014, we implemented a targeted AT protocol in patients with NS and persistent hypoalbuminemia who are steroid/immunosuppression resistant or have prior TEEs and who had no contraindication for anticoagulation. In patients with End Stage Renal Disease (ESRD), AT with enoxaparin was administered once daily after Hemodialysis (HD)/Peritoneal Dialysis (PD) with close monitoring of anti-Factor Xa (anti-FXa) levels and adjustment of dose and/or frequency to achieve target peak anti-FXa and maintain trough anti-FXa ≤0.3 IU/mL. AT was continued until remission of NS. We identified patients with NS-related TEEs and patients with NS who received AT. Relevant data were extracted from the electronic medical records and were summarized using descriptive statistics [median, (interquartile range)].
Results: Nine patients experienced 11 TEEs [pulmonary embolism (6), cerebral sino-venous thrombosis (2) and superficial/deep vein thrombosis (3)]. None of the patients were on AT prior to developing TEEs. TEEs in 6/9 patients were encountered ≤1 month of developing NS. Five patients were treated with enoxaparin (4) or warfarin (1). The remaining 4 patients (age >16 years, no ESRD) were prescribed rivaroxaban and rivaroxaban levels were monitored regularly during therapy [median rivaroxaban level 248 ng/ml (160-342)]. Nineteen patients with NS (median age 5 years, 12 patients had a CVC) received AT for median duration of 9 months (3.5-15). Ten patients with ESRD (9 HD, 1 PD) received AT with enoxaparin. The median peak and trough anti-FXa were 0.6 IU/mL (0.42-0.78) and 0.17 IU/mL (0.05-0.27), respectively. The remaining 9 patients without ESRD received AT with either enoxaparin (5) or rivaroxaban (4). Bioaccumulation of enoxaparin occurred in 1 patient with ESRD, which resolved after

decreasing dose frequency. There were no treatment/prophylaxis failures or major bleeding events. One patient with ESRD on enoxaparin AT developed clinically relevant non-major bleeding.
Conclusion: Serious TEEs remain a significant complication in pediatric NS. Targeted AT with close laboratory monitoring was feasible and appeared to be safe and efficacious. Our study also suggests that rivaroxaban is a promising agent for the treatment/prevention of NS-related TEEs and warrants further studies.

Poster # 819

OUTCOMES OF PEDIATRIC ACUTE PULMONARY EMBOLISM: A SINGLE-CENTER COHORT STUDY

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Background: Pulmonary embolism (PE) in children is a rare thrombotic event. However, PE can be associated with serious complications and its incidence in pediatric patients is rising. There is limited pediatric outcome data.
Objectives: To report outcomes of children with PE managed at a tertiary pediatric center.
Design/Method: We analyzed prospectively collected registry data from the Children's National Health System thrombosis database. We identified all patients with a diagnosis of PE followed at our institution since 2010 and compared patients who experienced recurrent events to those without recurrence. Relevant data were extracted and summarized using descriptive statistics [median (interquartile range) or frequency (%)]. Data comparisons were performed using Mann-Whitney U test or Fisher exact test. Two-tailed p-value <0.05 was considered statistically significant.
Results: We identified a total of 69 PEs affecting 59 patients. The median age at diagnosis was 17 years (15-19) and 35 patients (59%) were females. The median number of visits to the emergency room (ER) and the median duration of symptoms prior to diagnosis of PE were 1 visit (1-5) and 2 days (0.5-3), respectively. Of the 69 events, 28 events (41%) were hospital-associated PEs. A concurrent deep vein thrombosis was present in 21 events (30%). Twenty-three events (33%) were considered unprovoked PEs and the majority (78%) of provoked PEs were non-catheter-related events. Fifty-five events (80%) were non-massive PEs, 11 (16%) were sub-massive PEs, and 3 (4%) were massive PEs. A major thrombophilia-defined as inherited deficiency of antithrombin, protein C, or protein S, or antiphospholipid antibody syndrome-was identified in 9 patients (15%). All patients received anticoagulation with 14 remaining on indefinite anticoagulation. Additional therapies included systemic thrombolysis (7), catheter-based interventions (4), and surgical thrombectomy (1). Seventeen patients (24%) returned to the ER due to persistent or recurrent symptoms and 2 patients (12%) were found to have recurrence/progression. Seven patients (12%) experienced $\geq$1 recurrent events. Patients with recurrent PE were similar in characteristics to patients who did not have recurrent PE except for a significantly higher frequency of unprovoked events (77% vs. 19%, $p<0.01$) and major thrombophilia (57% vs. 6%, $p<0.01$). All three patients with massive PE (5%) died. Three patients (5%) developed chronic thromboembolic pulmonary hypertension.

Conclusion: Our study indicates that PE in children is associated with significant morbidity and mortality. Patients with unprovoked events and those with major thrombophilia appear to have higher risk for recurrence. Multicenter, prospective studies are needed for developing optimal evidence-based risk stratified treatment approaches.

Poster # 820

IS PEDIATRIC STROKE ON YOUR DIFFERENTIAL?

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Background: Twenty to forty percent of children who suffer a stroke will die. Of those who do live, 50-80% will have permanent neurologic deficits. Early identification and intervention increases survival and decreases sequelae yet recognition of a stroke is often missed. With an incidence of only 6.4/100.000 in children aged 0-15, the rarity, the atypical presentations compared to adults and potential confounding stroke mimickers often impede prompt diagnosis.
Objectives: Improve nurses and nurse practitioners recognition that children do have strokes and expedite early assessment and diagnosis that is imperative to good outcomes. This presentation will advance nursing skills in the recognition of stroke types and symptoms to familiarize them with the tools needed, such as the Pediatric National Institute of Health Stroke Scale (PedNIHSS), to aid timely diagnoses.
Design/Method: Retrospective institutional data review of children presenting with strokes between 07/2017-03/2018 was compared to the nationally recognized predisposing conditions. The prevalence of risk factors in this review exceeded what is commonly known and has been instrumental in refining our screening process, development of nurse assessment tools and a stroke alert protocol.
Results: Seventy-five incidences of stroke were identified during an 8 month period, the majority were through the Emergency department with initial triage by a nurse. The causes and risk factors were categorized and 11 diagnostic groups were documented. There were 7 outliers to the commonly recognized associated conditions. All children who met assessment criteria for suspected stroke, average two –three per month, received the PedNIHSS evaluation. This screening process also identified stroke mimickers who did not require additional evaluations such as MRI. Those who were positive for PedNIHSS, defined as a score greater than 4, received timely intervention which has shown to improve long term outcomes. An acute stroke alert protocol that includes an electronic order set was developed and its efficacy continues to be evaluated at quarterly multidisciplinary meetings.
Conclusion: Pediatric stroke is a reality and as nurse providers we need to be knowledgeable and attentive to presenting symptoms. Stroke needs to be in our differential, we need to be familiar with the PedNIHSS and we need to intervene promptly for the best possible outcomes. The results of this study will equip the nurse provider with diagnostic stroke knowledge, the screening tool for early identification and the stroke activation protocol that has been institutionally successful for prompt evaluation, stabilization and treatment.

Poster # 821

TREATMENT OUTCOMES OF INFANT ARTERIAL THROMBOSIS

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Background: The acute management of infant arterial thrombosis (AT) aims to prevent serious consequences such as skin necrosis, and loss of limb or organ viability. Consensus guidelines suggest immediate removal of the culprit indwelling catheter, if present, and anticoagulation with or without thrombolysis or surgical thrombectomy. However, data regarding the optimal duration and overall outcomes with these treatments is limited.
Objectives: We aimed to evaluate the treatment outcomes of infants with AT treated with a short course of anticoagulation at Texas Children's Hospital and to identify predictors of clot resolution.
Design/Method: We retrospectively reviewed the clinical and radiologic data of children under 1 year of age with radiologically proven AT.
Results: Seventy patients met inclusion criteria. Patients had a median age of 2 months (range 0 to 12 months) and weight of 3.7 kg (range 0.82 kg to 12.2 kg) at the time of diagnosis with AT. Fifty-six (81%) had congenital heart disease. A total of 42 (62%) patients had a limb that was viable or marginally threatened, 25 (36%) immediately threatened, and 1 (2%) had an irreversibly ischemic extremity at diagnosis. Forty-four (64%) patients received anticoagulation alone or in combination with antithrombin concentrate (n=15, 22%), aspirin (n=7, 10%), or thrombectomy (n=3, 4%). Median duration of anticoagulation was 4 weeks (range 0 to 12 weeks). Variables associated with complete clinical and radiological resolution during the four week (or less) treatment period were: partial arterial occlusion at diagnosis (compared to complete occlusion) (clinical: 100% vs 80%, p=0.0002; radiological: 70% vs 47%, p=0.0002), and clinical improvement during the first 24 hours of treatment (clinical: 90% vs 70%, p=0.05; no difference in radiological outcomes). No significant differences in clinical or radiological outcomes were noted when comparing patients who developed AT following an arterial catheterization procedure versus placement of an indwelling arterial catheter, or patients who had therapeutic levels of anticoagulation for more than 50% of the treatment period compared to those who did not. Four patients (6%) experienced minor GI bleeding and 1 patient developed worsening of an intracranial hemorrhage following initiation of therapy.
Conclusion: Most patients in this cohort had favorable clinical response to treatment but persistent arterial occlusion was seen in 21%. Partial arterial occlusion and clinical improvement noted within 24 hours of therapy initiation were associated with improved treatment outcomes in infant AT. These findings highlight the need to improve our current management of AT.

Poster # 822

CATASTROPHIC THROMBOSES AS A PRESENTATION FOR CONGENITAL DISORDER OF GLYCOSYLATION TYPE 1B

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Background: Congenital disorders of glycosylation (CDGs) are caused by inborn errors in glycan metabolism. There are several subtypes of CDGs and patient presentation could affect multiple organ systems with primary issues including hypoglycemia, neurologic deficits, liver dysfunction and coagulopathy among others. This case review highlights the importance of using clinical judgment to differentiate between common and rare causes of recurrent thromboses in children. CDG Type 1b is crucial to recognize and diagnose as it is effectively treated with oral mannose supplementation, however, without accurate diagnosis the patient may suffer from repeated thromboses and other complications. While advancement in genomic studies and availability of whole genome exome sequencing (WES) identified the underlying disorder in this case, an understanding of the presentations of CDGs may lead to earlier intervention and prevention of complications of a CDG in other patients.
Objectives: We present this case of an infant with Type 1B CDG to illustrate the various clinical presentations of the disorder which include severe thromboses, as well as the management of thromboses in patients with this condition.
Design/Method: This is a case presentation of a rare disease along with a general review of the management of CDG Type 1B.
Results: In this report, we describe a toddler who initially presented with a large MCA infarct and intracranial herniation. He also was found to have a venous sinus thrombosis and while receiving neurosurgical management for these clots, he developed multiple deep vein thromboses in his extremities. After an exhaustive hypercoagulable workup, which was unremarkable, he underwent WES, which revealed mutations in the Mannosephosphate Isomerase (MPI) gene that were consistent with a diagnosis of CDG type IB. He was successfully treated with oral mannose, the standard of care for this condition, and remains on long-term therapeutic anticoagulation.
Conclusion: CDGs are caused by enzymatic defects in the synthesis and processing of oligosaccharides or glycoproteins. Clinically, patients with type 1 CDGs can present with chronic diarrhea caused by a protein-losing enteropathy with coagulopathy and subsequently, failure to thrive. Type 1b of the CDGs is unique in that it can be treated effectively with oral mannose supplementation. This case review highlights the importance of using clinical judgment and reason to differentiate between the different causes of recurrent hypoglycemia as well as causes of recurrent thromboses in toddlers. If this rare condition is diagnosed early on, early treatment can avoid significant morbidity for patients.

Poster # 823

CONGENITAL GLYCOSYLATION DISORDERS AS AN UNUSUAL CAUSE OF THROMBOPHILIA

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Background: Congenital disorders of glycosylation (CDG) are genetic disorders in enzymes that synthesize glycan or attach glycans to glycolipids and glycoproteins. Phosphomannomutase

(PMM2)-CDG is the most common form and presentation ranges from severe neurological abnormalities to minimal manifestations. PMM2-CDG presents with coagulopathies from abnormal glycosylation of glycoproteins involved in coagulation including factor(F) VIII, FXI, antithrombin (AT), protein C and protein S.
Objectives: To describe a case of PMM2-CDG presenting with pulmonary embolism (PE) and AT deficiency. To discuss the thrombin generation assay (TGA) profile in CDG.
Design/Method: A 16-year-old African American female with cerebellar atrophy and developmental delay was diagnosed with PE. Thrombophilia workup was notable for decreased AT activity which remained low at 49%, 35% and 43%. Antithrombin antigen was low at 31% and she was presumably diagnosed with type I AT deficiency. Concomitantly, she experienced neurologic deterioration and an extensive evaluation included whole exome sequencing which was negative for mutations in SERPINC1 gene but positive for the mutation for PMM2-CDG. To further classify her thrombophilia, TGA was performed using calibrated automated thrombinoscope thrice when anticoagulation was appropriately held. The lag time (LT; min), endogenous thrombin potential (ETP; nMol.min), thrombin peak (nMol) and the time to peak (TTP; min) were determined as mean±SD.
Results: We compared TG parameters for our case to 1) healthy controls at our institution (n=42) and 2) type I AT deficiency patients based on published data*(n=14). Our patient has a prolonged LT of 4.33 min±0.8 and TTP of 8.44 min±0.9 compared to healthy controls (LT 2.07 min±0.34, TTP 4.45min±0.57) and type I AT deficiency (LT 1.9 min±0.8, TTP 5.5min±1.3). Thrombin peak of 249nM±32 in our case is similar to healthy controls (260nM±42) but lower than type I AT deficiency (493.4nM±75). ETP was elevated (2552nM.min±175) compared to healthy controls (1208nM.min±243) but was less than type I AT deficiency (3366nM.min±668).
Conclusion: CDG is a form of inherited thrombophilia that should be considered in the differential for AT deficiency without mutations in SERPINC1 gene or positive family history of thrombosis. CDG has differing TGA profiles from type I AT deficiency. CDG has overall increased thrombin burst compared to healthy controls to suggest hypercoagulability, however, is less hypercoagulable than type I AT deficiency based on TGA profiles. Further studies are needed to understand the role of hypoglycosylated forms of AT, discern the risk of recurrence and establish guidelines for anticoagulation management of CDG patients.*Alhenc-Gelas, Journal of Thrombosis and Haemostasis, 2010

Poster # 824

COAGULOPATHY AND RELATED COMPLICATIONS FOLLOWING SCLEROTHERAPY OF CONGENITAL VENOUS MALFORMATIONS

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Background: Congenital venous malformations (VM) are slow-flow vascular anomalies that are known to cause coagulation abnormalities. These abnormalities are caused by vessel injury and inflammation which activate coagulation and consumption of clotting factors, and generate thrombin and fibrin. This phenomenon is called localized intravascular coagulopathy (LIC) and is characterized by an elevated D-dimer, low plasma fibrinogen, and/or thrombocytopenia. LMWH is commonly given to prevent complications from LIC in patients with VMs undergoing

surgical or interventional procedures; however there are very few evidence-based guidelines to guide appropriate anticoagulation in high-risk patients.
Objectives: To retrospectively evaluate the incidence of LIC and other coagulopathic-related complications in patients following sclerotherapy of congenital venous malformations.
Design/Method: This study retrospectively reviewed medical records of 129 patients at a single, tertiary, multi-disciplinary vascular anomalies clinic from January 2016 to October 2018 with a diagnosis of congenital VM who underwent sclerotherapy and had coagulation profile, including D-dimer, fibrinogen and platelets, evaluated at or near the time of procedure. LIC was defined as a D-dimer five times upper limit of normal, fibrinogen <150mg/dl, and/or platelet count <150K/mcL and diagnoses were categorized as low or high risk based on suggested guidelines released through the ASPHO Vascular Anomalies Special Interest Group. High risk diagnosis included extensive (whole limb or multi-focal) VM, combined slow-flow vascular malformations, and CLOVES. Coagulopathy-related complications from sclerotherapy that were recorded included clinically relevant bleeding, deep vein thrombosis (DVT), and thrombophlebitis.
Results: In this cohort of 129 patients, 59.7% were females with the lower extremity at 46.5% (60/129) being the most common location of VM. Average age at the time of sclerotherapy was 10.9 yrs (range: 1.2-19.2). 17/129 (13.2%) had evidence of LIC at or near the time of sclerotherapy. Of patients with high-risk VMs [31/129 (24%)], 14/31 (45.2%) had laboratory values consistent with LIC. Only 5/129 patients (3.9%) were anticoagulated with LMWH pre and/or post sclerotherapy all with a high risk diagnosis. In sum, 418 sclerotherapy procedures were performed (347 with 3% STS, 17 with 1% STS, 26 with bleomycin, 24 with 3% STS and bleomycin, 1 with 1% STS with bleomycin and 4 with alcohol) with no complications of bleeding, DVT or thrombophlebitis related to sclerotherapy.
Conclusion: Despite abnormal coagulation laboratory values in patients with VM undergoing sclerotherapy, LMWH may not be necessary pre and post procedures. Further studies are needed to evaluate what patients and types of VMs may benefit from anticoagulation before and after sclerotherapy procedures.

Poster # 825

MOLECULAR CHARACTERIZATION OF FAMILIAL LYMPHEDEMA IN A PEDIATRIC PATIENT

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Background: Approximately one-third of familial cases of lymphedema will have identifiable molecular etiology, in comparison to less than 10% of sporadic cases. Although pathogenic variants in the FLT4 gene are the most common cause of hereditary lymphedema, variants in twenty other genes have also been associated with it, representing de novo, autosomal dominant, and autosomal recessive inheritance patterns. The causative variants affect VEGFR-3 signaling, and ultimately the RAS/MAPK and PI3K/AKT pathways.
Objectives: To present a case report of familial lymphedema with a HGF variant.
Design/Method: Case report.
Results: We report a 17-year-old Caucasian female who presented with right foot and ankle

swelling and tenderness persisting for two months. No history of trauma reported. Family history is significant for lymphedema, as her mother, maternal aunt, and maternal grandmother are all affected Ultrasound did not identify deep vein thrombosis and complete blood count and D-Dimer were normal. She was diagnosed with praecox lymphedema. Genetic testing was recommended given her family history highly suggestive of an autosomal dominant hereditary lymphedema. Next generation sequencing on patient's blood sample for a customized gene panel of sixteen genes associated with hereditary lymphedema in a CLIA-certified commercial laboratory identified a nonsense maternally-inherited variant of uncertain clinical significance in the HGF gene (c.1321C>T p.R441X), leading to protein truncation. The HGF gene, encoding hepatocyte growth factor, has been associated with autosomal dominant syndromic lymphedema in case report.
Conclusion: This case highlights the emerging association of HGF with familial lymphedema, and the importance of molecular characterization of these patients to further understand both familial and sporadic lymphedema, and develop targeted treatments. Testing for the identified HGF variant was highly recommended for the patient's affected maternal aunt, affected maternal grandmother, and unaffected sister to further characterize its clinical significance.

Poster # 826

TRIAL OF SIROLIMUS IN GORHAMS DISEASE

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Background: Gorhams Disease, also known as Gorham-Stout Disease, massive osteomyelitis, or vanishing bone disease, is a rare disorder of poorly understood etiology. Patients undergo bone resorption without proliferation and have significant soft-tissue swelling. No standard treatment is currently available. Novel use of the MTOR inhibitor sirolimus has shown some promise in slowing the progression of this devastating disorder.
Objectives: Immunosuppressant agents such as sirolimus have been used effectively in transplant patients for prophylaxis of organ rejection. We hypothesize that this agent can also successfully slow the progression of bone resorption in patients with Gorhams Disease. This case series describes the diagnosis, progression, and therapy of three patients at Cook Children's Medical Center with varying levels of severity of Gorhams Disease.
Design/Method: This case series employed the use of review of electronic medical records for three patients at Cook Children's Medical Center.
Results: Three patients were diagnosed with Gorhams Disease between 2011 and 2014 and are now being treated within the Cook Children's Medical Center Hematology-Oncology practice. One patient has involvement of her skull base and ear canals, diagnosed after ear canal abnormalities were detected on CT following meningitis. The second patient has involvement of her posterior ribs and T7-T12 vertebral bodies, with thoracic instability and necessity of either remaining in the supine position or wearing a back brace. The third patient has involvement of his left lower extremity and left hemipelvis, necessitating a left above the knee amputation and had subsequent disease progression prompting further treatment with sirolimus. The first two patients have had radiographic improvement after the addition of twice daily sirolimus, while the third patient has had stabilization of his disease.

Conclusion: Gorhams Disease is a rare condition with potentially devastating consequences. The introduction of sirolimus, in select cases, has appeared to either stabilize or slowly reverse the progression of the disease. While more studies need to be performed to understand the full effects of sirolimus on this disease, it has the potential to have a significant role in the treatment of Gorhams.

Poster # 827

INFANTILE HEPATIC HEMANGIOENDOTHELIOMA 9 YEARS SINGLE CENTER EXPERIENCE (CCHE 57357)

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Background: Infantile hepatic hemangioendothelioma (IHHE) is the most common hepatic vascular tumor in children
Objectives: We report our large single center experience of patients with IHHE over nine years to determine the outcome for those patients and strategic plan for treatment
Design/Method: Retrospective analysis of 28 IHHE patients treated at the Children Cancer Hospital Egypt (CCHE 57357) from April 2008 through April 2017 with a minimum follow up of one year
Results: Twenty-eight patients (18 females, 10 males) were diagnosed with IHHE with a median age at diagnosis of 3 months (range, 0.3 to 11 months). Twenty-four patients were diagnosed solely on radiologic criteria and four by biopsy when the lesions did not meet radiologic criteria. The lesions were multifocal (n=12), focal (n=10), and six were diffuse. The patients initially presented with hepatomegaly 22 (78.6%), pallor 16 (57.1%), mechanical respiratory distress 7 (25%), jaundice 4 (14.3%), and skin hemangioma 3 (10.7%). Six (21.4%) patients initially had low T3 and T4, two of whom needed L thyroxin and all of these were either with diffuse or multifocal disease. Eleven patients did not receive any treatment, one patient only underwent resectional surgery. Sixteen patients received treatment, nine patients responded well to first line propranolol / prednisolone while seven patients (1 focal, 3 multifocal, 3 diffuse) needed salvage treatment in the form of vincristine (n=1), cyclophosphamide(n=1), interferon(n=2), vincristine and cyclophosphamide (n=2) and one had embolization and cyclophosphamide. Twenty-five patients are alive while three patients have died, due to heart failure, coagulopathy and pneumonia as a disease complication. All the three patients who died initially presented by multifocal disease, two of them progressed early within 3-4 weeks of starting treatment
Conclusion: Overall patients do well with multiple approaches. For those with small focal lesions, these patients do well even without treatment while for those with multifocal/diffuse disease, there is a high incidence of low T3 T4. Some of these patients did well without additional therapy although those with rapidly progressive lesions during treatment may do poorly

Poster # 828

UNIQUE CASE OF ELEVATED AFP SECONDARY TO MULTIFOCAL INFANTILE HEPATIC HEMANGIOMAS

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Background: Infantile hemangiomas, the most common pediatric vascular malformation, are characterized by abnormal endothelial cell proliferation and blood vessel architecture. Multifocal cutaneous presentations are a risk factor for extracutaneous, most commonly hepatic, involvement. Alpha-fetoprotein (AFP) is a plasma protein produced in the fetus predominantly in the liver or yolk sac. It is often associated with hepatic lesions, yolk sac lesions, or teratomas when present postnatally. Here we describe a unique case of elevated AFP in a infant born extremely premature with multifocal hepatic hemangiomas.
Objectives: To describe a case of elevated AFP in an infant with multifocal infantile hemangiomas.
Design/Method: Case Report
Results: A 2 month old Caucasian female born at 25 weeks gestation presented with worsening direct hyperbilirubinemia. Abdominal ultrasound was obtained and showed four subcentimeter circumscribed hyperechoic liver lesions. Over the next few weeks, hepatic labs continued to worsen. Repeat ultrasound imaging four weeks later showed nine faintly hypoechoic hepatic lesions. AFP was obtained and was elevated at 82,486 ng/ml while VMA was unremarkable and HVA was slightly elevated. Abdominal MRI showed multiple high signal liver lesions consistent with hemangiomas. It was also noted at that time that patient had several subcutaneous hemangiomas. Repeat AFPs ranged from 450,607 to 307,358 ng/ml. Propranolol trial with close monitoring of size was initiated, but was held due to development of necrotizing enterocolitis (NEC). Once the patient recovered from NEC, liver biopsy confirmed the presence of multifocal infantile hepatic hemangiomas. The patient was restarted on propranolol. Serial ultrasounds were performed to monitor for treatment efficacy. The patient was discharged home on propranolol. Follow-up MRI and abdominal ultrasound was obtained showing resolution of almost all of the hemangiomas. AFP decreased significantly to 27.4 ng/ml. The patient was continued on propranolol until 1 year of age.
Conclusion: Elevated alpha-fetoprotein is a diagnostic marker for multiple hepatic and germ cell lesions. This case illustrates how the workup for malignant hepatic lesions is complicated in premature infants due to differences in baseline alpha-fetoprotein when adjusted for gestational age. It also emphasizes that a elevated serum AFP level is not always associated with solitary hepatic masses such as hepatoblastoma.

Poster # 829

TO TREAT OR NOT TO TREAT MULTIFOCAL EPITHELIOID HEMANGIOMA OF THE CALVARIUM

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Background: Epithelioid hemangioma (EH) is an intermediate grade vascular tumor that rarely involves the bony calvarium (2%) or presents multifocally (18-25%). There are no reports of skull-based EH in children less than 5 years of age. In adults, osseous EH can be locally aggressive, spreading to regional lymph nodes. Surgical curettage or resection is recommended. The natural history of this vascular tumor in asymptomatic children has not been previously described.
Objectives: We report a 29-month-old male with multifocal epithelioid hemangiomas of the skull who was managed conservatively and had spontaneous improvement in his disease burden over 1.5 years.
Design/Method: A healthy 29-month-old toddler presented with two swollen areas on his posterior skull incidentally detected by the family. One month later, these masses were larger and firmer with no associated pain, fever, or other symptoms. Past medical history and family history were unremarkable. The patient was admitted in March, 2017 with a suspected diagnosis of Langerhans cell histiocytosis. A head CT revealed multifocal expansile lytic lesions of the calvarium, the largest measuring 6.4cm transverse and 2cm in thickness. An open biopsy was diagnostic for an epithelioid hemangioma. This pathology was confirmed by three academic centers nationally. The child has been followed closely with periodic imaging studies for 1.5 years.
Results: Pathology revealed an intraosseous epithelioid hemangioma with secondary myofibroblastic proliferation involving the galea and skull. There were irregularly nodular areas of acute hemorrhage with prominent capillary proliferation and cellular spindle cells arranged in fascicles. Mitoses in spindle cell areas, necrosis, and sarcomatous changes were not identified. Immunostaining was negative for GLUT1 and positive for CD31, ERG, and FOSB, the latter diagnostic of EH. Genomic evaluation for CAMTA1 and TFE3 were negative (CHOP Cancer Fusion Panel), ruling out an aggressive epithelioid hemangioendothelioma. Serial imaging studies obtained every 3-6 months demonstrated interval resolution of the lytic lesions along with increased mineralization of the calvarium. The cranium was focally thickened in the affected areas. No intracranial or soft tissue involvement was noted. Clinically, the patient has remained healthy and well since diagnosis.
Conclusion: Epithelioid hemangiomas typically occur in the long tubular bones of adult patients (median age 35 years). Management guidelines are based upon the adult experience. This is the first report of a toddler with multifocal calvarial EH who has demonstrated spontaneous radiographic improvement over 1.5 years. Aggressive surgical treatment of EH may not be necessary for asymptomatic pediatric patients.

Poster # 830

MULTIFOCAL LYMPHANGIOENDOTHELIOMATOSIS WITH THROMBOCYTOPENIA (MLT) WITH PULMONARY HEMORRHAGE

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Background: Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT) is a rare vascular disorder characterized by skin and extracutaneous involvement. Gastrointestinal lesions

are most common, and pulmonary lesions have also been reported.
Objectives: Describe the clinical presentation, evaluation, and treatment of a pediatric patient with MLT manifesting as pulmonary hemorrhage.
Design/Method: Data was obtained by electronic medical record review of this patient's diagnosis, treatment, and outcome at the Monroe Carell Jr. Children's Hospital at Vanderbilt.
Results: A 5-month-old male presented with anemia (hemoglobin 8.7g/dL), thrombocytopenia (platelets 119,000), and history of apparent mild hematemesis, the latter of which resolved with change in formula. With normal bone marrow biopsy and endoscopy, immune thrombocytopenia was suspected; observation was undertaken. At ten months of age he presented with worsened microcytic anemia (hemoglobin 7.6g/dL), thrombocytopenia (platelets 16,000), cough, and continued apparent hematemesis at home. Evaluation revealed significant hemoptysis, hypoxemia, and air space disease on chest x-ray consistent with pulmonary hemorrhage. Differential diagnosis included vasculitis, pulmonary arteriovenous malformation, and idiopathic pulmonary hemosiderosis. CT showed extensive bilateral pulmonary and splenic nodules, prompting lung biopsy. Pathology demonstrated focal proliferative vascular lesions with endothelial cells positive for CD31, CD34, LYVE-1, and negative for D2-40, TTF-1, PROX1, and cytokeratin, consistent with MLT. A trial of corticosteroids produced stable respiratory status and normalized hemoglobin and platelets. Further MR imaging showed parenchymal nodules, hilar lymphadenopathy, and a vertebral body hemangioma. Secondary to the rarity of the presentation and disease, pathology and radiology were sent for outside review, confirming the diagnosis of MLT. Sirolimus therapy was initiated, and the patient was successfully weaned off corticosteroids over two months. At three years of age, after successful weaning of sirolimus, an attempt was made to discontinue this therapy, but there was recurrence of thrombocytopenia and worsened parenchymal nodular disease. Sirolimus was restarted, which was again weaned off at five years of age. The patient continues to be monitored with surveillance imaging and labs and has maintained normal cell counts and stable respiratory status off sirolimus.
Conclusion: Multifocal lymphangioendotheliomatosis with thrombocytopenia is a rare vascular anomaly with a diverse clinical phenotype. This entity usually presents with skin lesions and thrombocytopenia in the newborn period and can be misdiagnosed because of its variable presentation. Here we report a patient with MLT, who presented with extensive pulmonary involvement, manifesting as pulmonary hemorrhage in the setting of thrombocytopenia. MLT is an important diagnostic consideration in the evaluation of an infant with hemoptysis and/or hematemesis with thrombocytopenia.

PBMTC Abstracts
Poster # 1001

SIMULATION BASED EDUCATION FOR THE EVIDENCE BASED MANAGEMENT OF CHIMERIC ANTIGEN RECEPTOR -T CELL RELATED ENCEPHALOPATHY SYNDROME AND CYTOKINE RELEASE SYNDROME

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Background: Chimeric Antigen Receptor T-cell therapy (CAR-t) for pediatric and young adult patients with relapsed or refractory B cell precursor acute lymphoblastic leukemia (ALL) is associated with high overall remission rates but also with significant complications.[1] Cytokine release syndrome (CRS) and CAR-T cell Related Encephalopathy Syndrome (CRES), are life-threatening sequelae that may occur in patients who receive CAR-t. Prompt recognition and appropriate management may impact outcomes, since approximately half of patients require critical care intervention. [1] At our institution an interprofessional education (IPE) module (didactic and web-based tutorials) was used to foster initial interdisciplinary competency in CAR-t management. [1-4] In 2018, we developed an IPE simulation- based training module (SIM) to reinforce didactic training and provide a skill based assessment tool.
Objectives: Determine the feasibility and efficacy of an IPE SIM to train and foster confidence among interdisciplinary providers (including critical care and immunotherapy nurses, medical trainees, pharmacists, advanced practice providers and nocturnalists) in CAR-t management among pediatric patients.
Design/Method: An interdisciplinary training workshop organized by an IPE CAR-t committee will be held for 50-70 learners in February, 2019. A didactic lecture on CAR-t management will be followed by a SIM. The SIM will explore CAR-t patient selection, leukapheresis management, bridging chemotherapy and complications, CRS and CRES recognition, differential diagnosis and appropriate management. Promptness and efficacy of care escalation trees and transitions of care among interdisciplinary teams will be assessed. Validated tools will evaluate participants pre, immediately post and 2 months post SIM.
Results: The feasibility of SIM based training as a sustainable method for IPE in CAR-t management will be assessed by the IPE committee. Learner's baseline competency in CAR-t management will be compared to post-SIM competency. A pre and post self-assessment will be conducted to determine whether the SIM is effective in promoting interdisciplinary confidence in CAR-t management.
Conclusion: Early intervention for CRS and CRES may be critical for improved outcomes.[1] Provider groups may be inadequately prepared to manage patients with CRS and CRES due to lack of training or infrequent exposure. SIM training may create opportunities for bridging gaps between medical knowledge and clinical practice in a risk free, realistic environment without adverse patient effects.

Poster # 1002

ADOPTIVE T-CELL THERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA TARGETING MULTIPLE TUMOR ASSOCIATED ANTIGENS

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Background: HSCT is a curative option for patients with high-risk ALL but relapse remains the major cause of treatment failure. CD19 CAR T cells have shown remarkable efficacy in treating leukemic relapse post-HSCT but their use is limited to CD19+ malignancies and antigen

negative relapses are increasingly being reported.
Objectives: To overcome the limitations of single antigen targeting and immune escape, we developed a strategy to generate donor-derived T cell lines simultaneously targeting PRAME, WT1 and Survivin (multiTAAs) expressed by both B and T ALL for adoptive transfer to high risk HSCT recipients.
Design/Method: We generated donor multiTAA-T cells by culturing PBMCs with autologous DCs loaded with a mastermix of pepmixes spanning all 3 target antigens in the presence of a Th1-polarizing/pro-proliferative cytokine cocktail.
Results: To date, we have generated 14 clinical multiTAA-T cell lines comprising CD3+ T cells (mean 94±9%) with a mixture of CD4+ (mean 21±28%) and CD8+ (mean 52±24 %) cells, which expressed central and effector memory markers and recognized the targeted antigens based on IFNg ELIspot analysis. None of the lines reacted against non-malignant patient-derived cells (4±3% specific lysis; E:T 20:1) - a study release criterion.
Thus far we have treated 10 high-risk ALL patients to prevent disease relapse post-transplant. Eight of the 10 patients infused were children and the median age of the cohort was 17 years. Five patients were infused at dose levels 1 (5x10e6/m2), three at dose level 2 (1x10e7/m2) and 2 at dose level 3 (2x10e7/m2). Infusions were well tolerated with no dose-limiting toxicity, GVHD, CRS or other adverse events. Two patients were not evaluable per study criteria as they received >0.5mg/kg of steroids within 4 weeks of infusion and were replaced. Seven of the 8 remaining patients infused remain in CCR a median of 9 months post-infusion (range 2-25 months). We detected the expansion of tumor-reactive T cells in patient peripheral blood post-infusion against both targeted (WT1, Survivin, PRAME) and non-targeted antigens (SSX2, MAGE-A4, -A1, -A2B, -C1, MART1, AFP and NYESO1) reflecting epitope and antigen spreading. The single patient who relapsed showed no evidence of tumor-directed T cell expansion despite receiving 3 additional infusions at 4 week intervals.
Conclusion: Infusion of donor-derived multiTAA-T cells to patients with ALL post-HSCT is feasible, safe and as evidenced by expansion and antigen spreading in patients, may contribute to disease control. This strategy maybe a promising approach to prevent leukemic relapse after HSCT.

Poster # 1003

SUCCESSFUL USE OF ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANT IN THE TREATMENT OF A FAMILY WITH GATA2 DEFICIENCY

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Background: GATA2 deficiency is a rare genetic disorder caused by an autosomal dominant mutation. Affected individuals may present with Emberger syndrome characterized by lymphedema, hematologic anomalies, and predisposition for myelodysplastic syndrome (MDS) and leukemia. Additional manifestations include congenital deafness and immunodeficiency. Hematopoietic stem cell transplant remains the only curative therapy.

Objectives: We report a case of three siblings with GATA2 deficiency with a 1-bp deletion in exon 5 of the GATA2 gene. Congenital deafness and pancytopenia with monocytopenia were common amongst the three affected siblings. Each individual had characteristic features, which were unique compared to their siblings. All were successfully treated with a peripheral blood stem cell transplant (PBSCT).
Design/Method: Case series of three siblings with GATA2 deficiency.
Results: Case 1 is a 17 year old deaf female with lymphedema, pancytopenia, and severe acne. Testing confirmed heterozygosity for a GATA2 mutation, without evidence of MDS. She underwent a matched related PBSCT with her unaffected sister as her donor. Her preparative regimen included busulfan, fludarabine and abatacept. 5 months post-transplant, she is without transplant related morbidity. She has persistent lymphedema, but resolution of acne, and no other sequelae of GATA2 deficiency.
Case 2 is the 17 year old deaf twin brother of case 1, presenting with an incidental finding of pancytopenia, and history of lymphadenitis and acne. He was found to have the identical GATA2 mutation and MDS. He underwent a 9/10 matched unrelated PBSCT. He tolerated a regimen of busulphan, cyclophosphamide, and post-transplant cyclophosphamide. His course was complicated only by acute grade I GVHD of skin and esophagus. Thirteen months post-transplant, he remains without evidence of MDS.
Case 3 is the 13 year old deaf sister with a history of respiratory failure secondary to influenza, chronic warts, hypogammaglobulinemia, and pancytopenia. Work up demonstrated GATA2 deficiency without MDS. She underwent a 9/10 matched unrelated PBSCT with the same preparative regimen as her sister. Her course was complicated only by grade I skin acute GVHD. 5 months post-transplant she has no cytopenias or warts.
Conclusion: These cases highlight the varying phenotypes of GATA2 deficiency, even amongst a single family with an identical mutation. It further highlights that PBSCT is a feasible and safe option for patients with GATA2 deficiency, even prior to developing MDS or leukemia. This family consented to cryopreservation of bone marrow for research purposes, presenting a unique opportunity to further investigate the pathogenesis and heterogeneous manifestations of GATA2 deficiency.

Poster # 1004

ENDOTHELIN-1 INHIBITION IN A CHILD WITH TRANSPLANT ASSOCIATED THROMBOTIC MICROANGIOPATHY FOLLOWING AUTOLOGOUS STEM CELL RESCUE FOR HIGH RISK NEUROBLASTOMA - POSSIBLE THERAPEUTIC ROLE

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Background: Transplant associated-thrombotic microangiopathy (TA-TMA) is a serious complication among transplant recipients. Patients who undergo high dose chemotherapy along with autologous stem cell rescue can potentially develop severe TA-TMA. There is evidence that pro-inflammatory endothelial activation plays a central role in the pathophysiology of this condition. Therefore, endothelin blockage could be an additional therapeutic option. The use of

novel molecular analysis techniques has helped identify patients with genetic susceptibility for TA-TMA. Recent studies describe a number of complement gene variants that predispose to TA-TMA, including variants in the CFHR3-CFHR1 gene.
Objectives: To describe the clinical course in a case of TA-TMA (CHFR3-CFHR1 deletion) with refractory response to terminal complement blockage but very responsive to bosentan, an endothelin-1 receptor antagonist.
Design/Method: A PubMed search was conducted for queries including "transplant associated-thrombotic microangiopathy"□, "CFHR3-CFHR1", "endothelin-1 inhibition"• , and "bosentan"• .
Results: A 10-year-old African American female with high-risk neuroblastoma received tandem transplants with cyclophosphamide/thiotepa, and carboplatin/etoposide/melphalan (CEM). On day +80 following CEM therapy, she presented with severe hypertension, elevated creatinine, proteinuria, and signs of hemolysis. Further laboratory testing was consistent with TMA including elevated CH50 and terminal soluble C5b-9, and peripheral schistocytes. She started induction treatment with eculizumab with modest response. Subsequently she received immunotherapy, which flared up her TA-TMA with severe cytokine storm, leading to capillary leak syndrome and multiorgan failure requiring invasive respiratory support and hemodialysis. Due to the severity of the disease and minimal response to eculizumab, a genetic panel was sent, which was positive for a homozygous CFHR3-CFHR1 deletion. The patient continued to deteriorate, developing pulmonary hypertension. She was started on bosentan as a strategy to treat her pulmonary hypertension, and potentially her TMA-associated endothelial damage. There was a significant clinical improvement from a hematologic, cardiovascular, respiratory and renal standpoint, with decreased transfusions, antihypertensive medications, respiratory support, and dialysis requirements.
Conclusion: TA-TMA is a multiphasic entity in which constant systemic endothelial activation might represent an important therapeutic target. The clinical and laboratory improvement noted after initiation of bosentan suggests a beneficial role in the management of TA-TMA that warrants further investigation. The presence of a homozygous CFHR3-CFHR1 deletion is associated with multivisceral and often fatal TA-TMA.

Poster # 1005

IMPACT OF CORTICOSTEROID USE ON THE DEVELOPMENT OF OBESITY AND METABOLIC SYNDROME IN SURVIVORS OF PEDIATRIC HEMATOPOIETIC CELL TRANSPLANT

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Background: Despite improvement in overall survival, hematopoietic cell transplant (HCT) patients endure transplant-related complications including delayed cardiovascular and endocrine disorders. These complications are often secondary to adjunctive medications. Corticosteroids are commonly used in this population both as chemotherapy and in treatment of graft-versus-host-disease. Previous studies have identified patient and treatment-related risk factors for

developing cardiovascular disease. Few have investigated the impact of corticosteroid therapy on development of these late complications.
Objectives: To determine whether corticosteroid use impacts the development of metabolic syndrome in recipients of pediatric HCT.
Design/Methods: Retrospective study investigating pediatric (≤21 years) patients with hematologic malignancies who underwent HCT from 1999-2008 at Children's Hospital of Wisconsin. Chi-square and Fisher's exact tests were used to determine association between steroid usage and categorical outcomes. For continuous outcomes, Kruskal-Wallis and Mann-Whitney tests were used. Metabolic syndrome was defined by the presence of ≥ 3 of the following: hypertension (requiring treatment), diabetes, elevated BMI (overweight/obese), triglycerides > 150 or total cholesterol > 170. Per CDC guidelines, overweight is defined as BMI 85^{th}-94^{th} percentile and obesity greater than 95^{th}. All patients were evaluated 2 years post-HCT.
Results: Sixty-two patients met selection criteria (ALL, n = 34; AML, n= 23; CML, n=3; MDS, n=2). 40% received steroids prior to and 74% following HCT. Eighty-three percent received total body irradiation. At 2-year follow-up, 14% were prescribed an antihypertensive medication, 13% a lipid lowering agent, 8% had a diagnosis of diabetes mellitus, 38% were overweight or obese, and 17% met criteria for metabolic syndrome. Pre-transplant steroid exposure was a risk factor for elevations in BMI (p=0.05). There was no statistically significant association between pre and/or post-transplant corticosteroids with the following 2-year outcomes: Diabetes Mellitus (p=0.82), anti-hypertensive (p=0.79) or lipid-lowering prescriptions (p=0.17). There was no statistically significant association between any steroid exposure and triglyceride level at the 2-year follow-up when treated either as a continuous variable (p=0.17) or as a discrete variable (i.e. triglyceride>150) (p=0.24). Lastly, no statistically significant association was observed between any corticosteroid usage and metabolic syndrome in our cohort (p=0.52).
Conclusion: While pre- and/or post-transplant corticosteroid use did not demonstrate a significant effect on hypertension, diabetes, or dyslipidemia at 2-year follow-up, we did identify a relationship between pre-transplant steroid exposure and overweight/obese status. Given the high incidence of these diagnoses in HCT recipients, further research is needed to better understand how steroid exposure may influence the development of long-term cardiovascular and endocrine outcomes.

Poster # 1006

REGULATORY TYPE 1 T CELL INFUSION IN MISMATCHED RELATED OR UNRELATED HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR HEMATOLOGIC MALIGNANCIES

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Background: A major complication of unmanipulated mismatched hematopoietic stem cell transplant (HSCT) is Graft versus-Host Disease (GvHD), which results in significant morbidity and increased non-relapse mortality. Novel strategies to reduce GvHD and improve long-term tolerance between mismatched donor-host pairs include regulatory T cell therapy. We are

investigating a new cell product named T-allo10 which contains suppressive anergic cells and is enriched in regulatory type 1 T cells (Tr1). The main advantage of adoptive immunotherapy with Tr1 compared to other regulatory T cells is the host alloantigen specificity that is established in the donor Tr1 during in vitro culture in the presence of IL-10 and host tolerogenic dendritic cells.
Objectives: To assess the tolerability and safety of escalating doses of T-allo10 cell infusions that can be feasibly manufactured to meet release specifications in mismatched related or mismatched unrelated unmanipulated HSCT in patients with hematologic malignancies.
Design/Method: It is a single center, open label, phase 1 trial in 3+3 design for 3 escalating doses of T allo 10 cells.
Results: Here we report the preliminary results of our phase I trial (IND 17292) on the use of escalating doses of T-allo10 cells for patients aged 3-45 years affected by hematological malignancies. At present, we treated two patients. The donors were class I and class II HLA-mismatched for patients one and two, respectively. The GvHD prophylaxis consisted of Sirolimus and Mycophenolate and was serotherapy and Calcineurin inhibitory-free. Patients received 1x106 T-allo10 cells/Kg on Day-1. No adverse events were observed after the T-allo10 cells infusion. Both patients met the safety criteria and are alive and disease-free 15 and 7 months post-HSCT, respectively. Tr1, phenotypically defined as CD4+CD45RA-CD49b+LAG3+ were detectable in the peripheral blood of patients after the infusion. At day 28 post-HSCT, Tr1 represented 12% of circulating memory CD4+ T cells in patient #1 and 3% in patient #2. TCR sequencing of T-allo10 cells prior and after infusion showed a restricted clonotype diversity with persistence of certain clonotypes in vivo, demonstrating Tr1 cell survival.
Conclusion: Our preliminary data show that the T-allo10 cell infusion is safe and well tolerated. T-allo10 cells are detectable in the recipients after the infusion and traceable by TCR clonotype analysis.

Poster # 1006

TRANSPLANT ASSOCIATED THROMBOTIC MICROANGIOPATHY AFTER TRANSPLANT: A PBMTC/PALISI MULTI-CENTER COLLABORATIVE

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Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is a severe complication of hematopoietic stem cell transplant (HSCT).
Objectives: Determine incidence, risk factors and outcomes for patients who develop TA-TMA following HSCT.
Design/Method: All patients were prospectively screened for TA-TMA at participating centers with daily

CBC, renal panel, and blood pressure; twice weekly LDH; and weekly urine analysis, urine protein to creatinine from the start of the preparative regimen through the first 30 days. All labs were transitioned to weekly from day +30 to +100. TA-TMA was diagnosed if 1) pathologic evidence of TA-TMA (e.g., renal biopsy with evidence of TA-TMA), or if meeting laboratory/clinical markers diagnostic for TA-TMA (4 of 7 concurrent markers are required) including elevated LDH, schistocytes on peripheral blood smear, de novo thrombocytopenia or anemia, hypertension >99% for age, proteinuria, and/or terminal complement activation (elevated plasma sC5b-9). Each site retrospectively reviewed the data from screened patients from their respective center, and these data were aggregated to determine outcomes.
Results: 339 patients (203 males, 60%) received TA-TMA screening at seven centers from January 1, 2017, through June 30, 2018. Median age at the time of transplant was 5.4 years (IQR 2.8-14.3). The majority of patients underwent transplant for malignancy (n=223;66%) followed by immune dysfunction (n=64;19%). TA-TMA was diagnosed in 70 patients (21%) at a median of 22 days (IQR 14-44) post-transplant. Of patients with TA-TMA, 19 patients (27%) underwent autologous transplant and 51 (73%) allogeneic versus 111 (41%) and 158 (59%) transplant recipients without TA-TMA, respectively (p=0.04). Patients with TA-TMA had significantly increased bloodstream infections (35/70;50% vs. 83/269,30%; p=0.005) and higher need for intensive care admission (27/70,39% vs. 22/269,8%; p=0.0001). Non-relapsed mortality during the first 6 months was significantly higher in the TA-TMA group (9/70,13% vs. 9/269,3%; p=0.004). Acute kidney injury developed in 42 (61%) patients with TA-TMA, 6 (8%) were diagnosed with pulmonary hypertension, and 5 (7%) were diagnosed with moderate to large pericardial effusions. In patients diagnosed with TA-TMA, 27 (39%) were treated with eculizumab and 3 (4%) received plasmapheresis.
Five additional centers are in the process of obtaining IRB approval, and we anticipate an additional 150 patients will be included in the analysis at the time of PBMTC.
Conclusion: In this multi-center cohort we report a high incidence of TA-TMA after pediatric HSCT. Patients with TA-TMA have higher morbidity and mortality when compared to patients without TA-TMA.

Poster # 1007

TA-TMA – THE AUBMT EXPERIENCE AT CHILDREN'S HOSPITAL LOS ANGELES

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Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is recognized as severe transplant complication in neuroblastoma patients receiving tandem autologous stem cell transplants (aSCT). TA-TMA affects small vessels in the body and can result in multi-organ injury syndrome leading to significant morbidity and mortality. TA-TMA can be diagnosed by affected tissue biopsy or by constellation of clinical symptoms/laboratory tests.
Objectives: Identification of the patient population most at risk for developing TA-TMA, in an effort to educate nurses about prospective screening, early signs/symptoms, treatment of TA-TMA.

Design/Method: We performed prospective screening for TA-TMA using newly proposed diagnostic criteria by Jodele et al for one year and reviewed clinical/laboratory data in autologous aSCT patients.
Results: Twenty patients with solid tumors underwent total 37 aSCT using myeloablative chemotherapy. Thirteen patients had high risk neuroblastoma, each received tandem aSCT according to ANBL0532, regimen B. Seven patients had medulloblastoma (n=3), AT/RT (n=1), CNS germinoma (n=1), HD (n=1), non-HD (n=1).
In overall cohort TA-TMA was diagnosed in 4 patients (20% incidence). All TA-TMA cases occurred in patients with neuroblastoma after second tandem transplant with carboplatin, etoposide and melphalan (CEM), resulting in 30% (4/13) incidence of TA-TMA after CEM chemotherapy.
TA-TMA occurred at the median of 21 days after aSCT. All patients met required diagnostic criteria (elevated LDH, de novo anemia, thrombocytopenia, schistocytosis, severe hypertension and nephrotic range proteinuria). Two of 4 patients met high risk TA-TMA criteria, including the evidence of complement activation measured by elevated sC5b-9 level and received complement blocking agent eculizumab for TA-TMA therapy. The other 2 patients had earlier diagnosis of VOD, later developed TA-TMA while on defibrotide therapy. One patient received therapeutic plasma exchange for TA-TMA. All patients had severe hypertension requiring >2 antihypertensive medication with acute kidney injury. One patient required renal replacement therapy and remained in intensive care unit for 41 days, for combined VOD and TA-TMA therapy. Median hospitalization time was 29 days (range 22-145). All patients with TA-TMA are alive at 6 months after transplant, but had significant delay to start their maintenance therapy
Conclusion: We showed high incidence of TA-TMA in patients with neuroblastoma receiving CEM therapy in agreement with reports from other large centers. Prospective monitoring should be implicated for these high risk patients to initiate clinical interventions promptly. Awareness and education about TA-TMA symptoms, diagnostics and management should be increased among nursing teams as they play an essential role in the care of these complex patients.

Poster # 1008

$CD34^+$ CELL DOSE OF MARROW GRAFT PREDICTS OUTCOMES IN PEDIATRIC RECIPIENTS OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Studies analyzing transplant outcomes have focused on the influence of total nucleated cell (TNC) dose with bone marrow (BM) graft.
Objectives: We sought to determine the cell parameters associated with optimal outcomes in children.
Design/Method: The effect of donor graft dose and composition on outcomes in 257 children with hematologic malignancies at our institution from 2000 through 2015 using un- manipulated BM after first transplant was studied. Outcome measures included neutrophil and platelet engraftment, acute graft-versus-host disease, relapse, non- relapse mortality, and overall survival. Graft composition variables such as $CD34^+$, $CD3^+$, and TNC were categorized based on three cutoffs of 25%, 50%, and 75% percentiles, and compared above and below each cutoff for each of the outcomes.

Results: The median $CD34^+$ and TNC doses were 6.3 x 10^6 /kg, and 3.4 x 10^8/kg, respectively. $CD34^+$ dose greater than 9 x 10^6/kg (75^{th} centile) improved overall survival in patients receiving a BM graft (HR = .56, *P* = .04). The 2-year and 5-year OS for $CD34^+$ cell dose ≤ 9 x 10^6/kg was 69% and 59%, respectively, and for $CD34^+$ cell dose > 9 x 10^6/kg was 79% and 75%, respectively. $CD34^+$ dose greater than 6 x 10^6/kg (50^{th} centile) increased chance of platelet engraftment (HR 1.56, *P* = .002). Non-engraftment of platelets was associated with decreased OS (HR 3.58, *P* < .001). $CD34^+$ dose did not influence GVHD or relapse. TNC dose did not influence outcomes.

Conclusion: $CD34^+$ dose rather than TNC is associated with outcomes with a BM graft.

Poster # 1009

HEXAVIRAL SPECIFIC T-CELLS TARGETING HPIV3, CMV, EBV, ADV, HHV6 AND BKV AFTER STEM CELL TRANSPLANT

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Background: Viral infections are a significant cause of morbidity and mortality in patients awaiting immune reconstitution following hematopoietic stem cell transplantation. Adoptive immunotherapy using virus specific T-cells (VSTs) has been shown to prevent and treat viral infections in immunocompromised hosts. Human Parainfluenza Virus-3 (HPIV3) is a common cause of severe respiratory illness in immunocompromised patients. It has no approved antiviral therapies and has not previously been used as a target for T cell therapeutics.
Objectives: The primary aim was to determine whether donor derived hexaviral specific T-cells are effective in preventing and treating CMV, EBV, AdV, BK virus, HHV-6, and HPIV3.

Design/Method: This was a "first in man" study where we studied the antiviral effect in 8 patients who received hexa-valent VSTs after stem cell transplant on a Phase I trial. Assessment of virus-specific immunity was measured by IFN-g ELIspot. Viral loads for the primary targeted viruses were measured at specific time points post VST infusion.
Results: Three patients were treated for active CMV and had resolution of viremia. Two patients treated for active BK virus had complete resolution of symptoms and viremia, while one had resolution of hemorrhagic cystitis but fluctuating viral loads in the blood and urine. Three patients were treated prophylactically. Two patients did not develop any infections, while the other developed EBV viremia requiring rituximab. Two patients received VSTs under expanded access for emergency treatment -1 patient was treated disseminated adenoviremia and the second patient was treated for HPIV3 pneumonia. These critically ill patients demonstrated partial clinical improvements, but VST persistence was likely hindered by concomitant steroid use which resulted in incomplete antiviral responses. ELISpot showed evidence of antiviral T-cell activity in 3 of 4 evaluable patients by 3 months post-infusion, with in vivo VST expansion detectable in 2 patients.
Conclusion: Preliminary results show that hexaviral specific VSTs are safe and may be effective

in preventing and treating multiple viral infections. Further studies are warranted to determine if VSTs are effective against active HPIV3 infections.

Poster # 1010

PERICARDIAL EFFUSION FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN: FREQUENCY, RISK FACTORS, AND OUTCOMES

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Background: Pericardial effusion (PCE) may complicate hematopoietic stem cell transplantation (HSCT). However, existing data regarding incidence, risk factors, and outcomes of PCE in this setting have been derived from small single-center studies.
Objectives: This study aimed to assess the frequency of PCE, risk factors for PCE, and outcomes associated with PCE in children post-HSCT using the Pediatric Health Information System (PHIS) multi-center administrative database.
Design/Method: All patients < 21 years old who underwent first HSCT from 1/1/2005 to 9/30/2015 were identified from the PHIS database for inclusion. The occurrence of PCE was identified using ICD-9 code 420.xx present during or following the HSCT encounter. Diagnosis codes are not associated with exact dates in PHIS, so PCE during the initial HSCT encounter was assumed to occur halfway between the date of HSCT and the date of discharge, and at the time of admission for subsequent encounters. The Kaplan-Meier method was used to assess freedom from PCE. Multivariable Cox proportional hazard models were then used to assess independent risk factors for the development of PCE and the impact of PCE on post-HSCT survival.
Results: A total of 10,730 patients were included. Of this group, 766 (7.1%) developed a PCE at a median time of 70 days post-HSCT (IQR 33-166 days). Of those who developed a PCE, 85 (11.1%) developed tamponade at a median time of 116 days post-HSCT (IQR 62-251 days), and 248 (32.4%) received a pericardial intervention (i.e. pericardiocentesis or pericardial window). Independent risk factors associated with a PCE included older age (AHR 1.02, 95%CI 1.00-1.03), female sex (AHR 1.3, 95%CI 1.1-1.6), PCE prior to HSCT (AHR 1.9, 95%CI 1.2-3.0), graft-versus-host disease (AHR 1.3, 95%CI 1.1-1.5), thrombotic microangiopathy (AHR 3.3, 95%CI 2.3-4.6), malignant indication for HSCT (AHR 1.3, 95%CI 1.1-1.6), allogeneic HSCT (AHR 2.5, 95%CI 1.9-3.3), heart failure post-HSCT (AHR 2.9, 95%CI 2.4-3.6), and arrhythmia post-HSCT (AHR 2.0, 95%CI 1.7-2.4). The presence of a pericardial effusion following HSCT was associated with worse 5-year overall survival (54% vs 78%; log rank $p<0.001$) and was independently associated with post-HSCT death (AHR 2.0, 95%CI 1.6-2.4).

Conclusion: Among a large multi-center cohort of pediatric HSCT recipients, pericardial effusion occurred in 7.1% of patients. There are identifiable risk factors for developing a PCE, which may help delineate patients who require increased surveillance. Post-HSCT PCE is

associated with post-transplant death. Further research is required to determine the best approach to this complex population.

Poster # 1011

OUTCOMES AFTER ALLOGENEIC STEM CELL TRANSPLANT FOR PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND CNS INVOLVEMENT

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Background: Hematopoietic stem cell transplant (HSCT) is a curative strategy for pediatric patients with high risk and relapsed Acute Lymphoblastic Leukemia (ALL), including those with Central Nervous System (CNS) involvement. There are limited data on the outcomes following HSCT in pediatric patients with ALL and CNS disease and no consensus on optimal CNS prophylaxis and treatment
Design/Method: We performed a retrospective chart review of pediatric patients who underwent HSCT for ALL from 2006-2016 at our institution. We compared outcomes for patients with CNS positive and CNS negative ALL. CNS positivity was defined as any CNS leukemic involvement either at original diagnosis of leukemia or relapse prior to HSCT.
Results: One hundred and thirty two patients were evaluated of which 82 (62%) were CNS negative and 50 (38%) were CNS positive. Patient and transplant characteristics were similar in both group except for disease status (Table 1). There was a higher proportion of patients with CR2/> relapse (36, 72%) in the CNS positive group compared to the CNS negative group (43, 52%) (p=0.029). Majority received myeloablative conditioning (MAC) that was TBI based in all but 3 patients. Cranial boost (CB) was given prior to HSCT to 30/50 CNS positive patient per institutional standards. Outcomes for both CNS positive and CNS negative patients were comparable (OS, DFS and Cumulative Incidence (CI) of relapse in patients that were CNS positive was 58%, 50% and 26% respectively and for CNS-negative : 68%, 66%, 23% respectively; P-values: 0.301,0.297, 0.896). In the CNS negative group, 0/23 relapses after transplant occurred in the CNS compared to 4/14 relapses in the CNS positive group. All 4 patients with CNS relapse post-transplant were in CR3 and had relapsed in the CNS at referral to HSCT. Two of the 4 received a reduced intensity regimen and 1 had not received a CB pre-HSCT due to prior CNS irradiation.
Conclusion: Our experience demonstrates that the outcomes after HSCT for pediatric patients with ALL with and without CNS involvement are comparable. For CNS positive patients the use of TBI-based MAC regimens with CB pre-transplant is associated with similar rates of DFS and relapse without deleterious effect on OS compared to the CNS negative group, despite a higher proportion coming to HSCT in CR2> relapse. No additional CNS prophylaxis is required for patients that are CNS negative

Poster # 1012

IMMUNOMODULATION WITH ANAKINRA AS A POTENTIAL TREATMENT ROUTE FOR CONGENITAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

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Background: HLH is a life-threatening hyperinflammatory syndrome that results from immune system dysregulation. Primary HLH is often linked to immunodeficiencies such as Griscelli type 2 (GS2) syndrome. Current evidence suggests that the pathogenesis of HLH is distinct in such patients and aggressive immunosuppression is contraindicated. Without HSCT, patients with familial HLH are at high risk of succumbing to the syndrome. Newer agents that act to mitigate cytokine action, such as Anakinra, may be an innovative approach to avoid systemic chemotherapy while bridging these patients to HSCT.
Objectives: We report primary HLH treated with anakinra, an interleukin-1 receptor antagonist, and prior to HSCT in an infant with GS2 and heterozygous *Rab27a* mutations. We propose that Anakinra may mitigate hyperinflammation in such patients.
Design/Method: A PubMed search was conducted for queries including HLH, Griscelli syndrome, and anakinra. Relevant papers were reviewed.
Results: A 2-month-old male presented with HLH: cytopenias (hemoglobin 8.8 g/dL and platelets 26,000/mL), hypofibrinogenemia (109 mg/dL), sCD25 elevation (66300 U/Ml), low or absent NK cell function, and splenomegaly. Family history was significant for a full sibling who died at age 5 years presumably secondary to EBV-associated sepsis. She was thought to have Chediak-Higashi based on phenotype; however *LYST* gene testing was negative. Retrospectively, she likely carried a diagnosis of GS2 and died from unrecognized HLH. Genetic testing obtained from our patient noted heterozygous *RAB27A* gene mutation, confirming a diagnosis of HLH in the presence of GS2. He was started on anakinra, dexamethasone, and tacrolimus as a bridge to HSCT.
Upon initiation of immunotherapy, the patient's ferritin and fibrinogen levels improved to 105 and 131. Anakinra was weaned between Days -23 and -21 in preparation to HSCT. However, patient was noted to have an abrupt rise in ferritin, drop in fibrinogen, and 5 days of unexplained fever so the dose was steady until Day -10. His conditioning regimen consisted of melphalan, thiotepa, rATG, and fludarabine followed by methotrexate and tacrolimus GVHD prophylaxis. Patient tolerated 9/10 HLA-matched unrelated donor HSCT. Neutrophil engraftment occurred on Day +15 will full chimeric engraftment on Day +99. He is 5 months post-transplant and well with no infectious complications.
Conclusion: We report a case of an infant with GS2, heterozygous *Rab27a* mutations, and HLH who received immunomodulation with anakinra prior to HSCT. This presentation should alert providers to consider anakinra in immunodeficient patients with primary HLH awaiting HSCT for whom chemotherapy and aggressive immunosuppression pose substantial risks.

Poster # 1013

QUALITY IMPROVEMENT INITIATIVE TO IMPROVE SLEEP IN PEDIATRIC HSCT PATIENTS AND CAREGIVERS

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Background: Sleep is an essential biological function vital for physiological rest, healing and emotional well-being. Sleep disruption, defined as interruptions or alterations to the normal sleeping patterns, is commonly seen in patients and caregivers with lengthy hospital stays such as patients undergoing hematopoietic stem cell transplant (HSCT). Sleep disruption in the caregivers of hospitalized patients can lead to increased stress and fatigue, decrease quality of life and ultimately affect the caregiver ability to support their loved one.
Objectives: The global aim of our quality improvement initiative was to improve sleep quality in HSCT patients and caregivers. The smart aim of our project was to decrease nighttime noise from 46 decibels (dB) (mean baseline data) to 38dB (WHO recommends night outside noise of less than 40dB) in a 6-month period and increase sleep efficacy from a mean of 60 % (combined patient and caregiver) to 90% in the following 6 month period.
Design/Methods: Through a longitudinal observational cohort study, the quality and quantity of sleep in pediatric patients undergoing HSCT and their caregivers was studied; we identified a high level of sleep disturbance utilizing actigraphy and recounted poor sleep through qualitative assessments. We then performed a cross sectional focus group analysis of patients, caregivers and medical staff to identify the factors associated with poor sleep. Several PDSA (plan-do-study-act) interventions for each key driver took place and were adopted.
Results: The most common factors associated with sleep disruption were noisy room entries, overnight trash pulls, loud hallway noise and noisy hospital staff. A simplified failure mode analysis identified four main key drivers; reliable nighttime awareness system, quiet nighttime nursing system, unobtrusive nighttime cleaning process and nighttime awareness maintenance system. The overnight mean dB decreased to 42dB (9% reduction). Overnight noise spikes above 60dB have decreased from a mean of 271 spikes to a mean of 151 spikes (44% reduction). Percentage of sleep efficacy results and follow up of quantitative and qualitative sleep assessments of patients and caregivers is ongoing.
Conclusion: With a quality improvement initiative, we identified factors that negatively impact sleep and performed interventions that successfully mitigate these factors.

Poster # 1014

SUCCESSFUL HLA-IDENTICAL BONE MARROW INFUSION WITHOUT CONDITIONING IN A NEWBORN WITH PURINE NUCELOSIDE PHOSPHORYLASE DEFICIENCY: A NOVEL CASE REPORT AND REVIEW OF THE LITERATURE

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Background: Purine nucleoside phosphorylase (PNP) deficiency is a rare autosomal recessive immunodeficiency due to defective purine metabolism leading to Severe Combined Immunodeficiency (SCID). It is characterized by recurrent infections, failure to thrive and progressive neurological abnormalities. Age of presentation has ranged from 4 months to 6 years. The only curative treatment is hematopoietic stem cell transplantation (HSCT).
Objectives: Describe the first reported case of PNP identified by newborn screen, with contaminant congenital CMV, successfully treated and infused with unconditioned HLA-identical bone marrow.
Design/Method: Retrospective review of the patient electronic medical record and review of the literature.
Results: A small for gestational age (SGA) male infant was reported to have an abnormal newborn screen for SCID using the T cell receptor excision circle (TREC) assay on DOL 7. Initial studies revealed profound lymphopenia with low T, B and NK cells, abnormal lymphocyte proliferation to mitogens and no evidence of maternal engraftment. He was also noted to have CMV viremia and viruria on admission. PNP activity was low, and genetic testing found a pathogenic homozygous mutation in *PNP* (c.286-18G>A), confirming the diagnosis. In addition, with the constellation of CMV viremia and viruria, small for gestational age, failed hearing screen and head ultrasound with bilateral parenchymal calcifications, congenital CMV was diagnosed and subsequently treated with dual therapy ganciclovir and foscarnet. By DOL 30, CMV was undetectable by qPCR. At two months of age, he underwent 10/10 HLA-matched, unmanipulated, CMV positive, sibling hematopoietic stem cell infusion with no conditioning regimen. Two hundred days post-transplant, he remains stable with mixed chimerism, improving T and B cell function and increasing PNP activity. To date, he remains infection free and developmentally appropriate with no evidence of GVHD.
Conclusion: To our knowledge, this is the first reported case of PNP identified via newborn screen with disseminated congenital CMV successfully managed with unconditioned marrow infusion. This case of PNP deficiency and HSCT highlights the importance of early HSCT for this disorder to prevent recurrent infections and neurological deficits and possibility of successful transplant without a conditioning regimen.

Poster # 1015

NEXT-GENERATION SEQUENCING AS A NONINVASIVE TESTING MODALITY TO IDENTIFY PATHOGENIC ORGANISMS IN PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANT

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Background: Conventional diagnostic techniques in microbiology are limited by prolonged time for certain pathogens to grow in culture, poor sensitivity and the need for invasive procedures, often precluding our ability to implement appropriate antimicrobial therapy. Next-generation sequencing (NGS) detects sequences of circulating cell-free DNA in plasma to identify pathogenic organisms in a noninvasive manner.

Objectives: To describe our experience with a commercially-available plasma NGS test for detection of clinically relevant infectious pathogens and its impact on pediatric patient care.
Design/Method: A retrospective data analysis on all pediatric patients for whom plasma NGS testing for infectious pathogens was sent for clinical purposes at Lurie Children's Hospital from December 2016 through August 2018 was performed. Results of NGS testing were available for clinical use in real-time. We reviewed the indication for NGS testing, other infectious diagnostic tests utilized, and any relevant changes in the patient's care. Clinical relevance was determined by expert opinions from two pediatric ID physicians, with a third ID physician used to resolve discrepant opinions.
Results: One-hundred plasma NGS tests were sent on 79 patients, including 11 patients post-HCT in whom 16 NGS tests were sent. Eight (50%) of these NGS tests revealed clinically relevant pathogens: 6 (37.5%) identified the same pathogen as standard microbiological testing and 2 (12.5%) were confirmed in cases suspicious for an infectious process with no pathogen otherwise identified. Clinically relevant pathogens were *Nocardia abscessus*, *Pseudomonas aeruginosa*, *Prevotella* spp, *Enterobacter cloacae* complex, *Rothia mucilaginosa*, *Agrobacterium tumefaciens, Absidia idahoensis*, CMV and BK polyomavirus. Six tests (37.5%) identified organisms deemed non-pathogenic and 2 (12.5%) were negative. There were an additional 7 tests sent in 5 patients who were within two months of a planned HCT. Four (57%) of these 7 tests identified the same pathogen as standard microbiological testing and 2 (28.5%) demonstrated pathogens not otherwise identified, allowing for implementation of appropriate antimicrobial therapy pre-HCT. Combining the pre- and post-HCT patients, there were 10 diagnostic invasive procedures performed: 5 revealed a pathogen and NGS testing identified the same pathogen in all cases, while 5 did not reveal a pathogen and NGS identified a clinically relevant pathogen in 4.
Conclusion: Plasma NGS for infectious pathogens provided clinically relevant information in more than half of patients in whom testing was sent, including many for whom standard testing methods were non-diagnostic. The noninvasive test is promising in potentially avoiding procedures. Further evaluation of the performance characteristics of NGS testing in the clinical setting is warranted.

Poster # 1016

THE SAFETY AND EFFICACY OF PROPHYLACTIC DEFIBROTIDE ADMINISTRATION IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS (CAYA) WITH SICKLE CELL DISEASE FOLLOWING MYELOABLATIVE CONDITIONING (MAC) AND FAMILIAL HAPLOIDENTICAL (FHI) STEM CELL TRANSPLANTATION UTILIZING CD34 ENRICHMENT AND T-CELL (CD3) ADDBACK (IND 127812)

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Background: AlloSCT from HLA MSD is the only successful curative therapy for high-risk

SCD. We demonstrated 100% EFS and absence of sickle cell symptoms following reduced toxicity conditioning in HLA MSD/cord blood AlloSCT (Cairo, BMT, 2014). However, 5 out of 6 patients lack an HLA MSD without SCD. Results after both URD/UCBT with SCD are poor. Results utilizing MUDs in a multi-center trial showed unacceptable rates of cGVHD at 62% (CI95 41-77) (Shenoy, Blood, 2016). We demonstrated promising results of 90% 1yr EFS/OS, stable donor chimerism and minimal rates of GVHD in a previous FHI TCD AlloSCT protocol utilizing CD34+ enrichment/T cell addback in (<21yrs) patients with high-risk SCD (Cairo, ASH, 2018). One patient died of VOD and the rate is estimated to be 32% following BMT in SCD patients (McPherson, BMT, 2011).
Defibrotide has been successfully investigated in high risk pediatric AlloSCT recipients demonstrating a significant reduction of VOD (Corbacioglu, Lancet, 2012).
Objectives: This SCD consortium (www.sicklecelltransplantconsortium.org) is now investigating if defibrotide prophylaxis during MAC and up to 21 days post FHI AlloSCT in patients <21yr with high-risk SCD will be safe, well-tolerated and result in a low incidence of VOD.
Design/Method: Inclusion criteria: Hgb SS, Hgb S β0/+ thal or Hgb SC. Age 2-20.99 yrs, Patients ≥1 high- risk SCD, Complications: ≥1 CVA, ≥2 ACS, ≥3 VOC in past 2 years, or 2 abnormal TCDs or silent stroke. Patients receive hydroxyurea and azathioprine, day -59 – day -11, fludarabine (150mg/m^2), busulfan (12.8mg/kg) (targeted trough CSS of 600-900), thiotepa (10 mg/kg), cyclophosphamide (100mg/kg), R-ATG (8mg/kg), TLI (500cGy)and defibrotide 6.25 mg/kg q6, Day -10 to +21, followed by FHI T-cell depleted AlloSCT. AGVHD prophylaxis: FK506. We utilized the CliniMACS to enrich for peripheral blood HPC's; target dose of $10x10^6$ CD34+ cells/kg with a fixed dose of $2x10^5$ CD3+ T cells/kg as MNCs.
Results: Nine patients have been enrolled to date. Four patients have undergone AlloSCT. Age range 8-19yrs. Median age 11. 4M:5F. Three patients are >+100 days post AlloSCT. Time to ANC
>500 7-10 days. No toxicity attributed to defibrotide. No VOD. No bleeding complications. Including the past 19 pts without defibrotide, 1yr EFS is (n= 23): 90.4% (CI95: 66.8-97.5).
Conclusion: Early results are promising after FHI HCT in high-risk SCD patients who lack a MSD or URD with defibrotide prophylaxis. A larger cohort with longer follow-up is needed to assess long- term safety and outcomes. Supported by FDA R01FD004090 and Jazz Pharmaceuticals.

Poster # 1017

BONE MARROW TRANSPLANT USING FLUDARABINE-BASED REDUCED INTENSITY CONDITIONING REGIMEN WITH IN-VIVO T-CELL DEPLETION IN PATIENTS WITH FANCONI ANEMIA

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Background: Fanconi Anemia (FA) is the most common cause of the inherited bone marrow failure (BMF) syndromes and is characterized by bone marrow failure and cancer predisposition. The only cure for BMF in FA remains bone marrow transplant. Due to DNA instability in FA, reduced intensity conditioning has been used to diminish late complications including secondary malignancies. Most FA conditioning regimens in mismatched and unrelated donor transplants rely on total body irradiation (TBI), which increases the risk of secondary malignancies. Most of the non-TBI conditioning regimens use an Ex Vivo T cell depletion approach, but this is not feasible at all programs.
Objectives: To evaluate the success of bone marrow transplant in patients with FA using non-TBI conditioning regimens with In-Vivo T cell depletion approach
Design/Methods: Stem cell transplant using non-TBI based conditioning was performed on two siblings with Fanconi Anemia and homozygous 2bp deletion in the FANCG gene. The first sibling underwent matched unrelated donor transplant at 7 years of age with a bone marrow (BM) graft with fludarabine, alemtuzumab, busulfan, cyclophosphamide conditioning and cyclosporine (CSA) and mycophenolate as Graft Versus Host Disease (GVHD) prophylaxis. The second sibling underwent match sibling donor at 6 years of age with cord and BM grafts using fludarabine, alemtuzumab, cyclophosphamide for conditioning and CSA for GVHD prophylaxis.
Results: The first sibling had engraftment on D+12, there were no signs of acute GVHD and at 23 months post-transplant has no signs of chronic GVHD. The second sibling had engraftment on D+14, there were no signs of acute GVHD and at 13 months post-transplant has no signs of chronic GVHD. Major complications for both siblings included BK viremia and viruria
Conclusion: Conditioning regimens without radiation can lead to successful engraftment without development of GVHD and may reduce risk of developing secondary neoplasms, even with unrelated donor transplants. As FA is a rare disease, future studies should focus on pooling together BMT data to change current conditioning regiments.

Poster # 1018

SECONDARY HEMOPHAGOCYTIC SYNDROME AFTER AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANT AND IMMUNE THERAPY FOR NEUROBLASTOMA

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Background: The use of novel immunotherapeutic agents for the treatment of malignant and non-malignant diseases is on the rise, including in conjunction with standard treatment regimens. With the increasing use of immunotherapies, it is important for clinicians to recognize the risk of immune-mediated side effects, including secondary hemophagocytic syndrome (HPS).
Objectives: To describe the presentation of secondary HPS in patients receiving autologous hematopoietic cell transplant (AutoHCT) in conjunction with immunotherapy for high risk neuroblastoma, highlight the challenge of diagnosis in this patient population, and demonstrate the potential for treatment of HPS with targeted therapies.

Design/Method: Newly diagnosed patients with high-risk neuroblastoma received a novel consolidation regimen as part of an institutional phase 2 trial (NCT01857934). The consolidation regimen consisted of AutoHCT (busulfan/melphalan), followed immediately by immunotherapy with a humanized GD2-specific monoclonal antibody (hu14.18K322A), haploidentical natural killer cell infusion, interleukin-2 (IL-2), and granulocyte-macrophage colony-stimulating factor (GM-CSF).
Results: Herein we report two occurrences of secondary HPS, noted in the first 41 patients treated with the described consolidation regimen. The first case is a 3-year old boy whom at day +12 post-AutoHCT had neutrophil engraftment and subsequently developed mild VOD, which responded well to initial therapy. On day +23 he experienced an acute rise in bilirubin and transaminases, with coagulopathy, followed by hyperferritinemia, fever, ascites with associated respiratory distress, and hyperammonemia with progressive encephalopathy. Given suspicion for secondary HPS, he was treated with dexamethasone and later ruxolitinib, with some clinical response. Unfortunately, despite initial improvements, he developed focal seizures, worsening mental status with diffuse cerebral edema and subsequently died on day +33. Autopsy showed bone marrow with increased histiocytes with rare hemophagocytosis. Additional testing revealed elevated soluble IL-2 receptor.
The index case had similarities to a previously treated 22-month old boy. He also had neutrophil engraftment and was subsequently diagnosed with mild VOD. He then developed acute liver injury with fever, coagulopathy, hyperbilirubinemia, hyperammonemia, hyperferritinemia, ascites, and hepatorenal syndrome. He recovered without receiving systemic steroids. In retrospect, the presence of fever, hyperferritinemia, and hypofibrinogenemia, along with noted splenomegaly and cytopenias in this patient are consistent with secondary HPS.
Conclusion: Identification of secondary HPS requires a high index of suspicion given the multiple confounding factors present in the HCT population. Identification may allow for the application of targeted treatments, potentially sparing patients from receipt of treatments which may be in direct opposition with the intent of the primary immunotherapeutic regimen.

Poster # 1019

BLINATUMOMAB REDUCES MINIMAL RESIDUAL DISEASE PRIOR TO ALLOGENEIC STEM CELL TRANSPLANT FOR CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Children with relapsed/refractory B-cell precursor acute lymphoblastic leukemia (B-ALL) and minimal residual disease (MRD) prior to allogeneic hematopoietic cell transplantation (allo-HCT) are at significant risk of relapse.
Objectives: Our objective was to analyze a multi-institutional experience using blinatumomab in children with ALL and MRD prior to allo-HCT to evaluate whether it effectively reduces MRD burden without hindering progression to allo-HCT and to report short term outcomes after blinatumomab and allo-HCT.

Design/Method: This retrospective analysis included B-ALL patients, aged 0-21 years, referred for allo-HCT at five centers between 2016-2017 for the indication of B-ALL with persistent MRD (by flow cytometric analysis). All patients were treated with blinatumomab with the goal of reducing MRD prior to allo-HCT.
Results: Fifteen patients were identified, and at the time of blinatumomab treatment, the median age was 9 years (range 0.5-19 years) and MRD level was 0.57% (range 0.01-2.18%). The median follow-up was 371 days post-HCT (range 134-749 days).

Twelve patients received a single 28-day course of blinatumomab (15 mcg/m^2/day), two had shortened courses (18 and 20 days) to initiate allo-HCT preparative therapy, and one received two courses (56 total days) to acquire an unrelated donor. Blinatumomab had minimal impact on the neutrophil or lymphocyte counts. One patient experienced a Grade 3 seizure during blinatumomab therapy. Notably this patient had CNS leukemia and had received medication associated with lowering the seizure threshold. There were no other Grade 3 or 4 toxicities or cytokine release syndrome events.
Fourteen of the fifteen patients were MRD negative following blinatumomab therapy and proceeded to allo-HCT. The time from blinatumomab completion to the start of allo-HCT chemotherapy was 0-21 days. Patients were transplanted with a variety of stem cell sources. Incidence of GVHD appeared unaffected, with aGVHD grades II-III in 14.3% and extensive cGVHD in 21.4% of patients. The cumulative incidence of relapse at 1-year post-HCT was 27.8%. Of the four patients who relapsed post-HCT, all achieved a subsequent remission with additional therapy and remain in remission at the time of report. The 1-year overall survival was 93.3%. The 100-day TRM was 0%.
Causes of death include disease progression in the one patient who did not proceed to HCT and complications related to cGVHD in a second patient.
Conclusion: Prior to allo-HCT, blinatumomab cleared MRD in children with B-ALL with minimal toxicities and no additional delay to allo-HCT. Post-HCT outcomes appear unaffected and favorable.

Poster # 1020

TANDEM AUTOLOGOUS ALLOGENEIC STEM CELL TRANSPLANTATION IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH RELAPSED/REFRACTORY MATURE B-CELL NON-HODGKIN LYMPHOMA (B-NHL)

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Background: Despite excellent cure rates for children, adolescents and young adults (CAYA) with mature B-NHL (Burkitt (BL), Diffuse Large B-Cell (DLBCL), Primary Mediastinal B-Cell (PMBL)) (Cairo/Patte, *JCO,* 2012), the results are dismal (≤30%) in those with relapsed/refractory (r/r) disease who failed FAB/LMB 96 chemotherapy following reinduction chemoimmunotherapy with myeloablative conditioning (MAC) and autologous stem cell transplantation (AutoSCT) (Cairo/Patte, *BJH,* 2018). Sequential MAC AutoSCT and reduced

intensity conditioning (RIC) allogeneic stem cell transplantation (AlloSCT) has achieved a 59% 10-year event-free survival (EFS) in CAYA with Hodgkin lymphoma (Satwani/Cairo, *Leukemia*, 2015). Administration of Y-ibritumomab tiuxetan (radioimmunotherapy) to a cohort of children with high risk B-NHL was proven to be safe and efficacious (Cooney Qualter/Cairo, *Clinical Cancer Research,* 2007) and may further improve outcomes in conjunction with a MAC AutoSCT and RIC AlloHSCT.
Objectives: To investigate the safety and efficacy in CAYA with poor risk r/r B-NHL of sequential MAC AutoSCT followed by RIC AlloSCT with or without targeted radioimmunotherapy.
Design/Method: CAYA patients with poor risk r/r mature B-NHL who underwent MAC AutoSCT followed by RIC AlloSCT ± targeted radioimmunotherapy are included in this study. Twelve of thirteen patients with chemo-sensitive disease underwent sequential MAC AutoSCT followed by RIC AlloSCT. Six patients received radioimmunotherapy with Yttrium-90 ibritumomab tiuxetan prior to RIC AlloSCT. In addition to EFS, patients were assessed for time to hematological recovery, graft failure, whole blood chimerism, aGVHD ≥ Gr 2 and extensive chronic GVHD.
Results: Thirteen patients (8 BL, 3 DLBCL, 2 PMBL) with a mean age of 15.3 years and mean follow-up of 68 months were analyzed. Median time to neutrophil and platelet engraftment is 18.8 and 36.4 days, respectively. Whole blood chimerism at D+100 is 98.4 ± 1.5 %. Eleven patients (7/8 BL) are in complete remission with a 10-year EFS of 84.6%. The transplant-related mortality was 0% and no graft failures developed. One patient developed severe Sinusoidal Obstructive Syndrome (SOS). The overall incidence of ≥ grade 2 aGVHD was 7.7% and of extensive cGVHD was 0% (n=13).
Conclusion: CAYA with r/r B-NHL receiving MAC AutoSCT, targeted radioimmunotherapy, and RIC AlloSCT can achieve a long-term EFS. The combination of MAC AutoSCT, radioimmunotherapy and subsequent RIC AlloHSCT was safe and effective. A graft versus lymphoma effect and the addition of radioimmunotherapy in part likely explains the favorable outcomes in this cohort of patients with otherwise dismal outcomes. Both a larger cohort of patients and a longer follow-up time are required to confirm these pilot results.

Poster # 1021

REDUCED INTENSITY CONDITIONING FOR PEDIATRIC THERAPY-RELATED MYELODYSPLASTIC SYNDROME/ACUTE MYELOID LEUKEMIA IS ASSOCIATED WITH REDUCED NON-RELAPSE MORTALITY BUT NO IMPROVEMENT IN OVERALL SURVIVAL

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Background: Therapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/AML) are rare but well-recognized complications of cancer therapy. Allogeneic hematopoietic cell transplantation (alloHCT) with myeloablative conditioning (MAC) remains the mainstay of treatment but is associated with a high incidence of non-relapse mortality (NRM). Reduced intensity conditioning (RIC) may reduce NRM in these heavily pre-treated patients.
Objectives: To compare outcomes following RIC and MAC regimens in pediatric patients (<21 years) receiving an alloHCT for t-MDS/AML.
Design/Method: This study involved retrospective chart review of patients <21 years of age who underwent HCT for t-MDS/AML from 1995-2017 at 16 centers in the United States and Mexico. We compared outcomes between MAC and RIC regimens. Probabilities of overall survival (OS), event free survival (EFS) were calculated using the Kaplan Meier estimator (log-rank) and Cox proportional-hazards model for multivariate analysis.
Results: 147 patients were included in the study, 44% of these were females and 71% were White. The primary diagnosis prior to development of t-MDS/AML was a hematological malignancy in 42%, solid/brain tumor in 52% and a non-malignant hematological disorder in 10% patients. 43% patients had tMDS and 57% had tAML at the time of transplant. While 20% received RIC, 80% received MAC regimens. The median age at transplant was 13 years and median follow-up of entire cohort was 13 months. OS and EFS of the entire cohort were 45% and 40% at 3 years respectively, and conditioning regimen intensity (RIC vs MAC) did not affect overall survival. Karnofsky performance status of the patients (>=90) was the only factor associated with improved EFS (HR 0.49, p=0.01). Cytogenetic risk score was not associated with a difference in survival after alloHCT. Deaths were from non-relapse causes in 61% of patients after MAC compared to 28% after RIC, whereas disease relapse was the primary cause of death after RIC. A majority of transplants were performed after 2005 (82%) and outcomes seem to be slightly better in contemporary era due to improved supportive care and decreased NRM.
Conclusion: This is one of the largest reported cohorts of pediatric patients receiving allogeneic transplantation for t-MDS/AML. Outcomes are poor relative to de novo MDS/AML due to high rate of NRM with MAC and high rate of disease related death after RIC. Novel strategies that lead to a reduction in transplant-related mortality in these heavily pre-treated patients while providing sufficient disease control are needed to improve survival in t-MDS/AML patients receiving HCT.

Poster # 1022

EFFICACY AND SAFETY OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR PEDIATRIC BONE MARROW FAILURE SYNDROMES (BMFS) USING A REDUCED INTENSITY CONDITIONING (RIC) REGIMEN -UPDATED OUTCOMES

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Background: We previously reported encouraging outcomes-100% overall survival (OS) at 100 days and 1 year with a median follow-up of 650 days- using a RIC regimen for pediatric patients with BMFs undergoing HSCT.
Objectives: This report updates our previous retrospective analysis of safety and efficacy outcomes for patients at our institution who underwent HSCT from 2009-2017 for inherited or acquired BMFs using an irradiation-free RIC regimen.
Design/Method: We analyzed outcomes for 14 pediatric patients with BMFs who received a RIC regimen with fludarabine, thiotepa, and melphalan prior to HSCT between 2009 and 2017. Patients received fludarabine 30 mg/m2/day x5 days on day -9 to -5, thiotepa 5 mg/kg/dose every 12 hours on day -4, and melphalan 70 mg/m2/day x2 days on days -3 and -2. Patients received acute GvHD (aGvHD) prophylaxis as follows: rabbit ATG (rATG), cyclosporine, and mycophenolate (n=5); rATG, tacrolimus, and mycophenolate (n=6); alemtuzumab, abatacept, tacrolimus, and methotrexate (n=1); alemtuzumab, cyclosporine, and prednisone (n=1); and alemtuzumab, cyclosporine, and mycophenolate (n=1).
Results: Our cohort of 14 patients included the following diagnoses: severe aplastic anemia (n=7), congenital amegakaryocytic thrombocytopenia (n=4), severe congenital neutropenia (SCN) (n=1), congenital red cell aplasia (n=1), and non-Fanconi congenital BMF (n=1). Seven patients received stem cells from a 10/10 matched sibling donor (MSD): MSD BMT (n=5); MSD PBSCT (n=2). Seven patients received stem cells from an unrelated donor: 10/10 MUD BMT (n=5); 9/10 MMUD BMT (n=1); 6/6 unrelated UCBT (n=1).
All patients are alive with median follow-up of 1112 days (range 455-2549 days). The median time to neutrophil engraftment was 16 days (range 10-26 days). All were transfusion independent by day +100. The highest grade of aGvHD was Grade 2; 8 did not develop aGvHD. Four developed extensive chronic GvHD (cGvHD), 4 developed limited cGvHD, and 6 did not develop cGvHD. One remains on immunosuppression at day +1130 for extensive cGvHD; 1 SCN patient developed delayed graft rejection and remains on immunosuppression and GM-CSF at day +455 to sustain engraftment. The remaining 12 were weaned off immunosuppression. Four patients experienced some degree of mixed donor chimerism. No patients experienced veno-occlusive disease. Six patients were readmitted prior to day +100 and five were readmitted after day +100 for treatment of non-fatal infectious complications.
Conclusion: Allo-HSCT with RIC with fludarabine, thiotepa, and melphalan for BMFs was effective with a tolerable safety profile. Probability of OS at 100 days and 1 year was 100% with median follow-up of 1112 days.

Poster # 1023

IMMUNOTOXINS TARGET STEM CELLS IN FANCONI ANEMIA TO AVOID LEUKEMOGENESIS AND FACILITATE ENGRAFTMENT

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Background: Fanconi anemia (FA) is an inherited bone marrow failure and cancer predisposition syndrome due to defective DNA repair. The marrow failure phenotype is rectified by a bone marrow transplantation (BMT) where conditioning chemotherapy depletes hematopoietic stem cells (HSC) in the recipient marrow, facilitating donor cell engraftment. While effective, a major issue with chemotherapy includes systemic genotoxicity increasing the risk of secondary malignancies. Another complication with BMT is the presence of mixed chimerisms, where residual host hematopoiesis persists. This is particularly worrisome as FA HSCs possess the innate predisposition towards leukemogenesis. Similarly, current gene therapy trials for FA do not use conditioning prior to cell infusion also resulting in FA HSC persistence and risk for oncogenesis. Antibody-drug-conjugates (ADCs) are an emerging method addressing the aforementioned issues of BMT and gene therapy by avoiding genotoxicity while eliminating HSCs.
Objectives: To evaluate the ability of CD45 and CD117 saporin immunotoxins to eliminate HSCs in a FA mouse model and assess donor engraftment as compared to cyclophosphamide (Cy).
Design/Method: Our approach utilizes immunotoxin conjugates targeting the HSC niche in an FA mouse model. These non-genotoxic ADCs utilize either CD45 or CD117 epitopes conjugated to saporin, a ribosomal toxin, to eliminate HSCs while leaving the remainder of the marrow compartment intact. *Fanca* knockout mice were selected as our model as they recapitulate the marrow sensitivity seen in FA. Mice conditioned with either ADC received various doses of donor marrow from healthy heterozygotes as a surrogate for autologous transplantation. A separate cohort of mice were necropsied on the day of transplantation to assess HSC depletion after ADC conditioning.
Results: Mice conditioned with either immunotoxin demonstrated significantly reduced HSC populations in the marrow similar to Cy controls. However, Cy resulted in an aplastic marrow compartment whereas cellularity was preserved after immunotoxin conditioning. Mouse cohorts conditioned with either immunotoxin receiving donor cell infusions demonstrated superior levels of engraftment compared to Cy-treated animals, even at lower cell doses. Additionally, Cy treated mice demonstrated sustained weight loss and lower gastrointestinal losses compared to immunotoxin treated mice.
Conclusion: CD45 and CD117 ADCs eliminate host HSCs and subsequently facilitate superior engraftment as compared to Cy. Achieving both of these conditions with immunotoxin conjugates represents a major advancement in cellular therapies for FA. Ultimately, we hope these studies will inform future clinical trials and provide the groundwork for the next-generation of therapy for patients with FA and other cancer predisposition syndromes.

Poster # 1024

VITAMIN D SUPPLEMENTATION IN PEDIATRIC PATIENTS UNDERGOING TRANSPLANT: ROOM FOR IMPROVEMENT

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Background: Up to 70% of pediatric patients have low vitamin D (VD) levels (VDL) prior to hematopoietic stem cell transplantation (HSCT). Studies have found that patients with VD deficiency before HSCT and at day +100 have significantly lower 1-year overall survival and increased mortality associated with graft-versus-host disease (GVHD). VDL <20ng/mL are considered deficient, <30ng/mL are insufficient, ≥30ng/mL are sufficient, and >50ng/mL are optimal.
Objectives: This study assessed practices of VD evaluation and VD supplementation (VDS), and investigated the association between VDL and complications (GVHD, veno-occlusive disease [VOD]). This is one of the largest retrospective studies investigating practices surrounding VD, and the association between VDL and complications in the pediatric population.
Design/Method: Records were abstracted for VDL through a retrospective review of patients that received HSCT at CHLA between January 2013 and April 2018. Overall survival (OS) is defined as the time between HSCT and the time of death, from any cause. Those who remained alive were censored at the time of last contact.
Results: Of 314 encounters included in the study, baseline (BL) VDL were available for 135 patients. Of these, 61% had insufficient or deficient BL VDL, and 9% had optimal VDL. VDS was higher among those with insufficient or deficient BL VDL ($p = 0.008$). Only 16% of patients achieved an optimal VDL during the HSCT process, regardless of supplementation status. There was no difference in demographics between those with and without BL VD assessments or between those who did and did not develop GVHD or VOD. There was no difference in VDS by GVHD or VOD status. There was no difference in survival by baseline VDL or by VDS.
Conclusion: We found that 43% of patients had BL VDL assessed. Patients with insufficient or deficient VDL were significantly more likely to receive VDS, but still less than half received supplementation and only 16% ever achieved optimal VDL. There was no association between BL VDL or VDS and HSCT complications or survival, which is expected since such few patients achieved, and none sustained, optimal VD levels. This demonstrates that regular supplementation is not adequate to achieve or maintain the optimal VDL that may be associated with improved outcomes. VD deficiency is a known and, importantly, modifiable risk factor that may be implicated in transplant outcomes. Further prospective studies are required to establish effective practices for monitoring and sustaining optimal VDL and to examine how this affects outcomes.

Poster # 1025

TIME TO TRANSPLANTATION (TTT) FOR ACUTE MYELOID LEUKEMIA (AML) IN FIRST COMPLETE REMISSION (CR1) IS COMPARABLE AMONG ADOLESCENT AND YOUNG ADULTS (AYAS) AND OLDER ADULTS.

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Background: AYA patients have a myriad of specific psychosocial and other challenges which may influence their ability to obtain appropriate treatment. Healthcare disparities regarding access to healthcare have been well described in this population. We hypothesized that hurdles faced by the AYA patient population also apply to patients with AML requiring allogeneic hematopoietic cell transplantation (HCT), resulting in AYAs having a longer TTT compared to older adults.
Objectives: In this study we aimed to compare TTT, defined as time from diagnosis to transplant for AML in CR1 between AYAs and older adults. Additionally, we aimed to determine if TTT has changed over time for this cohort and to identify factors associated with TTT.
Design/Method: BMT Program database was used to identify allogeneic HCT recipients with AML in CR1 from January 2007 to June 2018 for AYAs (age 18-39 years) and older adults (age 40-60 years). All the identified patients underwent allogeneic stem cell transplant in complete remission 1 (CR1). Patients receiving cord blood graft source were excluded. AYA and older adults were compared with Wilcoxon, Chi-square, or Fisher's exact test. Change in TTT over time was assessed with Spearman correlation (r). Factors associated with TTT were assessed with Wilcoxon or Jonckheere-Terpstra test.
Results: A total of 105 patients were identified: 24 AYAs and 81 older adults. Baseline characteristics were similar between AYAs and older adults aside from Karnofsky performance status; AYAs had better performance status than older adults (p=0.012). Time to Transplant did not differ from between AYA and older adults (median 4.1 vs 4.0 months, p=0.61). There was no evidence of a change in TTT in more recent years in AYA (r=0.15, p=0.48) or older adults (r=-0.02, p=0.85). The only variable associated with TTT, as expected, was donor type (unrelated donors median 4.3 vs related donors 3.8 months, p=0.022).
Conclusion: Time to transplant for AYAs in AML is comparable to older adults and has not changed over time. Our analysis is limited to experience from a single center and a larger multicenter effort that takes into account other sociodemographic mediators of healthcare disparities is needed to better describe the association of age and time to allogeneic HCT in AML CR1. Our next step is to explore various psychosocial factors in this cohort and determine if they play a role in the TTT and also determine if TTT has an impact on outcomes.

Poster # 1026

N-803 (IL-15 SUPERAGONIST) AND DINUTUXIMAB SIGNIFICANTLY ENHANCE EXPANDED NATURAL KILLER CELL ACTIVITY AGAINST GD2$^+$ PEDIATRIC SOLID TUMORS (ST)

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Background: Children with recurrent and/or metastatic osteosarcoma (OS), neuroblastoma (NB) and glioblastoma (GBM) have a dismal event-free survival (EFS) (<25%). Most of these tumor cells highly express GD2 protein on the surface. Dinutuximab is an anti-GD2 monoclonal antibody (mAb) that has significantly increased EFS in children with GD2$^+$ neuroblastoma.[1]

Although the adoptive transfer of NK cells alone has not demonstrated clinical responses in patients with solid tumors, NK cell-mediated antibody-dependent cell cytotoxicity (ADCC) is highly associated with anti-GD2 efficacy. Thus, approaches to increase NK cell numbers and activity, improve lifespan, persistence and trafficking, and enhance tumor targeting may further improve the clinical benefit of anti-GD2 mAb therapy.[2] Our group has successfully expanded peripheral blood Natural Killer cells (exPBNK) with irradiated feeder cells.[3] IL-15 is a critical factor that supports the development, proliferation, survival and trafficking of NK.[4,5] N-803 is a superagonist of an IL-15 variant bound to an IL-15RαSu-Fc fusion with enhanced biological activity.[6]

Objectives: To determine if the combination of N-803 and dinutuximab significantly enhances the functions of exPBNK cell against $GD2^+$ OS, NB and GBM.

Design/Method: PBMCs were expanded with lethally irradiated K562-mbIL21-41BBL cells.[7] ExPBNK cells were isolated using Miltenyi NK cell isolation kits as we previously described.[3] N-803 was generously provided by Altor BioScience. NK proliferation, NK receptors expression and cytotoxicity were assessed as we previously described.[3] Dinutuximab (generously provided by United Therapeutics) was used for antibody-dependent cellular cytotoxicity (ADCC) assays. Cytokines/growth factors were examined by ELISA/multiplex cytokines assays. $GD2^+$ OS, NB and GBM cell lines were used as target cells.

Results: N-803 significantly promoted exPBNK *in-vitro* proliferation by increasing the phosphorylation of Akt, Stat3/5 and p38 MAPK. N-803 increased expression of NK activating receptors NKG2D, NKp30, NKp44, and NKp46. N-803 significantly enhanced exPBNK-mediated ADCC with dinutuximab in a E:T dependent manner ($p<0.001$) against OS, NB and GBM. N-803 significantly enhanced IFN-γ, perforin, and MIP-1β ($p<0.001$) release from exPBNK when combined with dinutuximab against OS, NB and GBM. From cytokine/growth factor screening assays, we also found that the combination of N-803, dinutuximab and exPBNK cells significantly reduced PDGF-ββ and SCGF-β ($p<0.001$) secretion from OS and GBM. Importantly, the combination of N-803, dinutuximab and exPBNK cells significantly reduced tumor burden and extended mice survival in human OS xenografted NSG mice.

Conclusion: The combination of N-803 and dinutuximab significantly enhanced the functions of exPBNK against $GD2^+$ solid tumors *in-vitro* and *in-vivo*.

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Poster # 1027

REGULATION OF CYTOKINES/CHEMOKINES RELEASE AND ANTI-TUMOR EFFECT OF EXPANDED NATURAL KILLER (NK) CELLS BY A NOVEL FUSION OF N-820 (2B8T2M), AN IL-15 SUPERAGONIST WITH 4 SINGLE-CHAIN ANTI-CD20 ANTIBODY DOMAINS, AGAINST RITUXIMAB RESISTANT BURKITT LYMPHOMA (BL)

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Background: The prognosis of patients with relapsed or progressed B-cell ($CD20^+$) non-Hodgkin lymphoma (B-NHL), including BL, is dismal due to chemo-radiotherapy resistance (Cairo et al, *BJH*, 2016). Some patients retreated with rituximab relapse, which limit patient treatment options. Novel strategy is needed for these patients. Nature Killer (NK) cells play a major role in the rejection of tumors. However, NK therapy is limited by small numbers of active NK cells, lack of tumor targeting specificity, and multiple mechanisms of tumor escape from NK cell immunosurveillance. Our group has successfully expanded functional and active peripheral blood NK cells (exPBNK) with irradiated feeder cells (Chu/Cairo, et al, *Can Imm Res* 2015). N-820 was generated by fusing N-803 (ALT-803, IL-15 superagonist) to four single-chains of the tumor-targeting monoclonal antibody, rituximab (Liu/Wong, et al, *JBC*, 2016). N-820 displayed tri-specific binding activity through IL-15 mediated NK stimulation, recognition of CD20 on tumor cells and enhanced ADCC by NK (Liu/Wong, et al, *JBC*, 2016).
Objectives: To investigate N-820 mediated-crosstalk between BL and exPBNK cells and the anti-tumor effects of N-820 combined with exPBNK against rituximab-sensitive and -resistant BL.

Design/Method: PBMCs were expanded with lethally irradiated K562-mbIL21-41BBL. N-803 and N-820 were generously provided by Altor Bioscience. Rituximab (ritux)-sensitive Raji and -resistant Raji-2R and Raji-4RH were used as targets. The levels of mRNA and proteins of cytokines, chemokines and growth factors were monitored by real-time PCR and ELISAs, respectively. *In-vitro* cytotoxicity was performed and Raji-2R xenografted NSG mice were generated as we previously described (Chu/Cairo, et al, *Oncoimmunology* 2017).
Results: N-820 significantly enhanced the expression of NK activating receptors such as NKG2D, NKp30, NKp44, and CD16 on exPBNK cells compared to controls. N-820 also significantly enhanced exPBNK cells cytotoxicity against Raji, Raji-2R and Raji-4RH compared to the controls ($p<0.001$). We examined 84 genes of cytokines, chemokines and growth factors by real time PCR and confirmed that N-820 significantly enhanced IFN-γ, granzyme B, and GM-CSF release from exPBNK against Raji-2R and Raji-4RH compared to controls ($p<0.001$). We also found that N-820 significantly reduced CCL22 release from Raji-2R compared to controls ($p<0.05$). In NSG mice bearing Raji-2R tumor, we found that N-820 added to exPBNK significantly reduced tumor burden ($p<0.05$) and increased mice survival ($p<0.05$) compared to control groups.
Conclusion: N-820 significantly enhanced exPBNK cytotoxicity, IFN-γ, granzyme B, GM-CSF release from exPBNK, inhibited CCL22 release from BL and increased anti-tumor activity against BL xenografts in NSG mice.