2017 ASPHO Annual Meeting Papers and Posters

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Odd-numbered posters will present on Thursday, April 27 from 6:30-7:30pm in the Exhibit Hall.

Even-numbered posters will present on Friday, April 28 from 1:15-2:15pm in the Exhibit Hall.

Two poster tours have been add this year-Friday, April 28:

- **Odd-numbered 7:30-8am**
- **Even-numbered 10:45-11:15am**

Plenary Paper # 4001

TRANSGENIC EXPRESSION OF IL15 IMPROVES ANTIGLIOMA ACTIVITY OF IL13Rα2-CAR T CELLS

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Background: Diffuse intrinsic pontine glioma (DIPG) and glioblastoma (GBM) are the most aggressive primary brain tumors in children. Immunotherapy with T cells expressing chimeric antigen receptors (CARs) specific for the DIPG and GBM antigens is an attractive approach to improve outcomes. IL13Rα2 is expressed at a high frequency in DIPG and GBM but not in normal brain, making it a promising target for CAR T-cell immunotherapy. We recently generated the first scFv-based CAR that is specific for IL13Rα2 and demonstrated that it had potent anti-GBM activity in preclinical models. However, CAR T-cell persistence was limited, resulting in recurrence of IL13Rα2-positive GBMs.
Objectives: The goal of this project is to evaluate if transgenic expression of IL-15, a cytokine that is critical for T-cell proliferation and survival, enhances persistence and anti-tumor activity of IL13Rα2-CAR.CD28.ζ T cells.
Design/Method: We generated IL13Rα2-CAR.CD28.ζ T cells expressing IL-15 (IL13Rα2-CAR.IL15 T cells) by double transducing T cells with retroviruses containing expression cassettes encoding i) IL13Rα2-CAR.CD28.ζ or ii) IL-15, tNGFR, and iC9 separated by 2A sequences. We determined the effector function of IL13Rα2-CAR.IL15 T cells in vitro using standard assays, and in the U373 GBM xenograft model.
Results: Double transduction of CD3/CD28-activated T cells resulted in T-cell lines that expressed both transgenes in 45-50% of T cells. At a baseline, IL13Rα2-CAR.IL15 T cells produced on average 69.5 pg/ml of IL15. Production was significantly increased after CD3 or antigen-specific T-cell stimulation (176.7 pg/ml; $n=6$; $p<0.001$). IL13Rα2-CAR.IL15 T cells were as efficient as IL13Rα2-CAR T cells in killing IL13Rα2-positive GBMs in vitro. After intratumoral injection into U373 glioma-bearing mice IL13Rα2-CAR.IL15 T cells persisted significantly longer than IL13Rα2-CAR T cells ($p<0.05$). This resulted in a significant increase in progression free (84 vs 49 days; $p=0.008$) and overall survival ($p=0.02$) of treated mice. Up to date, 4/10 IL13Rα2-CAR.IL15 T-cell treated mice remain glioma free with a follow up of at least 80 days. 3/5 examined, recurring U373 gliomas post IL13Rα2-CAR.IL15 T-cell therapy had downregulated IL13Rα2 expression, indicating immune escape. While all recurring GBMs expressed the glioma-associated antigen EphA2, 1/5 GBMs had also downregulated the expression of the glioma-associated antigen HER2.
Conclusion: Here we demonstrate that transgenic expression of IL15 enhances the in vivo persistence of IL13Rα2-CAR T cells resulting in improved anti-glioma activity. However, enhanced T-cell persistence resulted in the development of antigen-specific and -unspecific loss variants highlighting the need to target multiple glioma-associated antigens in tumors with heterogeneous antigen expression such as GBM and DIPG.

Plenary Paper # 4002

P2Y12 RECEPTOR FUNCTION AND IN VIVO PLATELET RESPONSE TO CANGRELOR IN NEONATES WITH CYANOTIC CONGENITAL HEART DISEASE

Thomas Diacovo, Elisabeth Kaza, Matthew Egalka, Hairu Zhou, Jianchun Chen, Richard Li, Scott Diamond, Julie Vincent, Emile Bacha

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Background: Neonates with cyanotic congenital heart disease (CHD) palliated with a systemic-to-pulmonary artery shunt are at risk for thrombosis in the early post-operative period. Thus, there is an urgent need to identify a target and therapy suitable for thromboprophylaxis during this vulnerable period.
Objectives: This study sought to determine whether the P2Y12 receptor on platelets from neonatal cardiac patients supports in vivo thrombus formation and whether cangrelor, a direct acting and reversible receptor antagonist, can reduce clot size.
Design/Method: Blood samples from patients with CHD (neonates to 18 years) and healthy adults were collected to assess platelet reactivity and response to cangrelor in laser injured arterioles of avatar mice that support human platelet-mediated thrombosis. Drug effect was also evaluated in whole blood using a microfluidic device with collagen as a thrombogenic surface. EC50 and IC50 values for ADP and cangrelor, respectively, were determined by light transmission aggregometry (LTA).
Results: Platelets from neonates with CHD formed thrombi of similar size to those from older patients and adults, with cangrelor reducing clot size by >45%. P2Y12 receptor response to ADP and cangrelor was also nearly identical based on EC50 and IC50 values, respectively. The potency of cangrelor was further established in a microfluidic assay yielding results comparable to LTA.
Conclusion: Platelets isolated from neonatal patients with CHD at the time of surgical repair / palliation have a robust response to ADP and are as amenable to P2Y12 inhibition with cangrelor as their adult counterparts. Moreover, our findings appear to be independent of age and type of cardiac lesion. Unique to this study was our ability to establish the in vivo efficacy of cangrelor using an avatar mouse model that permits real-time evaluation of human platelet interactions with the injured vessel wall, yielding a biological response consistent with P2Y12 inhibition: disruption of thrombus shell formation. We also demonstrate the value of a microfluidic device that can serve as a PD biomarker, requiring significantly less blood to assess changes in platelet reactivity than LTA. This multi-analytic approach will be employed in the upcoming clinical trail at our institution that will assess the PK and PD properties of cangrelor in neonatal patients with CHD requiring palliation with a systemic-to-pulmonary artery shunt (NCT02765633).

This study was supported by grants from the NIH National Heart (HD081281-01), American Heart Association (16CSA28260000), and The Medicine Company, Parsippany, NJ.

Paper Session # 4003/Young Investigator Award Recipient

MECHANISM OF ACTION AND COMBINATION THERAPY STUDIES ON THE

XPO1 INHIBITOR SELINEXOR IN PEDIATRIC HIGH-GRADE GLIOMA AND DIFFUSE INTRINSIC PONTINE GLIOMA

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Background: Pediatric high-grade gliomas (HGG) and diffuse intrinsic pontine gliomas (DIPG) account for the majority of pediatric brain tumor deaths and respond poorly to chemotherapy. We have shown that selinexor, an inhibitor of the nuclear transporter XPO1, is effective against HGG and DIPG in cell culture and patient-derived xenograft (PDX) models, but resistance to treatment develops. In addition, selinexor's mechanism of action, in these diseases and in general, is poorly understood. We are now studying selinexor in national pediatric clinical HGG/DIPG trials, making these issues crucial to address. Selinexor increases nuclear levels of the NF-κB inhibitor IKB-α through XPO1 inhibition, which leads to NF-κB inhibition. IKB-α levels are also regulated by proteasomal inhibition. NF-κB transcriptional activity is thought to be upregulated by NGFR.
Objectives: To determine the mechanism of action and effective combination therapies of selinexor in pediatric HGG and DIPG
Design/Method: We conducted a proteomics study using tandem mass spectrometry of HGG cells treated with selinexor versus control. Using functional genomics techniques, we knocked down expression of NGFR, IKB-α, and NF-κB, studied the effects using qPCR and immunofluorescence (IF), and quantified the impact of knockdown on selinexor's effectiveness. We screened HGG and DIPG cells with all FDA-approved chemotherapy agents. We subsequently conducted viability assays using the proteasome inhibitors bortezomib, carfilzomib, and marizomib, alone and in combination with selinexor and radiation therapy (RT).
Results: Selinexor treatment of HGG cells induced the overexpression of NGFR in proteomic analyses, neurosphere culture ($p<0.01$), and PDX models ($p<0.0005$) versus control. shRNA knockdown of NGFR in HGG/DIPG cells increased HGG/DIPG proliferation rate ($p<0.05$) and neurosphere formation ($p<0.0005$) versus shNull. NGFR knockdown increased the nuclear expression of NF-κB ($p<0.0005$) and induced selinexor resistance ($p<0.05$), while NF-κB inhibition increased sensitivity to selinexor ($p<0.05$). Proteasome inhibitors showed synergy with selinexor in our screen. On validation assays, bortezomib and carfilzomib showed IC50 levels of 1-200 nM and synergy with selinexor across a range of HGG/DIPG lines, while marizomib showed IC50 levels of 2-5 uM and antagonism with selinexor. Selinexor, bortezomib, and RT showed synergy (CI 0.1).
Conclusion: The mechanism of action of selinexor in pediatric HGG/DIPG appears to involve NF-κB inhibition through the induction of IκB-α, and, surprisingly, NGFR, calling into question current understanding of this pathway. FDA-approved proteasome inhibitors, which are known to upregulate IκB-α, show potential as a synergistic combination with selinexor and RT. We are now testing the combination in PDX studies for future clinical trial application.

Paper Session # 4004a/Young Investigator Award Recipient

REGULATION OF C-KIT ONCOGENE BY IKAROS AND CASEIN KINASE II (CK2) IN T CELL ACUTE LYMPHOBLASTIC LEUKEMIA (T-ALL)

Chandrika Gowda, Malika Kapadia, Chunhua Song, Meixian Xiang, Yali Ding, Kimberly Payne, Sinisa Dovat

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Background: The c-kit oncogene encodes CD117, the receptor for stem cell factor. CD117 and its ligand, stem cell factor, are essential for normal hematopoiesis. Expression of CD117 has been detected in 9% of T cell Acute Lymphoblastic Leukemai (T-ALL), and is associated with a very early T lineage phenotype, LMO2 overexpression, activating flt3 mutations and features of early T-cell precursor leukemia (ETP). Recent studies suggest that c-kit expression in T-ALL regulates engraftment potential and radio sensitivity of transformed T lineage cells
Objectives: It has been hypothesized that expression of c-kit is necessary for leukemia stem cell survival and c-kit inhibitors have been tested for the treatment of human leukemia. The mechanisms that regulate c-kit expression in T-ALL remain unknown. Here, we present evidence that expression of c-kit in T-ALL is regulated at the transcriptional level by Ikaros, a tumor suppressor whose deletion is associated with T-ALL development
Design/Method: Retroviral transduction, Ikaros ShRNA transfection, real time-PCR, luciferace assay, quantitative chromatin immunoprecipitation (qChIP) coupled with the next-generation sequencing (ChIP-seq), cytotoxicity assay and western blot.
Results: ChIP-seq and qChIP showed Ikaros binding at the promoter of the c-kit gene in primary T-ALL. Ikaros knock-down with shRNA, results in increased transcription of c-kit in T-ALL, while overexpression of Ikaros in T-ALL, reduced c-kit transcription. Increased Ikaros binding was associated with the formation of heterochromatin, characterized by enrichment of histone H3K27me3 and H3K9me3 markers, and concomitant loss of H3K9ac at the c-kit promoter. In T-ALL, Ikaros activity is negatively regulated by the oncogenic CK2. We tested the effect of CK2 inhibition on Ikaros function as a transcriptional repressor of c-kit in T-ALL. Inhibition of CK2 with shRNA and/or a specific inhibitor (CX-4945), enhanced Ikaros binding to the c-kit promoter resulting in c-kit repression. Ikaros knock-down abolished c-kit repression in T-ALL following treatment with CK2 inhibitors. These data showed that Ikaros is a key regulator of c-kit transcription in T-ALL and that CK2 inhibition represses c-kit transcription by enhancing Ikaros function.
Conclusion: These results provide evidence that expression of the c-kit oncogene is regulated by Ikaros and CK2 in T-ALL. Targeting CK2 with specific inhibitors is a therapeutic strategy tested in preclinical models of T-ALL. The presented results identify a novel mechanism of therapeutic action of CK2 inhibitors – repression of c-kit expression via Ikaros. These results provide a rationale for the use of CK2 inhibitors in T-ALL with c-kit overexpression.

Paper Session # 4004b/Young Investigator Award Recipient

LIM DOMAIN ONLY PROTEIN 2 (LMO2) EXPRESSION IS REGULATED BY IKAROS AND CASEIN KINASE II (CK2) IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: LIM domain only protein 2 (LMO2) is a regulator of hematopoiesis and an oncogene that is overexpressed in a subset of T-cell acute lymphoblastic leukemia (T-ALL). Overexpression of LMO2 in T-ALL is associated with a poor prognosis. The mechanisms that regulate LMO2 expression in T-ALL are still unknown. Ikaros is a tumor suppressor protein that is encoded by IKZF1, whose deletion is associated with development of T-ALL. Casein Kinase II (CK2) oncogene impairs Ikaros function which can be restored by using CK2 inhibitors.
Objectives: To investigate the role of Ikaros and CK2 in regulation of LMO2 in leukemia.
Design/Method: Over expression of Ikaros via retroviral transduction, Ikaros ShRNA transfection, real time-PCR, luciferace assay, quantitative chromatin immunoprecipitation (qChIP) coupled with the next-generation sequencing (ChIP-seq), cytotoxicity assay and western blot.
Results: Ikaros occupancy of the promoter of LMO2 gene was demonstrated by ChIP-seq studies in primary human acute lymphoblastic leukemia cells. Ikaros binding to LMO2 promoter was confirmed by qChIP. Functional experiments demonstrated that Ikaros knock-down with shRNA, results in increased transcription of LMO2, while overexpression of Ikaros, reduced LMO2 transcription in ALL. Ikaros binding was associated with a loss of H3K4me3 and H3K9ac marks at the LMO2 promoter. Since Ikaros function in ALL is negatively regulated by pro-oncogenic Casein Kinase II (CK2), we tested whether CK2 inhibition can enhance Ikaros-mediated transcriptional repression of LMO2. CK2 inhibition resulted in LMO2 repression, along with an increased Ikaros binding at the LMO2 promoter. Ikaros knock-down restored high expression of LMO2 in ALL cells that are treated with CK2 inhibitors showing that Ikaros activity is essential for LMO2 repression.
T-ALL cells that are derived from Ikaros-knockout mice express high level of LMO2 and show T cell arrest. Transduction of these cells with Ikaros-containing retrovirus, results in significant reduction of LMO2 expression coupled with T cell differentiation.
Conclusion: These data showed that Ikaros is a major regulator of LMO2 transcription in T-cell and B-cell ALL. CK2 inhibition represses LMO2 transcription via Ikaros. These results demonstrate that expression of LMO2 oncogene is regulated by Ikaros and CK2 in leukemia. Targeting CK2 with specific inhibitors has been used as therapeutic strategy in preclinical model of lymphoid Leukemia. Presented data revealed the novel mechanism of therapeutic action of CK2 inhibitors which is repression of LMO2 expression via Ikaros. Results provide the rationale for the use of CK2 inhibitors in leukemia with LMO2 overexpression.

Paper Session # 4005

CHIMERIC ANTIGEN RECEPTOR (CAR)-MODIFIED T CELLS (CTL019) INDUCE DURABLE CNS REMISSIONS IN CHILDREN WITH CNS/ COMBINED BONE MARROW AND CNS RELAPSED/REFRACTORY CD19+ ACUTE LYMPHOBLASTIC LEUKEMIA

Mala Talekar, George Hucks, Shannon Maude, Nicholas Kawchak, Laura Motley, David Barrett, Simon Lacey, Bruce Levine, Jan Melenhorst, Pamela Shaw, Colleen Callahan, Claire White, Christine Barker, Diane Baniewicz, Mark Duckworth, Richard Aplenc, David Teachey, Carl June, Stephan Grupp, Susan Rheingold

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Background: Refractory/Relapsed Acute Lymphoblastic Leukemia (R/R ALL) remains a leading cause of death in children with cancer. Single agent CTL019 immunotherapy is highly efficacious in inducing potent and durable marrow responses in patients with R/R CD19+ALL. We present here an updated report on outcome of 17 patients with CNS involvement of ALL treated with CTL019, including 3 patients who had active CNS3 status at time of infusion.
Objectives: Establish safety and efficacy of CTL019 for children with CNS relapse of CD19+ALL.
Design/Method: We identified patients who had isolated CNS or BM/CNS relapse as their indication for CTL019 therapy up to 5/1/16. CNS relapse was defined as CNS3 by lumbar puncture (LP; ≥ 5 WBC/uL with blasts) or brain/ocular involvement by imaging within 12 months of infusion. Post-infusion, patients had diagnostic LP/ +/- neuroimaging done months 1, 3, 6, 9, and 12.
Results: Seventeen of 60 CTL019 treated patients were identified who were CNS3 a median of 4 months prior to infusion; including 3 patients with active CNS3 status at time of infusion. Patients ranged from 1st to 7th CNS relapse(s) pre-CTL019. Ten had isolated CNS relapse and seven had combined BM/CNS relapse. Six patients had ocular involvement and the 3 with active CNS3 had parenchymal changes on brain/spine MRI. Sixteen patients had prior CNS directed radiation and thirteen had undergone prior BMT.
Interestingly, neurotoxicity was not enhanced in the CNS cohort. Encephalopathy grade 2-3 was seen in 3/17(18%)CNS vs 12/43(28%)non-CNS and seizures grade 2-4 in 1/17(6%)CNS vs. 3/43(7%)non-CNS patients.
Sixteen of 17 patients were CNS1 by CSF on day 28 post infusion, one patient was not evaluable (N/E) due to rapid progression of BM disease. In 2/3 patients with active CNS3 disease at infusion, 1 was in CR by Day 28, 1 had initial pseudo-progression with CR by 3 months and 3rd was N/E.
Twelve of 17(71%) CNS patients remain in CR 2-31 month's post-infusion (median 11 months). Five had recurrent BM disease but were CNS negative at relapse, and 1 had no response in BM and CNS was N/E. Three Ph+ patients with 3-7 CNS relapses remain in CR at 8-31 months (median 23 months). To date, none of 60 patients, regardless of site of prior relapse, has had subsequent CNS relapse (100% CNS remission).
Conclusion: Single agent CTL019 immunotherapy can induce potent and durable CNS responses in patients with CNS involvement of their R/R ALL. Neurotoxicity is not enhanced in CNS relapsed patients.

Paper Session # 4006

PRECLINICAL EFFICACY OF DARATUMUMAB FOR T-ALL

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Background: Targeted immunotherapy has become critical for the successful treatment of many forms of cancer, particularly therapeutic antibodies with cytotoxic abilities. No safe and effective immunotherapies have been developed for T-cell acute lymphoblastic leukemia (T-ALL). CD38 is a transmembrane glycoprotein found on the cell surface of activated T cells, terminally differentiated B cells, but relatively low levels on normal lymphoid and myeloid cells. Daratumumab (dara) (Darzalex, Janssen Biotech, Inc.) is a human IgG1κ monoclonal antibody that binds to a unique CD38 epitope and was recently FDA approved for the treatment of refractory multiple myeloma.
To ensure CD38 is a relevant target in T-ALL, we evaluated CD38 expression by flow cytometry (FACS) from 21 patients with T-ALL (10 early T-cell precursor (ETP) and 11 non-ETP) at diagnosis and after one month of induction chemotherapy. All of the samples had detectable CD38 expression which did not change significantly after induction (mean CD38 MFI at diagnosis vs end-induction: 3.27 log vs 3.19 (S.I.; $p = 0.25$). Therefore we hypothesized that targeting CD38 would be effective in T-ALL.
Objectives: To determine whether targeting CD38 with Dara would be effective against T-ALL.
Design/Method: We xenografted primary ALL blasts from 15 different patients, including 7 with ETP-ALL and 8 with non-ETP T-ALL. Mice were randomized to dara (200 μg /mouse intraperitoneally (IP) weekly) vs control (isotype control at 200 μg/mouse IP weekly; 5 mice per arm for each sample) after they developed >1% peripheral blood (pb) blasts by FACS. Disease burden was assessed by FACS enumeration of pb blasts weekly and splenic blasts at sacrifice.
Results: We demonstrate striking efficacy of Dara monotherapy in 6 of 7 ETP-ALL samples with reduction of pb and splenic blasts. Mice treated with high disease burden from 5 of the 8 non-ETP samples were moribund immediately after Dara injection, possibly from aggregates of antibody bound to tumor cells leading to pulmonary embolism or tumor lysis, and were therefore inevaluable. We have since repeated the experiments for 4 of the samples, treating the mice after injection but before detectable engraftment of peripheral blasts. Dara was effective in all 4 samples. Overall, we have found Dara was effective in 5 of 6 evaluable non-ETP T-ALL samples.
Conclusion: In summary, we found dara is a highly effective novel monotherapy for T-ALL in preclinical models. Based on these results, we are developing an early phase trial for children and young adults with relapsed/refractory T-ALL.

Paper Session # 4007

MINIMAL RESIDUAL DISEASE ASSESSMENT OF REMISSION AFTER INDUCTION THERAPY IS SUPERIOR TO MORPHOLOGIC ASSESSMENT FOR RISK STRATIFICATION IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

Sumit Gupta, Meenakshi Devidas, Si Chen, Cindy Wang, Mignon Loh, Elizabeth Raetz, Patrick Brown, Andrew Carroll, Nyla Heerema, Julie Gastier-Foster, Kimberly Dunsmore, Eric Larsen, Kelly Maloney, Leonard Mattano, Stuart Winter, Naomi Winick, William Carroll, Stephen Hunger, Brent Wood

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Background: Minimal residual disease (MRD) assessment after initial therapy is integral to risk

stratification in both B- and T-precursor acute lymphoblastic leukemia (B-ALL and T-ALL). While MRD is used to determine depth of remission, remission is still defined by morphology in both clinical practice and clinical trials.
Objectives: We aimed to determine the outcomes of children with discordant assessments of remission by morphology vs. by MRD. In doing so, we also aimed to determine the extent to which morphologic assessment of remission contributes to risk assessment in modern ALL risk stratification.
Design/Method: We analyzed a cohort of 9,350 patient's age 1-30.99 years enrolled on Children's Oncology Group clinical trials for newly diagnosed ALL that underwent bone marrow assessment at the end of induction therapy. Morphologic response was assessed by institutional pathologists and categorized as M1 (<5% lymphoblasts; remission), M2 (5-25%), or M3 (>25%). MRD was measured by flow cytometry at two centralized laboratories.
Results: Discordance (M1 morphology but MRD≥5%) was uncommon in B-ALL (66/7,748; 0.9%) but significantly more common in T-ALL (97/1,400; 6.9%; p<0.0001). Among subjects with B-ALL, significant predictors of discordance included: age ≥10 years [odds ratio (OR)=1.7, 95th percentile confidence interval (CI) 1.1-2.8; p=0.03], white blood cell count ≥50,000/μL (OR=2.1, CI 1.3-3.6; p=0.004), and unfavorable cytogenetics (OR=31, CI 8.9-109; p<0.0001). In B-ALL, discordant subjects had superior 5-year event-free survival (EFS) when compared to those with M2 morphology and MRD ≥5% (59.1%±6.5% vs. 39.1%±7.9%; p=0.009), but significantly inferior to those with M1 morphology and MRD <5% (87.1%±0.4%; p<0.0001), with similar trends observed in overall survival (OS) rates. Absolute levels of MRD were higher in those with M2/MRD ≥5% than in discordant patietns. In T-ALL, EFS of discordant subjects was not significantly different from those with M2 morphology and MRD ≥5%.
Conclusion: Patients in morphologically defined remission but with MRD ≥5% have EFS and OS similar to those who fail to achieve morphological remission and significantly inferior to those with M1 marrow and concordant MRD findings. These results suggest that MRD should replace morphology in defining remission in ALL, with consequent implications for risk stratification, treatment assignment, and eligibility for experimental agents.

Paper Session # 4008/Early Career Travel Stipend Award Recipient

MERTK IS A POTENTIAL THERAPEUTIC TARGET IN EARLY THYMIC PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Early thymic precursor acute lymphoblastic leukemia (ETP-ALL) is a subclass of T-cell ALL (T-ALL) characterized by an immature T-cell phenotype, resistance to therapy, and high rates of induction failure and relapse. MERTK receptor tyrosine kinase is not expressed in normal T cells but is ectopically expressed in 40-50% of T-ALLs, particularly those with an immature T-cell phenotype, suggesting a role in ETP-ALL. Further, inhibition of MERTK using shRNA delayed leukemia progression and prolonged survival in a T-ALL xenograft model, implicating MERTK as a therapeutic target.

Objectives: To test the effects of MRX-2843, a MERTK tyrosine kinase inhibitor, in cell culture and murine models and validate MERTK as a therapeutic target in ETP-ALL.
Design/Method: Publicly available MERTK mRNA expression data from T-ALL patient samples were analyzed. MERTK protein expression was determined in ETP-ALL cell lines and patient samples by immunoblot. ETP-ALL cell lines were incubated with vehicle or MRX-2843 for 48 hours, then stained with PoPro-1-iodide (POPRO) and propidium iodide (PI) dyes and apoptotic (POPRO+, PIneg) and dead (PI+) cells were identified using flow cytometry. Orthotopic xenografts were established in NSGS mice using an ETP-ALL patient sample. Leukemia engraftment in peripheral blood was monitored by immunophenotyping using an anti-human CD45 antibody. After engraftment, mice were treated once daily with 75 mg/kg MRX-2843 or saline administered by oral gavage. Mice were euthanized when clinical symptoms of advanced leukemia were evident and survival was monitored.
Results: MERTK mRNA and protein were expressed at significantly higher levels in ETP-ALL cell lines and patient samples relative to other T-ALLs. Treatment with MRX-2843 induced dose-dependent apoptosis in the ETP-ALL cell lines PEER (43.2% of cells versus 16% in vehicle-treated cultures, $p<0.01$) and Loucy (36.6% of cells versus 19.2% in vehicle-treated cultures, $p<0.05$). Moreover, in an orthotopic patient-derived xenograft model of ETP-ALL treatment with MRX-2843 reduced peripheral blood disease burden by 53.9% ($p<0.001$) and decreased spleen weight by 64% ($p<0.001$) compared to vehicle-treated controls. Furthermore, treated mice survived for a median of 41 days post-treatment compared to 29 days for control mice ($n=8$, $p=0.003$).
Conclusion: MERTK is ectopically expressed in ETP-ALL and MRX-2843, a MERTK inhibitor, has robust therapeutic activity in both in vitro and in vivo ETP-ALL models. These data implicate MERTK in ETP-ALL leukemogenesis and validate MRX-2843 as a novel agent with potential for clinical application in patients with ETP-ALL. In this context, MRX-2843 may be particularly effective in combination with cytotoxic chemotherapy or other targeted agents.

Paper Session # 4009

RISK ADAPTED THERAPY UTILIZING UPFRONT BRENTUXIMAB VEDOTIN (Bv) AND RITUXIMAB (R) WITH REDUCED TOXICITY CHEMOTHERAPY IN THE TREATMENT OF CHILDREN, ADOLESCENTS AND YOUNG ADULTS (CAYA) WITH NEWLY DIAGNOSED HODGKIN LYMPHOMA (HL)

Jessica Hochberg, Liana Klejmont, Lauren Harrison, Allyson Flower, Qiuhu Shi, Jaclyn Basso, Mitchell Cairo

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Background: Cure rates for CAYA patients with Hodgkin Lymphoma remain high, however are limited by significant toxicity of chemoradiotherapy. Investigation of the novel targeted agents Brentuximab Vedotin and Rituximab, which target CD30 and CD20 on the Reed-Sternberg cell and the microenvironment, have shown efficacy in relapsed HL. We hypothesize that the addition of both to combination chemotherapy will be safe and effective in all stages of newly diagnosed HL resulting in preserving current EFS with the elimination of more toxic chemoradiotherapy.
Objectives: To evaluate the safety and overall response and EFS of Brentuximab and Rituximab

in combination with risk adapted chemotherapy in CAYA with newly diagnosed Hodgkin Lymphoma.
Design/Method: Patients age 1 to 30 years old with any stage newly diagnosed classical HL were given 3 to 6 cycles of chemoimmunotherapy based on risk assignment: Brentuximab vedotin with Doxorubicin, Vincristine, Prednisone and Darcarbazine (Bv-AVPD) for Low risk patients or Doxorubicin, Vinblastine, Darcarbazine and Rituximab (Bv-AVD-R) for Intermediate/High risk patients. Early response was measured by PET/CT scan following 2 cycles. Slow responders received an additional 2 cycles of Bv-AVD-R for Intermediate Risk or Ifosfamide/Vinorelbine for High Risk patients. Radiation therapy was given ONLY to those patients who have not achieved a complete response (Lugano Classification).
Results: Total = 19 patients. Median age = 15yr (range 4-23yr). There have been 2 low risk, 13 intermediate risk and 4 high risk patients. Therapy has been well tolerated. There has been 1 episode of Grade III mucositis and 1 episode of Grade III infusion reaction to Brentuximab. To date, 17 patients have completed therapy. All 17 patients achieved a complete response to therapy for a CR = 100%. Eleven (58%) have achieved a rapid early response. No patient has required radiation therapy. For 17 patients who have completed therapy, the EFS and OS is 100% with a median follow up time of 915 days (30 months).
Conclusion: The addition of Brentuximab vedotin and Rituximab to combination chemotherapy for newly diagnosed Hodgkin Lymphoma appears to be safe. Our early results show significant promise with a CR rate of 100% and 58% rapid early response. We have successfully deleted toxic alkylator, topoisomerase inhibitor, bleomycin and radiation from this treatment regimen. The EFS/OS to date is 100% with a median follow up time of 2.5 years. Further follow up and a larger cohort is needed to determine long term outcomes and morbidities of this approach.

Poster # 4010

EXCELLENT OUTCOMES FOLLOWING RESPONSE-BASED OMISSION OF RADIOTHERAPY IN CHILDREN AND ADOLESCENTS WITH INTERMEDIATE OR ADVANCED STAGE HODGKIN LYMPHOMA

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Background: Long-term survival of children and adolescents with Hodgkin Lymphoma (HL) treated with combination of chemotherapy and radiotherapy (RT) exceeds 90%. Several pediatric HL consortia have already demonstrated safe omission of RT in a subset of patients with low-risk disease. The COG AHOD0031 intermediate risk study showed RT could be omitted in rapid early responders in complete response after 4 cycles of ABVE-PC chemotherapy. However, feasibility of eliminating RT in pediatric advanced disease is still under investigation.
Objectives: We report single institution outcomes of 64 patients with intermediate or advanced stage HL treated before and after adoption of response-based omission of RT.
Design/Method: We retrospectively identified 64 patients with classical HL, treated between 1/1/2005 and 12/31/2014, whom we risk stratified into intermediate (Ann Arbor 2A bulk, 2B and 3A) and advanced stages (3B, 4A and 4B) similar to the recently completed EuroNet Pediatric

HL C1 trial. Review of medical records showed 100% concordance between clinician documentation of clinical staging and radiology report. From 2005-2011, 43 patients were treated with either Stanford V x 12 weeks (n=31) or ABVD x 6 cycles (n=12) plus 21-25.5 Gy involved field RT (except 1 patient). A later cohort (n=21) was treated with 6 cycles of OEPA-COPDAC/COPP, our current institutional standard of care. After multidisciplinary review, patients were offered omission of RT if PET negative (Deauville criteria) with CT anatomic shrinkage (>75%) after 2 cycles of OEPA.
Results: Median age was 15.5 yrs. In the Stanford V/ABVD (2005-2011) cohort, 30% of patients had advanced disease versus 67% in the OEPA (2012-2014)(p=0.006). Distribution of bulky disease was similar in both cohorts (30% versus 29%). RT was omitted in 12/21(57%) patients in the OEPA cohort (equal in both intermediate and advanced stages) versus 1/43 in the Stanford V/ABVD cohort. Median follow up was longer in the Stanford V/ABVD cohort (6.7 years versus 3.9 years). The 4-year PFS and OS for all patients were 89% and 98% respectively. The 4-year PFS in the OEPA cohort was 100% versus 84%(95% confidence interval(CI) 69-92%) in the Stanford V/ABVD cohort(p=0.06). Most of disease progression occurred in Stanford V patients who received cyclophosphamide instead of mechlorethamine when the latter was unavailable.
Conclusion: Our analysis demonstrates excellent outcomes in children and adolescents with intermediate or advanced stage HL treated with 6 cycles of OEPA-COPDAC/COPP with or without RT. We successfully omitted RT in > 50% of patients with either intermediate or advanced stage disease.

Paper Session # 4011

TARGETING INTEGRIN-MEDIATED SIGNALING IN METASTATIC EWING SARCOMA

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Background: Metastatic Ewing sarcoma (ES) has an extremely poor overall survival, necessitating examinations into molecular mechanisms to identify novel targets and develop new therapies. We performed a novel in vivo study designed to provide insights into metastatic transcriptomic and proteomic signatures for ES to identify potential therapeutic targets. Established human ES cells were orthotopically transplanted into the tibia of mice and, after 4-6 weeks, the primary bone tumors and distal metastatic lesions were isolated and processed. Comparing profiles of primary tumors to corresponding metastatic lesions, we identified aberrant expression of integrin ß3 (ITGB3) and downstream activation of integrin-linked kinase (ILK) in metastatic lesions compared to primary tumors, implicating this pathway as a key regulator in the ability of ES to establish and enhance metastasis. Our hypothesis is that upregulation of ITGB3 and its downstream signaling events play a key role in metastasis of ES and are viable therapeutic targets.
Objectives: To investigate the role of ITGB3 and its downstream signaling pathways in driving establishment of metastasis in ES and to investigate this pathway as a potential therapeutic target.
Design/Method: To investigate the role of ITGB3 and ILK in ES metastasis, we used siRNA to

knock down ITGB3 and ILK expression in established ES cell lines and then performed functional assays in vitro, including cell proliferation and invasion/migration assays. We also tested inhibition of this ITGB3 signaling pathway using available small molecule inhibitors targeting ITGB3, ILK and the downstream target AP-1, using Cilengitide, Compound 22 and SR11302, respectively. To provide a direct patient correlation, we assessed the expression of ITGB3 and ILK in primary and metastatic human ES tissue samples using immunohistochemistry (IHC).
Results: Knockdown of ITGB3 and ILK in our siRNA cell lines resulted in decreased cell proliferation and decreased invasion and migration compared to controls. We also found significantly decreased cell proliferation and increased apoptosis using each of the small molecule inhibitors in vitro. IHC studies confirmed increased ILK expression in metastatic lesions compared to primary tumors in our human samples.
Conclusion: These results support our hypothesis that ITGB3 and its downstream signaling events play a key role in the ability of ES to establish metastatic foci and may serve as a potential therapeutic target. We continue to investigate this pathway in vitro. We are also using our small molecule inhibitors and inducible shRNA and overexpression approaches to study these effects on metastatic tumor development in vivo using our mouse model.

Paper Session # 4012/Early Career Travel Stipend Award Recipient

THE TRANSCRIPTIONAL CO-ACTIVATOR TAZ IS A POTENT MEDIATOR OF ALVEOLAR RHABDOMYOSARCOMA TUMORIGENESIS

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Background: Despite increasing evidence that the transcriptional co-activator TAZ conveys stem-like characteristics to epithelial cancers, the role of TAZ in sarcomas is poorly understood. Alveolar rhabdomyosarcoma (aRMS) is a soft tissue sarcoma driven by the signature PAX3/7-FOXO1 (PF) chimeric transcription factor. Survival for aRMS is <30% at 5 years, and there are no therapies that target the transcriptional programming of PF. Given that TAZ is a co-activator of wildtype PAX3-mediated transcription, and that TEADs (the main binding partner for TAZ) are among the top enriched transcription factor motifs in PF binding sites, we hypothesized that TAZ serves as a PF co-activator, and interrogated the role of TAZ in aRMS sarcomagenesis.
Objectives: To define the requirement for TAZ in aRMS tumorigenesis utilizing in vitro and in vivo genetic and pharmacologic approaches.
Design/Method: After determining in NCI Oncogenomics data sets that TAZ is upregulated in human aRMS transcriptomes, we evaluated whether TAZ is also upregulated in a microarray from our previously published model of PF transcriptional changes. To assess TAZ abundance in human aRMS tumors, we performed immunohistochemical staining of 64 human aRMS samples from tissue microarrays (TMAs) obtained from the COG. Next, we examined TAZ loss-of-function using two independent, lentivirally-delivered, stable or conditionally expressed TAZ shRNAs to interrogate the role of TAZ in supporting transformation in in vitro assays as well as in murine xenografts. Finally, we performed in vitro and in vivo pharmacological studies using porphyrin compounds, which have been shown to interfere with TAZ/TEAD transcriptional

activity.
Results: TAZ is upregulated in our model of PF transcriptional changes and TMA staining reveals high nuclear TAZ expression in aRMS tumors. TAZ suppression via shRNAs decreases aRMS cell growth and proliferation, and decreases tumor growth and prolongs survival in murine xenografts. Median survival was 17 days in control groups and 31 days in the two shRNA groups ($p=0.006$, $p=0.041$). TAZ is required for transit through the G2/M phase of the cell cycle, opposes aRMS myogenic differentiation, and supports aRMS cancer cell stemness. Preclinical studies revealed decreased cell and tumor growth with porphyrin compounds alone and synergistically in combination with vincristine.
Conclusion: Our work demonstrates that TAZ is important in aRMS tumor biology. Genetic and pharmacologic inhibition of TAZ abrogates aRMS tumor growth. While PF is currently not therapeutically tractable, we hypothesize that targeting TAZ may attenuate PF activity and could be a promising novel target for treating this aggressive sarcoma.

Paper Session # 4013

DECREASED MICROVASCULAR PERFUSION IS A PHYSIOLOGICAL BIOMARKER OF VASO-OCCLUSIVE CRISIS DUE TO MENTAL STRESS AND PAIN ANTICIPATION IN SICKLE CELL DISEASE

Saranya Veluswamy, Payal Shah, Maha Khaleel, Wanwara Thuptimdang, John Sunwoo, Patjanaporn Chalacheva, Roberta Kato, Jon Detterich, John Wood, Jennie Tsao, Lonnie Zeltzer, Richard Sposto, Michael Khoo, Thomas Coates

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Background: Sickle cell disease (SCD) is an inherited blood disorder characterized by vaso-occlusive crises (VOC). Abnormal hemoglobin-S polymerizes after releasing oxygen to tissue which leads to the formation of sickled red blood cells (RBC) that obstruct the blood flow in the capillary circuit. Any trigger that decreases microvascular perfusion can further promote vaso-occlusion with increased risk of VOC. We used a novel methodology to quantify the regional microvascular blood flow (MBF) as a physiological biomarker of neural response to thermal pain and showed that there was a greater change in MBF due to thermal pain in patients with SCD. Interestingly, we noticed that there was decrease in MBF when subjects were told they were about to experience pain, suggesting that neural induced vasoconstriction might be a physiologic link between common VOC triggers like stress and vaso-occlusion.
Objectives: To determine if pain anticipation and mental stress causes decrease in MBF in SCD.
Design/Method: Twenty-four SCD and sixteen controls were recruited at Children's Hospital Los Angeles. Patients were exposed to thermal pain pulses without being instructed of upcoming pain and MBF was measured. Additionally, subjects were exposed to a novel pain anticipation task by instructing that they will be receiving pain, but no pain was applied. Two standard mental stress tasks (N-back and Stroop) were performed and MBF was assessed.
We measured MBF using photo-plethysmography (PPG) on the left thumb and calculated the average drop in MBF compared to baseline. Decrease in PPG amplitude indicates vasoconstriction.
Results: When subjects were told that they were about to experience severe pain from heat applied to their arm in the pain anticipation task, there was a significant decrease in MBF

compared to baseline($p<0.0001$). However, there was no significant difference in MBF compared to baseline when heat pain was applied without verbal instructions. There was a significant decrease in MBF during N-back and Stroop compared to baseline ($p<0.01$).
Conclusion: There was a profound vasoconstriction response (VCR) to anxiety induced by pain anticipation and stress tasks which is congruent with clinical observations that social and mental stress can trigger VOC. Unlike our previous studies, the VCR response during thermal pain was not significant, in the absence of induced anxiety. This could explain objectively how stress may play a role in the initiation of VOC in SCD by enhancing neural mediated vasoconstriction and increasing the likelihood of vaso-occlusion. Importantly, the methodology presented here offers a way to quantify physiological response to mental stress.

Paper Session # 4014

REALIZING EFFECTIVENESS ACROSS CONTINENTS WITH HYDROXYUREA (REACH): ENROLLMENT AND BASELINE CHARACTERISTICS

Patrick McGann, Peter Olupot-Olupot, Léon Tshilolo, Thomas Williams, Brigida Santos, José Reis da Fonseca, Robert Kitenge, George Mochamah, Ham Wabwire, Susan Stuber, Teresa Latham, Banu Aygun, Stephen Obaro, George Tomlinson, Russell Ware

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Background: Using evidence gathered from US-based research trials, children with sickle cell anemia (SCA) can now survive into adulthood with improved quality of life. In contrast, >240,000 infants are born with SCA annually in sub-Saharan Africa, and most do not survive to their fifth birthday. Hydroxyurea is the primary disease-modifying therapy for SCA, but its use in Africa is limited due to lack of availability, safety concerns, and inexperience by providers. Realizing Effectiveness across Continents with Hydroxyurea (REACH, NCT01966731) is a large, prospective multi-national study in four African countries (Angola, Democratic Republic of Congo, Kenya, and Uganda), and includes an international collaborative clinical research team.
Objectives: Primary aims of REACH are to determine the feasibility, safety, and effects of hydroxyurea in sub-Saharan Africa. Endpoints include hematological toxicities and benefits, clinic attendance, medication adherence, and clinical adverse events.
Design/Method: REACH is approved by appropriate Ethics Committees, IRBs, and regulatory agencies in the US and Africa. Children with SCA age 1-10 years are eligible and after a two-month screening phase, begin hydroxyurea with a six-month fixed dose (15-20 mg/kg/day) phase, followed by a dose escalation phase to maximum tolerated dose, and then a maintenance phase. Hydroxyurea for the study has been philanthropically provided by the Bristol-Myers Squibb Foundation.
Results: REACH has now achieved full enrollment with 637 participants, including some withdrawn or ineligible during screening. All sites enrolled 2-3 participants per week to reach the goal of 150 per site. Many children had acute or chronic malnutrition with average weight-for-height (-0.65±1.0) and height-for-age (-0.85±1.1) z-scores at enrollment. Baseline laboratory values include hemoglobin = 7.3±1.1 g/dL and HbF = 10.4±6.7%. Nearly all patients reported previous vaso-occlusive pain (99.5%), dactylitis (79.5%), and malaria (81.7%), while 10% reported a history of acute chest syndrome, 9.3% had acute splenic sequestration and 5.5% had

previous stroke. Most participants had received a blood transfusion (67%), but this was site-dependent; only 42% of patients in Kenya received transfusion compared to >70% at all other sites. There were important differences among the four clinical sites with regard to hematological and nutritional parameters.
Conclusion: REACH is the first large, multi-national study of hydroxyurea for children with SCA in sub-Saharan Africa. This collaborative research study demonstrates that with strong team-building, training, and close oversight, high-quality clinical research can be successful in limited-resource settings. Data from REACH will more clearly define the safety profile, as well as the appropriate dosage and monitoring program, for hydroxyurea in Africa.

Paper Session # 4015

REDUCED GLUTAMATE CHANNEL PHOSPHORYLATION IN PAIN-RELATED BRAIN AREAS IN A TRANSGENIC MODEL OF SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is associated with chronic, debilitating pain beginning in childhood and persisting throughout life. SCD patients also tend to exhibit elevated rates of depression and anxiety disorders, indicating a possible connection between recurring pain episodes and affective or emotional dysregulation in this population. How SCD physiologically manifests within brain circuitry to mediate this link is currently unknown.
Objectives: In the current study, we utilized a transgenic mouse model of SCD to examine expression of signaling proteins of specific brain regions associated with pain and emotional processing in order to better understand the physiologic effect of recurring pain episodes known to affect sickle cell patients on brain circuitry.
Design/Method: We used western blot technique to measure protein kinase A (PKA)-mediated phosphorylation of the AMPA glutamate receptor channel subunit GluR1 in specific brain regions of transgenic sickle cell mice that are associated with central nociception and the emotional dimension of pain, including the periaqueductal gray (PAG), prefrontal cortex (PFC), and hippocampus.
Results: Transgenic sickle mice (HbSS-BERK) expressing human sickle hemoglobin display significant mechanical, thermal, and cold hyperalgesia and exhibit reductions in GluR1 phosphorylation compared to littermate controls (HbAA-BERK) in the PAG, PFC, and hippocampus. In comparison, GluR1 phosphorylation is unchanged in the dorsal striatum, a brain region not traditionally associated with pain or negative emotionality.
Conclusion: This neuroadaptative reduction in GluR1 phosphorylation is indicative of reduced excitatory transmission potential in these pain-associated areas (PAG, PFC and hippocampus). Our data are consistent with other preclinical pain models that have linked chronic, peripheral pain conditions with compromised excitatory brain signaling. These results make a strong case for greater appreciation and investigation into mechanisms of possible affective disorder in individuals suffering from SCD.

Paper Session # 4016

QUICK START HYDROXYUREA INITIATION PROJECT (Q-SHIP): TARGETED EDUCATION AFTER CRISIS TO INCREASE THE USE OF HYDROXYUREA IN CHILDREN WITH SICKLE CELL ANEMIA

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Background: Sickle cell anemia (SCA) is an inherited hemoglobinopathy characterized by episodic painful crises, progressive multi-organ injury, and early death. Hydroxyurea (HU) is the only FDA-approved disease modifying medicine for SCA. Recent NHLBI guidelines recommend offering HU to all children with SCA. Despite this, many eligible children are not on this treatment. Novel strategies to increase HU use in children with SCA are needed.
Objectives: To evaluate the effectiveness of an intervention to start HU in children with SCA soon after a disease complication.
Design/Method: The protocol was approved by the Children National Health System(CNHS) IRB. Patients with SCA >9 months old, not on HU or chronic transfusions, who presented to the CNHS emergency department (ED) with pain or acute chest syndrome (ACS) were eligible for the intervention. Eligible patients and their family were encouraged to attend a weekly Quick-Start Hydroxyurea Initiation Project (Q-SHIP) education session in our hematology clinic. Participants completed a brief questionnaire, received comprehensive education about HU, and were offered an HU prescription. Primary hematologists were notified if HU therapy was started.
Results: Over 9 months (2/17/2016 – 12/1/2016), 69 eligible patients presented to our ED. 68% (n=47) attended a Q-SHIP session a median of 5 days (IQR 1.5-15.5) after ED or hospital discharge. Median patient age was 8.1 years (IQR 5.0-16.5). Nearly half of participants (parents or patients >18 years old), reported no previous HU offer (49%, n=23/47), but documentation in 69% (n=15/23) of these patients' charts stated that HU had been offered and declined. Patients/parents who reported a previous HU offer (n=24) had not previously accepted HU due to concern for treatment side effects (n=8), infrequent SCA complications (n=6), and wanting more information (n=6). Post-intervention, 51% of patients (n=24/47) started HU. The intervention was equally effective for participants who reported a previous HU offer compared to those who reported no previous offer (13/24, 54%, vs. 11/23, 48%, p=0.66). At follow-up (median 5.5 months, IQR 1.9-7.6), 91% of patients (n=22/24) who started HU after Q-SHIP continued taking it.
Conclusion: Targeted HU education for patients who recently suffered a SCA complication led to HU initiation in over half of participants. This raises the intriguing possibility that intervention after an acute SCA complication will increase parent/patient HU acceptance. Surprisingly, many parents/patients reported no prior HU offer despite documentation to the contrary. This may reflect an unappreciated communication barrier between parents/patients and providers that requires further study.

Paper Session # 4017

OUTCOMES OF CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA BASED ON BLAST GENETICS AT DIAGNOSIS: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

Mignon Loh, Elizabeth Raetz, Meenakshi Devidas, Yunfeng Dai, Michael Borowitz, Andrew Carroll, I-Ming Chen, Julie Gastier-Foster, Alison Friedmann, Richard Harvey, Nyla Heerema, Eric Larsen, Kelly Maloney, Leonard Mattano, Charles Mullighan, Karen Rabin, Shalini Reshmi, Kathryn Roberts, Cheryl Willman, Brent Wood, Patrick Zweidler-McKay, Jinghui Zhang, Naomi Winick, Stephen Hunger, William Carroll

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Background: Survival for childhood acute lymphoblastic leukemia (ALL) now approaches 90% with risk adapted therapy based on National Cancer Institute risk group (NCI RG) at diagnosis, somatic lymphoblast genetics, and early response to therapy as measured by minimal residual disease (MRD). The Children's Oncology Group AALL03B1 ALL Classification trial enrolled 11,145 patients with newly diagnosed ALL between December 2003 and September 2011. Companion therapeutic trials for B-lineage ALL included AALL0331 (n= 5226) for NCI standard risk (SR-ALL) and AALL0232 (n=2907] for NCI high risk (HR) ALL.
Objectives: To assess outcome by lymphoblast genetics amongst NCI RG, as well as differences in event-free and overall-survival (EFS, OS).
Design/Method: Cytogenetic and FISH data were integrated and analyzed with clinical characteristics.
Results: Favorable genetic groups of Trisomy 4/10/17 (TT) and ETV6/RUNX1 were more common in NCI SR ($p< 0.0001$ for each) while those with unfavorable characteristics (KMT2A rearranged [KMT2Ar], iAMP21, BCR/ABL1 and hypodiploidy [n<44]) occurred more frequently in NCI HR patients ($p<0.0001$). Notably, hypodiploidy was associated with the worst EFS and OS regardless of NCI RG, with 5-year EFS and OS of 51.3±5.0% and 58.2±5.0%, respectively, suggesting that these patients continue to fare poorly with salvage therapies. Multivariable analysis demonstrated age, WBC, and day 29 MRD as significant independent risk factors for sustained CR, and the individual genetic groups of TT, ETV6/RUNX1, iAMP21, BCR/ABL1 and hypodiploidy, but notably, not KMT2Ar, all retained independent prognostic significance when added to the model individually.
Six hundred and five consecutively enrolled AALL0232 patients underwent additional genomic interrogation, including assessment of Ph-like status, ABL1 class fusions, CRLF2r, JAK mutations (JAKm), and IKZF1 alterations. There were 85/605 (14.0%) Ph-like patients. Ph-like status was significantly associated with IKZF1 alterations (75%) ($p < 0.0001$) and day 29 MRD > .01% ($p < 0.0001$). Five-year EFS for Ph-like versus non Ph-like was 62.3±5.8% vs. 83.9±1.7% ($p < 0.0001$). The outcome of Ph-like ALL was no different with or without IKZF1 alterations (61.5±7.0% vs. 64.6 ±11.1%). Five-year EFS for patients with IKZF1 alterations (n=155, 27.1%) was 66.8±4.0% ($p < 0.0001$) versus 86.4±1.8% for those without IKZF1 lesions. Multivariable analysis demonstrated age, WBC and day 29 MRD as independent risk factors for sustained CR while only Ph-like status, IKZF1 alteration, BCR/ABL1 and ETV6/RUNX1 retained independent prognostic significance.
Conclusion: In summary, somatic sentinel cytogenetic alterations are independently prognostic in ALL and are strongly associated with NCI RG and outcome, supporting continued incorporation into risk stratification algorithms.

Paper Session # 4021

RUXOLITINIB IN PEDIATRIC PATIENTS WITH SEVERE OR REFRACTORY GRAFT-VERSUS-HOST DISEASE: A SINGLE-INSTITUTION CASE SERIES

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Background: Graft-v ersus-host disease (GVHD) is a common and potentially life-threatening complication of allogeneic hematopoietic cell transplantation (HCT). Ruxolitinib, a JAK1/2 inhibitor, has recently been shown to be an effective treatment for adults with refractory GVHD. However, the tolerability and efficacy of ruxolitinib in treating GVHD has not been studied in children.
Objectives: To evaluate the safety and efficacy of ruxolitinib for severe or refractory GVHD in pediatric HCT patients.
Design/Method: We conducted a retrospective single-center chart review of pediatric and young adult patients with GVHD who were treated with ruxolitinib within the past two years.
Results: Six patients (ages 18 months to 20 years at time of HCT) were identified. All patients had undergone HCT using a matched related donor, matched unrelated donor, or mismatched unrelated donor with standard conditioning regimens and prophylactic immunosuppression. Patients developed GVHD symptoms between day +41 to +76 following either stem cell infusion or donor lymphocyte infusion. All patients ultimately developed severe extensive chronic GVHD. Patients previously received multiple other systemic GVHD therapies, including systemic corticosteroids (n=6), sirolimus (n=3), anti-tumor necrosis factor agents (n=3), mycophenolate mofetil (n=3), photophoresis (n=2), rituximab (n=1), basiliximab (n=1), IL-2 (n=1), alemtuzumab (n=1), tocilizumab (n=1), methotrexate (n=1), mesenchymal stem cells (n=1), and narrowband UVB (n=1). In most cases ruxolitinib was added to the patient's current GVHD therapy. Median studied period of ruxolitinib therapy was five months (range: three to seven months).
Ruxolitinib was generally well tolerated. One patient required dose reduction and ultimately cessation of therapy due to persistently elevated liver function tests. A second patient experienced neutropenia which improved with dose reduction. Only one patient was noted to have new CMV reactivation and newly detected BK viremia during the course of ruxolitinib treatment. One patient experienced Citrobacter sepsis. No other significant related morbidities were observed during the treatment period.
Patients had overall favorable therapeutic responses to ruxolitinib. All patients experienced improvement of specific organ GVHD scores during therapy, with four patients showing improvement in overall severity. Median time to organ score improvement was 21 days. Additionally, four patients had an associated sustained improvement in performance score while on ruxolitinib. Of three patients for whom systemic immunosuppression weaning was attempted during ruxolitinib therapy, all patients tolerated taper without resultant GVHD flare.
Conclusion: Similarly to recent reports of adult HCT patients, ruxolitinib appears to be well-tolerated and potentially effective in treating severe and refractory GVHD in the above pediatric HCT patients.

Paper Session # 4022

PATIENT AND PARENT EXPERIENCE OF CANCER SYMPTOMS AS ASSESSED BY THE MEMORIAL SYMPTOM ASSESSMENT SCALE FOR CHILDREN

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Background: Treatment for childhood cancer is associated with symptoms that contribute to poorer psychological and physical functioning and decreased quality of life. The prevalence of such symptoms has been shown to be positively correlated with global distress, while negatively correlated with levels of daily physical and psychological functioning. Symptom assessment scales have been used to identify the prevalence, severity and distress related to cancer treatment. Such tools require parents and patients to score their symptoms with regards to severity, frequency and distress, with such scores being used to calculate global symptom scores for each patient. While these scores provide means for statistical analysis of symptoms in childhood cancer, the clinical relevance of the scores are not well understood.
Objectives: Explore patient and parent experiences of treatment related cancer symptoms and associated distress as assessed by the Memorial Symptom Assessment Scale (MSAS).
Design/Method: Eligible participants were children ages 7-18 receiving chemotherapy and their primary caregiver. This mixed methods study included the completion of an age appropriate MSAS scale, as well as a semi-structured interview, in which the caregiver and child were asked follow-up questions about expectations and experiences of symptoms as well as the frequency, severity and distress levels endorsed on the MSAS scale. MSAS scores were calculated and interviews were themed using consensual qualitative analysis.
Results: Sixteen mother/child dyads completed an MSAS scale and a semi-structured interview exploring their experience of symptoms endorsed. The most prevalent symptoms in children were pain (60%), tiredness (50%) and vomiting (50%). Symptoms most prevalent in adolescents included dry mouth (100%), as well as nausea, drowsiness and not looking the same (83% each). Patients and parents reported expecting to be sick during chemotherapy and therefore accepted the severity and distress of symptoms as a part of the process. Symptom distress was often related to limitations in ability to function in age related activities with friends and family. Lastly, patients reported experiencing co-occurring symptoms that clustered together over the course of their cancer treatment.
Conclusion: Symptom assessment tools for childhood cancer have provided evidence that children and adolescents experience multiple distressing symptoms during treatment. This preliminary exploration of patient and parent experiences of symptoms suggests that patient and parent expectations about cancer treatment and the impact of symptoms on daily functioning may influence perceptions of symptom severity and distress, warranting further research on the clinical interpretation of symptom assessment scales in childhood cancer treatment.

Paper Session # 4023

IMPACT OF ETHNICITY AND EDUCATION LEVEL ON PARENTAL

PREFERENCES FOR INFORMATION GIVING AND DECISION MAKING IN THE PEDIATRIC CANCER SETTING

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Background: Information gathering can be an essential component to the decision making and coping processes of families faced with a pediatric cancer diagnosis. Previous studies demonstrate that personal characteristics influence information needs and parental preference for the quantity and technicality of information is variable. In the pediatric cancer setting, parents have expressed a preference for a collaborative or passive role in treatment decision making. However, these preferences have not yet been explored in ethnically diverse populations.
Objectives: Compare information and decision-making preferences and understanding of genetic concepts based on parental ethnicity and education level of parents at entry into a cancer genomic trial.
Design/Method: The NHGRI/NCI-funded BASIC3 trial examines the clinical utility of tumor and germline whole exome sequencing in the care of newly-diagnosed pediatric solid tumor patients. Upon enrollment, participating parents are asked to complete surveys, electronically or on paper, in English or Spanish. The surveys elicit parental race, ethnicity, and education level. They assess factors including: parent preference to receive numerical or descriptive information, preference for involvement in decision making for their child's treatment as measured by the Control Preferences Scale for Pediatrics modified by Pyke-Grimm et al., and understanding of basic genetic concepts presented in the informed consent process.
Results: The survey was completed by 140 parents (30.5%), with 42.9% identifying as Hispanic and 61.3% as female. Parents were grouped by education level: high school degree or less (n=32), some college/college degree (n=74), or graduate degree (n=32). Parents (42.1%) reported a preference for a collaborative role in treatment decision making, for example stating "I prefer that my child's doctor and I share responsibility for deciding which treatment is best for my child." This preference did not differ significantly by ethnicity or parental education level. Parents with less education prioritized verbal description of information, with preference for numeric descriptions increasing by education level ($p<0.001$). Although parents with less education scored lower on the genetic concepts assessment ($p<0.001$), all educational groups scored well (average 88-100% accuracy).
Conclusion: The results from this ethnically diverse population of pediatric cancer patients demonstrate that parents prefer collaboration with their child's oncologist regarding treatment decisions, independent of ethnicity and education level. Parents across education levels demonstrated a good understanding of the presented genetic concepts. Oncologists should elicit parents' preferences for the format of information delivery and may need to tailor information based on the parents' education level in order to develop a collaborative decision-making relationship.

Paper Session # 4024

PROCESSING SPEED AND ACADEMIC FLUENCY IN YOUTH WITH SICKLE CELL DISEASE

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Background: Children with sickle cell disease (SCD) are at risk for global neurocognitive deficits. Even in youth with SCD who have not endured a stroke, subtle white matter changes are common and can disrupt specific functions such as cognitive efficiency. However, processing speed deficits in SCD and their relation to academic outcomes and perceptions of academic success have not been systematically investigated.
Objectives: To measure processing speed and explore associations with academic fluency, academic achievement, and children's self-perception of scholastic competence.
Design/Method: Participants included 64 children with SCD ages 7-16 (M=10.58, SD=2.87, 42% male) enrolled in a larger study of the efficacy of a computerized cognitive training program. As part of this study, youth completed neuropsychological measures (for each standardized task, M=100; SD=15) of processing speed (Wechsler Intelligence Scale for Children, Fifth Edition) and reading and math fluency (Wechsler Individual Achievement Test, Third Edition), and a scholastic competence questionnaire assessing self-efficacy related to school. Parents completed demographic information and subjective ratings of their child's academic performance (below, at, or above grade-level).
Results: Participants' standard scores on measures of processing speed were lower than expected compared to the normative sample (M=88.13-94.91). In regards to academic tasks, children exhibited the greatest difficulty in math fluency (M=83.17, SD=13.58). Processing speed predicted performance on both reading and math fluency tasks (β=0.60, and β=0.52 respectively, p0<.001). Academic fluency predicted children's perceptions of scholastic competence (β=0.47, p=0.013). A regressing model including processing speed and academic fluency predicted 22% of the variance in parent-reported school performance (p=0.003). Youth who repeated a grade (n=6) scored lower on processing speed and academic fluency tasks compared to youth who did not repeat a grade (Processing Speed Index median=68.5 and 82.0, respectively; Academic Fluency median=68.5 and 82.0, respectively).
Conclusion: Youth with SCD scored in the Low-Average to Average range on measures of processing speed, representing a generalized weakness in quickly and efficiently processing information. This weakness appears to negatively impact academic performance, particularly in regards to math fluency. Such problems affect children's sense of scholastic competence and were associated with poorer academic achievement, as reported by parents. Furthermore, slowed processing was associated with a greater incidence of grade retention in this population. Results have implications for the identification of youth with SCD at risk for academic difficulties and the development of interventions to promote positive academic outcomes.

Paper Session # 4025

HEMATOPOIETIC ORIGIN AND TARGETS FOR THERAPY IN CNS LANGERHANS CELL HISTIOCYTOSIS: BRAF-V600E IN BLOOD AND BRAIN AND RESPONSE TO BRAF INHIBITION SUGGEST HEMATOPOEITIC ORIGIN OF NEURODEGENERATION IN LCH

Olive Eckstein, Kenneth McClain, Jennifer Picarsic, Rikhia Chakraborty, Howard Lin, Harshal Abhyankar, Daniel Zinn, Brooks Scull, Albert Shih, Karen Phaik Har Lim, Tricia Peters, Thomas Burke, Nabil Ahmed, John Hicks, Brandon Tran, Jeremy Jones, Robert Dauser, Michael Jeng, Robert Baiocchi, Deborah Schiff, Stanton Goldman, Kenneth Heym, Harry Wilson, Benjamin Carcamo, Ashish Kumar, Carlos Rodriguez-Galindo, Nicholas Whipple, Patrick Campbell, Geoffrey Murdoch, Simon Heales, Marian Malone, Randy Woltjer, Joseph Quinn, Paul Orchard, Michael Kruer, Ronald Jaffe, Markus Manz, Sergio Lira, William Parsons, Miriam Merad, Carl Allen

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Background: Langerhans cell histiocytosis (LCH) is a myeloid neoplasia characterized by inflammatory lesions with pathologic CD207+ dendritic cells. Central nervous system (CNS) involvement may include mass lesions or a progressive neurodegenerative syndrome (LCH-ND). In addition, differentiation of isolated pituitary lesions from other conditions is difficult due to risks associated with biopsy. LCH-ND may arise several years after LCH is presumably cured, the mechanisms of pathogenesis are unknown, and there are no standard approaches to surveillance or therapy.
Objectives: To define the pathogenesis of LCH CNS lesions by studying molecular biomarkers in CSF, brain and blood.
Design/Method: We evaluated cerebral spinal fluid (CSF) biomarkers including 121 proteins associated with inflammation or neurodegeneration and extracellular BRAFV600E DNA in CSF from 40 patients with LCH CNS tumors and/or LCH-ND and compared these to results from patients with brain tumors and other neurodegenerative conditions. Peripheral blood and brain biopsy specimens were tested for the presence of cells harboring BRAFV600E+mutations and levels of osteopontin expression were simultaneously measured.
Results: Osteopontin was significantly elevated in CSF from patients with LCH-ND compared to patients with brain tumors and other neurodegenerative conditions. Surprisingly, extracellular BRAFV600E DNA was detected in the CSF of only 2/23 (9%) patients with both positive cases in patients with active meningeal lesions. In contrast to CSF, BRAFV600E mutations were detected in peripheral blood of 14/40 (35%) cases, most of which did not have detectable LCH lesions outside the CNS. Brain biopsies of patients with LCH-ND demonstrated significant infiltration by BRAFV600E+ cells with osteopontin expression highest in areas with BRAFV600E+ cells. Three of the four patients with refractory LCH-ND who were treated with BRAF inhibitors experienced significant clinical improvement.
Conclusion: Previously, speculation on the pathogenesis of LCH-ND evoked autoimmune or inflammatory mechanisms. Our results demonstrate that BRAFV600E+ cells are found in the peripheral blood and brain of patients with LCH-ND and supports a model of LCH arising from a common hematopoietic precursor where BRAF-V600E+ cells may migrate to the CNS and mediate an inflammatory process resulting in LCH-ND. These observations support evaluation of LCH mutations in serial blood samples prospectively along with long-term clinical surveillance to identify patients at risk for LCH-ND. Further, patients with LCH-ND may benefit from early initiation of therapy directed against a circulating myeloid precursor with activated MAPK signaling.

Paper Session # 4026

MOLECULAR SUBGROUPING AND OUTCOMES FOR YOUNG CHILDREN WITH NEWLY DIAGNOSED EPENDYMOMA TREATED ON THE MULTI-INSTITUTIONAL SJYC07 TRIAL

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Background: Children with gross totally resected (GTR) ependymoma (EPN) treated with adjuvant conformal radiotherapy (CRT) have a 5-year survival of 65-85%. However, outcomes are inferior for those < 3 years of age, sub totally resected (STR) tumors and posterior fossa primary. Systemic chemotherapy has demonstrated a beneficial effect on survival for those with incompletely resected tumors. Tumor DNA methylation profiling enables subgrouping and prognostication of EPN patients.
Objectives: 1) Estimate event free (EFS) & overall survival (OS) for EPN patient's ≤ 3 years of age treated with risk adapted therapy. 2) Use DNA methylation profiling to determine subgroup specific outcomes for study cohort
Design/Method: Children ≤ 3 years of age with centrally reviewed and confirmed EPN (WHO grade II/ III) were prospectively enrolled on the multi-institutional, risk adapted treatment protocol, SJYC07. Following a maximal safe surgical resection all patients received 4 cycles of systemic chemotherapy with high dose methotrexate, vincristine, cisplatin and cyclophosphamide. Second look surgery was offered for those with less than GTR prior to consolidation therapy using focal CRT (M0 disease) or additional chemotherapy with cyclophosphamide and topotecan (M+ disease), followed by 6 months of oral maintenance chemotherapy. DNA methylation profiling using the Illumina Infinium Human-Methylation 850K BeadChip array was performed to determine molecular subgroups and identify copy number changes.
Results: Median age at diagnosis for the 50 children treated from June 2008 to October 2016 was 1.7 years (range, 0.4-3.1 years). The majority (40/50, 80%) had a posterior fossa (PF) primary and grade III (anaplastic) histology (34/50, 68%). Thirty were males and 48/50 had M0 disease. At a median follow up of 3.2 years (range, < 1 month-8.3 years), 46/50 (92%) are alive with 5-year EFS and OS of 74±10% and 84±8% respectively. Median time to progression for 11 subjects who failed was 27.3 months (range, 1.7-71.7 months). Subgrouping information was available for 43/50, with a predominance of PF-A tumors (33/43, 77%) followed by EPN-RELA (6/43, 14%) and EPN-YAP (4/43, 9%). There was no significant difference in EFS between the different subgroups (5-year estimates: PF-A, 71±11%; ST-RELA, 67±22%; ST-YAP, 100%) or between histological subtypes among PF-A patients (5-year estimates: Grade II, 63±17%; Grade III, 74±13%).
Conclusion: Young children with ependymoma have excellent survival when treated with maximal safe resection, adjuvant chemotherapy and CRT. These children predominantly belong

to the PF-A EPN subgroup. Additional molecular risk factors need to be sought to determine those at high risk of relapse.

Paper Session # 4027

SAFETY AND TOLERABILITY OF COMBINING THE IDO-INHIBITOR INDOXIMOD WITH RE-IRRADIATION FOR PEDIATRIC PATIENTS WITH PROGRESSIVE BRAIN TUMORS TREATED ON THE NLG-2105 PHASE 1 TRIAL (NCT02502708)

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Background: The indoleamine 2,3-dioxygenase (IDO) immune-checkpoint pathway is a natural mechanism that inhibits immune responses and is often exploited by tumors to overcome anti-tumor immunity. Small-molecule inhibitors of IDO, such as indoximod, are in early-phase clinical trials. Until recently these studies have been limited only to adults. For children with progressive brain tumors, adding indoximod immunotherapy to re-irradiation therapy is a very novel approach.
Objectives: Present interim results for the ongoing pediatric phase-1 study (NCT02502708).
Design/Method: The ongoing phase-1 study assesses the feasibility, safety, and preliminary evidence of efficacy of combining indoximod either with temozolomide, or with radiation followed by maintenance therapy with indoximod/temozolomide, for children age 3 to 21 with progressive malignant brain tumors (excluding DIPG). The study includes two dose-escalation cohorts using a standard 3+3 design to determine a recommended phase-2 dose (RP2D) for indoximod in combination with either temozolomide (planned n=12) or radiation (planned n=12). Indoximod dose-levels are 80%, 100%, and 120% of the adult RP2D (NCT02052648). Histology-specific expansion cohorts for phase-2 efficacy investigation will open once the pediatric RP2D is established. Here, we present up-to-date toxicity/side-effect data and follow-up results for all patients treated with indoximod plus radiation.
Results: To date, 12 children with relapsed/refractory CNS tumors, including ependymoma (n=8), medulloblastoma (n=2), glioblastoma (n=1), and PNET (n=1), have received a total of 16 independent re-irradiation treatment plans in combination with indoximod. Some children received more than one radiation plan over time. All patients were heavily pre-treated, and for many it was necessary to constrict target volumes to minimize adjacent tissue toxicities. Overall, indoximod combined with re-irradiation has been well tolerated, with only 1 FDA-reportable adverse event of spinal cord compression during radiation in a patient who, at study entry, already had a rapidly growing upper-cervical cord tumor. Aside from this reportable AE, no patient had a significant decline in performance score at the end of their radiation plan or developed overt radiation necrosis, somnolence syndrome, or other unanticipated side-effects associated with radiation. All patients were able to complete their radiation plans and start maintenance therapy with indoximod/temozolomide without delay. Follow-up duration ranges

from 1-12 months.
Conclusion: Indoximod is well tolerated in pediatric brain tumor patients receiving re-irradiation and does not seem to potentiate radiation-mediated toxicities. The long-term goal is to incorporate indoximod into multimodal therapy platforms in up-front treatment settings.
*Sponsored by grants from: Alex's Lemonade Stand Foundation, Cannonball Kids' cancer Foundation, Hyundai Hope on Wheels Foundation, NewLink Genetics Corporation.

Paper Session # 4028

WHOLE-EXOME SEQUENCING STUDY OF MEDULLOBLASTOMA CASES TO IDENTIFY DISEASE ASSOCIATED EXONIC MUTATIONS

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Background: Medulloblastoma is the most common malignant CNS tumor in children. Most cases are sporadic, but medulloblastoma also occurs in patients with nevoid basal cell carcinoma syndrome (NBCCS) and Turcot's syndrome. These syndromes are associated with germline mutations in PTCH1 and APC. Germline mutations in PTCH1, SUFU, and APC have also been associated with sporadic medulloblastoma.
Objectives: We used whole-exome sequencing to evaluate rare exonic variants in pediatric medulloblastoma patients and their parents to identify potential deleterious variants associated with disease.
Design/Method: We whole-exome sequenced (WES) blood-derived DNA from 26 children with medulloblastoma (n=26) and parents when available (n=40), and compared them with 1,001 European adult cancer-free controls and our 2,000 in-house database of familial samples sequenced at the same time. We focused our analyses on rare variants in candidate genes, including PTCH1, SUFU, APC and genes in their functional pathways, plus 126 established cancer predisposing genes (CPG).
We evaluated rare non-silent genetic variants that passed quality control filters. Variants were considered rare if the minor allele frequency was less than 1% in public databases (ESP, ExAC, and 1000 genome), controls, and in-house database. We used in-silico prediction programs, the variant impact on the protein (i.e., nonsynonymous, nonsense), and public mutation databases to assess potential pathogenicity. Rare variants that matched our candidate gene list were considered of interest if they were (a) previously reported as disease-causing in NBCCS or Turcot's, or (b) predicted high impact (i.e., nonsense, frameshift), or (c) predicted damaging by at least five of seven in-silico prediction programs (CADD, PolyPhen 2, SIFT, Mutation Assessor, Mutation Taster, LRT, FATHMM).
Results: Overall, 16 of 26 patients had a rare predicted damaging heterozygous variant in a gene on one of our candidate lists: four were within the PTCH1/SUFU pathway, three genes from the APC pathway, and eleven in an established CPG. Seven of the 11 CPG variants were in an autosomal dominant CPG and four in an autosomal recessive CPG. Two predicted damaging rare variants were present in two patients each, but neither were a candidate gene. There were no mutations in PTCH1 or SUFU genes. Interestingly, one patient had a rare predicted damaging

variant in APC, a nonsynonymous heterozygous T to G transversion (chromosome 5, position 112,176,023) that was previously reported in a patient with colorectal adenoma.
Conclusion: These rare predicted damaging variants in genes of interest are potentially important in medulloblastoma, further evaluation with functional studies are needed to determine their significance.

Paper Session # 4029/Early Career Travel Stipend Award Recipient

THE GENOMIC LANDSCAPE OF PEDIATRIC MYELODYSPLASTIC SYNDROMES

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Background: Myelodysplastic syndromes are uncommon in children (incidence of ~2 cases/million) and have a poor prognosis. Despite the wealth of knowledge about the genomic landscape of adult MDS, much less is understood about pediatric MDS, and many recurrent mutations found in adults are not common in children.
Objectives: To define the somatic and germline genomic landscape of pediatric MDS and test the in vitro activity of signaling alterations identified.
Design/Method: Seventy-eight diagnostic bone marrow samples obtained from the St. Jude Children's Research Hospital Tissue Bank (Memphis, TN, USA) were analyzed. This cohort contains 48 primary MDS, including Refractory Cytopenia of Childhood/RCC (n=24) and Refractory Anemia with Excess Blasts/RAEB (n=24). We also included 22 MDS/MPN (including 18 Juvenile Myelomonocytic Leukemia/JMML), and 8 cases of AML with Myelodysplasia-Related Changes/AML-MRC given their clinical overlap with primary MDS. WES was completed for 55 tumor/normal pairs using the Nextera Rapid Capture Expanded Exome (Illumina), and targeted sequencing was completed with a custom amplicon strategy for 23 tumor-only cases. Normal comparator gDNA was obtained from flow-sorted lymphocytes.
Results: Copy number information, obtained from WES data, determined that deletions involving chromosome 7 were more frequent in primary MDS (n=12, 36%) as compared to MDS/MPN (n=1, 7%) and AML-MRC (n=2, 25%). RAS/MAPK pathway mutations were present in 55% of the patients (46 total mutations in 43 cases, including 3 germline variants). Mutations in RNA splicing genes (germline, n=0; somatic, n=4; 5% of cohort) were much less common. Germline variants in transcription factors seen in familial MDS/AML (e.g., RUNX1, CEBPA, ETV6) were uncommon. Presumed germline GATA2 variants were found in 4 patients (5%). RNA-sequencing performed on 42 samples showed that fusion transcripts were uncommon in primary MDS.
Although many of the mutations affecting the RAS/MAPK pathway were in common genes (NRAS, PTPN11), many other mutations were in genes less frequently reported to be mutated in myeloid neoplasms, such as BRAF. We demonstrated that the mutations in BRAF (G469A, D594N) found in our cohort activate the RAS/MAPK pathway to variable levels, as measured by ERK phosphorylation, and confer IL3-independence in Ba/F3 cells.
Conclusion: The genomic landscapes of pediatric and adult MDS are different, namely in patterns of RAS/MAPK pathway and RNA splicing gene mutations, thus supporting the notion that MDS in adults and children comprise unique biological entities. The enrichment of

RAS/MAPK mutations in pediatric MDS suggests biologic overlap with JMML and may provide direction for future therapeutic options.

Paper Session # 4030

CHARACTERISTICS AND OUTCOMES OF OSTEOMYELITIS IN CHILDREN WITH SICKLE CELL DISEASE: A RETROSPECTIVE REVIEW OF A 10-YEAR SINGLE-CENTER EXPERIENCE

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Background: Patients with sickle cell disease (SCD) are at increased risk for Osteomyelitis (OM). Diagnosis of OM in this population is challenging and there is limited pediatric data on the characteristics and outcomes of OM in this population.
Objectives: To report characteristics and outcomes of OM in children with SCD treated at our center over the last 10 years.
Design/Method: We conducted a retrospective chart review of all patients with SCD who were diagnosed at our center with OM over a 10-year period (2006-2016). Cases were identified utilizing radiology data mining software (MONTAGE™ Search and Analytics). The radiology reports and medical charts of potential OM cases were reviewed to identify true OM cases. Relevant data were collected and summarized using descriptive statistics.
Results: Thirty children with SCD (18 males, median age 12 years) were treated for OM at our institution during the study period. The genotype was SS in 27 patients, SC in 2, and SF in 1. Sites of involvement included lower extremity (11), upper extremity (10), pelvis (2), vertebrae (2), scapula (1), clavicle (1), hand (1), ribs (1) and mandible (1). Leukocytosis (>15,000/mm3) was observed in 13 patients (43%) at presentation. Baseline erythrocyte sedimentation rate was elevated (>20 mm/hour) in 29 patients (97%) but marked elevation (>100 mm/hour) was present in 3 patients (10%). Baseline C-reactive protein was elevated (>10 mg/L) in 13 patients (43%). Bacteremia was present in 6 patients (20%). Magnetic resonance imaging (MRI) findings were suggestive of OM in 18 patients (60%) and indeterminate in the remaining patients. The diagnosis of OM was confirmed in 3 patients (bone biopsy), probable in 6 patients (organism isolated from blood or abscess), and presumed in the remaining cases based on clinical, laboratory, and MRI findings. Non-typhoidal Salmonella was isolated from cultures in 9 (30%) patients [bone biopsy (3), abscess (3), and blood (6)] while no organism was found in the remaining 21 (70%) patients. All patients were treated with prolonged antibiotic therapy. Six patients required surgical drainage/debridement. Two patients developed chronic OM. There were no mortalities and complete resolution of OM was achieved in all patients.
Conclusion: Despite improvements in the management of SCD over the past decade, OM continues to be a serious infection in children with SCD associated with significant morbidity. The majority of patients are treated for presumed diagnosis of OM without definitive confirmation. Non-typhoidal Salmonella was the only organism identified in our patient cohort.

Paper Session # 4031

RETROSPECTIVE STUDY OF HEMATOLOGIC COMPLICATIONS IN VASCULAR

MALFORMATION PATIENTS WITH LOCALIZED INTRAVASCULAR COAGULOPATHY UNDERGOING SCLEROTHERAPY

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Background: Slow-flow vascular malformations, most commonly multifocal or diffuse venous (VM), venous-lymphatic (VLM) and capillary-lymphatic-venous malformations (CLVM), are associated with coagulation abnormalities affecting hemostasis and thrombosis and increase risk of hematological complications with procedural interventions. Although not completely understood, pathogenesis of this coagulopathy, called localized intravascular coagulopathy (LIC), is presumed secondary to stagnant blood in abnormal vessels and consumption of coagulation factors. LIC is characterized by elevated D-dimer, low fibrinogen, and/or mild thrombocytopenia and may progress to disseminated intravascular coagulopathy following surgical procedures. In patients with high-risk malformations, hematologic complications of sclerotherapy and use of low molecular weight heparin (LMWH) as a preventative measure have not been well studied.
Objectives: To retrospectively evaluate hematologic complications in patients undergoing sclerotherapy with slow-flow vascular malformations and LIC
Design/Method: This study reviewed medical records of adult and pediatric patients with slow-flow vascular malformations who underwent sclerotherapy at Cincinnati Children's Hospital Medical Center from July 2008 to December 2016 with LIC as defined by high D-dimer (5 times upper limit of normal), fibrinogen <150mg/dL and/or platelet count <150K/mcL. Hematologic complications included any clinically relevant bleeding or clotting abnormality that occurred 2 weeks post-sclerotherapy and/or while on LMWH prophylaxis, up to 2 weeks, prior to sclerotherapy. Relevant hematuria included gross and large microscopic hematuria. Use of LMWH including dose, frequency and course length was evaluated.
Results: Forty of 300 patients had slow-flow vascular malformations with associated LIC (25 with extensive VM/VLM, 9 with multiple VM/VLM, 4 with CLVM, 2 with localized VM/VLM) and underwent a total of 241 sclerotherapy procedures with 86% occurring in individuals under 18 years of age. In 87% of cases, LMWH was administered at 0.5mg/kg/dose once daily for 2 weeks before and after sclerotherapy. No thrombotic complications occurred in children. One adult patient on LMWH developed pulmonary emboli, presumably from deep vein thrombosis of the treated extremity. Two patients developed transient, asymptomatic hematuria. In 5 patients fibrinogen levels dropped below 100 mg/dL post-sclerotherapy for which cryoprecipitate was administered; no bleeding complications occurred. Prior to sclerotherapy, one individual developed mild bleeding from cutaneous lesions on LMWH. No intra-op bleeding or thrombotic events occurred.
Conclusion: Prophylactic LMWH use was common in this patient population and did not appear to increase the risk of significant bleeding before, during or after sclerotherapy. In children receiving LMWH, thrombotic complications after sclerotherapy appear rare but may still occur. Further studies evaluating peri-procedural LMWH are needed to determine benefit and optimal dosing.

Paper Session # 4032

CLINICAL AND LABORATORY OUTCOMES FOLLOWING TOTAL OR PARTIAL SPLENECTOMY IN PATIENTS WITH HEREDITARY SPHEROCYTOSIS

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Background: Hereditary spherocytosis (HS) results from a primary defect in the erythrocyte membrane which increases membrane fragility. Spherical erythrocytes are removed by the spleen, causing anemia, jaundice, gallstones and splenomegaly. Total splenectomy (TS) reduces erythrocyte destruction but is associated with increased risk of sepsis from encapsulated bacteria and thrombotic complications. Partial splenectomy (PS) is an alternative to TS, however the spleen remnant occasionally regrows and causes recurrent symptoms. Long-term outcomes could inform surgical decision-making.
Objectives: To compare outcomes for patients with HS following TS or PS.
Design/Method: We retrospectively reviewed the records of HS patients who underwent TS and/or PS at Boston Children's Hospital between 1998-2016.
Results: Sixty-six patients were identified following TS (24) and PS (42). The mean duration of follow-up was significantly longer for PS than TS patients (5.0 vs. 1.3 years, $p < 0.001$). The most common indications for surgery were anemia (n=43), jaundice (n=35), abdominal pain (n=31), gallstones (n=29), splenomegaly (n=21), and fatigue (n=16).
The surgical approach was mainly laparoscopic for TS (n=23) and open for PS (n=30). Longer length of stay occurred following PS than TS (5.8 vs. 4.3 days, $p < 0.001$). Immediate increase in hemoglobin and reduction in reticulocyte count and bilirubin was observed after both procedures. By 5 years post-procedure, the mean hemoglobin was significantly lower for PS patients compared to TS (n=22, 12.2 vs 13.1 g/dl, $p < 0.001$). The reticulocyte count (7.3 vs 2.8%, $p< 0.001$) and bilirubin (2.3 vs 1.3 g/dl, $p < 0.001$) were significantly higher in the PS group. Short-term adverse events occurred less frequently in TS than PS patients (29 vs 62% $p = 0.02$). Long-term adverse events were not statistically different between PS and TS patients (56% vs 21%, $p = 0.06$). During 15,686 person-years of follow-up, we identified no deaths, sepsis or thromboembolic events. One case of meningoencephalitis was reported after a TS (4%). The spleen regrew and symptoms recurred in 5 PS patients (12%), leading to a completion splenectomy procedure.
Conclusion: PS for HS results in the relief of symptoms and improvement of hematologic parameters. However 12% of patients eventually require a completion splenectomy. While TS is associated with a statistically higher hemoglobin at 5 years, the difference over PS is not clinically relevant. PS is a reasonable choice for HS, especially for preservation of spleen function. TS results in lower rates of adverse events, better hematologic outcomes and low risk of severe infection.

Poster # 001

PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) OF ROMIPLOSTIM IN PEDIATRICS WITH IMMUNE THROMBOCYTOPOPENIA (ITP)

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Background: Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a low circulating platelet count, as a result of increased platelet destruction and/or impaired platelet production. Romiplostim (Nplate®) is an Fc fusion peptibody that increases platelet production by binding to the thrombopoietin (TPO) receptor and activating intracellular signaling pathways, similar to endogenous TPO.
Objectives: This study describes the pharmacokinetics (PK) and pharmacodynamics (PD) of romiplostim in children with ITP, and compare them to adult data for supporting a pediatric dosing regimen.
Design/Method: The PK and PD of romiplostim have been investigated in 2 pediatric clinical studies following weekly subcutaneous administration with dose titration based on the platelet response. In study 20090340, intensive romiplostim concentrations were available from 4 subjects (2 at 7 µg/kg and 2 at 9 µg/kg). In study 20060195, pre- and post-dose romiplostim concentrations were available from 31 subjects at doses ranging from 1 to 10 µg/kg.
Results: Romiplostim serum concentrations were highly variable in both pediatric studies. The concentrations of romiplostim from both studies generally fell within the range observed in adults. In study 20090340, the maximum concentration of romiplostim was reached by 24 hours post dose and then declined. In study 20060195, no obvious association between romiplostim doses and serum concentrations was observed, suggesting that factors other than the romiplostim dose may impact clearance. Most subjects who received romiplostim achieved an increase in platelet count above baseline for at least 2 consecutive weeks during the treatment period. However, pre-dose romiplostim concentrations and the corresponding platelet counts did not show notable correlation in this pediatric study, similar to what has been observed in adults. Therefore, to achieve the optimal romiplostim dose in children with ITP, a strategy was proposed to titrate dose based on platelet response, similar to adult dosing strategy. Pediatric clinical trials demonstrated the feasibility and effectiveness of using patient platelet response to titrate dose.
Conclusion: The romiplostim serum concentrations were highly variable in children with ITP and generally fell within the range observed in adults with ITP. The same complex PKPD relationship of romiplostim was observed in children and adults, supporting the same dose titration regimen in children with ITP based upon platelet response as adults.

Poster # 002

PRE-AND POST-TESTS FOR ASSESSING THE EFFECTIVENESS OF LECTURING AS A TOOL FOR TEACHING VENOUS THROMBOEMBOLISM (VTE) TO PEDIATRIC RESIDENTS: PILOT STUDY TO ASSESS LEARNING IN HEMATOLOGY

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Background: A marked increase in the incidence of VTE is recently observed in hospitalized children. This rise emphasizes the need for adequate education among pediatric residents.

Research evaluating curriculum development and validated testing in pediatric hematology has not been done to date.
Objectives: To assess the reliability and validity of pre- and post-lecture tests as tools to determine whether a lecture on VTE in children will increase medical knowledge.
Design/Method: A needs assessment was performed to evaluate gaps in VTE knowledge among pediatric residents at the University of Iowa. Pre- and post-tests were designed to align with lecture objectives. Pre-test assessed baseline knowledge and post-test assessed knowledge gained; both consisted of three multiple-choice questions and one open-ended question. Both tests were administered on the lecture day. Test analysis was performed to evaluate test quality. We conducted an item analysis and investigated test reliability and validity. Cronbach's alpha was used to estimate test reliability. A paired t-test was used to compare knowledge pre- and post-lecture.
Results: Ten residents participated in 2015 and six in 2016. Pre-test reliability in 2015 = 0.7941 (acceptable defined as $0.8 > \alpha \geq 0.7$); post-test reliability = 0. Average score on pre-test = 2.10 and post-test = 3.00. Average inter-item correlation = 0.5624. Pre-test standard deviation (SD) = 0.56, post-test SD = 0. Pre-test item discrimination (ID) = 33% (acceptable defined as ID > 30%), post-test ID = 0.The 2016 pre- and post-test reliability = 0. Average pre- and post-test scores = 2.17. Pre-test SD = 0.75, post-test SD = 0.41. Pre-test ID = 67%, post-test ID = 33%. Mean assessment scores from the 2015 group increased significantly from pre-lecture (70%) to post-lecture (100%), P = 0.0004. The 2016 group mean assessment scores were unchanged (72%, P = 0.5).
Conclusion: Results of this study suggest test quality and lecture efficacy are difficult to judge based on standard quantitative metrics of test assessment alone. Evidence for validity can be found within the content. Expert judges reviewed lecture content, interactive discussion and appropriateness of content used for the assessment instrument. Construct underrepresentation is a threat to the validity of our assessment instrument. Future directions for our assessment instrument include a larger set of test items and sample size to adequately determine its validity.

Poster # 003

EFFECT OF TREATMENT ON PROGRESSION TO CHRONIC ITP

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Background: Since serious consequences of immune thrombocytopenia purpura such as intracranial hemorrhage are rare, comparing the clinical outcome of treatments is difficult. The incidence of chronic disease however, is common enough that it can be more readily studied as an outcome. Decreasing the risk of chronic ITP would decrease the need for subsequent follow-up and treatment. Also, in spite of the low incidence of significant bleeding in chronic ITP, such children are often restricted from activities such as contact sports. Guidelines for ITP treatment have been developed by the American Society of Hematology but many of the recommendations are consensus rather than evidence based. The guidelines point out the lack of evidence for preventing intracranial hemorrhage and do not address the incidence of chronic disease.
Objectives: To determine whether treatment of ITP at presentation has an impact on the progression of patients to chronic ITP.

Design/Method: We evaluated 379 children with ITP (mean age 7.3) over 16 years. Patients' files were examined for whether and how they were treated, and if the condition became chronic. For 249 patients, data was adequate for inclusion.
Results: 126 (66 male, 60 female) of the patients (51%) progressed to chronic ITP. The percentage of chronic ITP for the treated and untreated group was 51.1% and 49.3% respectively. A total of 43 of the 80 treated females (53.8%) became chronic and 49 of the 100 treated males (49%) became chronic. The data suggest no effect of treatment on outcome for the majority of patients. For two subgroups, treatment was related to outcome: In females ages 0-3, those who were treated actually had a higher proportion of chronic ITP than those who were not treated (58 % vs. 0%, p=.008), as did females ages 0-6 (45% vs. 0%, p=0.002), suggesting that treating these subgroups of patients may actually negatively impact outcome. In a multivariate analysis, a higher platelet count and older age at presentation predicted chronic ITP, while treatment with steroids predicted acute ITP.
Conclusion: There is some statistical support that treatment of females ages 6 years and younger may be associated with a higher risk of progression to chronic disease, but overall, results suggest that treatment does not prevent chronic disease. We believe treatment bias explains why previous studies falsely show that treatment protects against chronic ITP.

Poster # 004

INTERNATIONAL SURVEY OF THE MANAGEMENT OF DISSEMINATED INTRAVASCULAR COAGULATION AMONG PEDIATRIC AND NEONATAL HEALTH CARE PRACTITIONERS

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Background: The International Society on Thrombosis and Hemostasis (ISTH) developed a diagnostic scoring system for disseminated intravascular coagulation (DIC) which has been used widely in adult intensive care units. However, controversies exist in pediatric and neonatal DIC diagnosis and management regarding the normal ranges and the choice of diagnostic coagulation tests.
Objectives: 1) To evaluate current practice in pediatric/neonatal DIC management among neonatologists (NICU), pediatric intensivists (PICU), hematologists/oncologists (PHO), emergency physicians, and general pediatricians; 2) To explore age-specific issues in DIC diagnosis including age-specific reference ranges in the context of the DIC scoring system.
Design/Method: An online questionnaire was developed using LimeSurvey software and consisted of 3 sections: Respondent Demographics; DIC Diagnosis; and DIC Management. International dissemination was ensured via pediatric and neonatal professional societies to their members. The study was coordinated by sites in Hamilton (Canada) and Melbourne (Australia) in collaboration with Manchester (England) and members of ISTH Pediatric and DIC Scientific and Standardization Committees. Data collection was conducted from January to September 2016.
Results: A total of 211 responses were obtained: 160 full, 51 partial. There were 133 (63%) respondents from PHO, 45 (21%) from NICU, and 23 (11%) from PICU. Response geographic distribution: 96 (46%) from North America, 56 (27%) from Asia, 25 from Australia (12%) and

24 from Europe (11%). Most frequent cause of DIC was sepsis (163/211; 77%), mostly bacterial. To investigate DIC, 79 (42%) respondents use clinical experience only, 52 (28%) use the ISTH guidelines, and 28 (15%) use local institutional guidelines. Of those who use only clinical experience, 96% order platelet count and approximately 80% order INR, PT, aPTT, fibrinogen, and D dimer. Fibrin degradation products and smears for schistocytes are ordered by 28% and 41%, respectively, while thromboelastography (TEG) is ordered by only 6% of respondents. Age-specific laboratory cut offs for PT, INR, aPTT, fibrinogen, and platelet count were reported by approximately 60% of respondents, and for protein C, S and anti-thrombin by 46%, and for TEG by 13%. Transfusion of platelets (69%), plasma (64%) and cryoprecipitate (47%) were the most commonly used treatments, while antithrombin (18%), fibrinogen concentrate (16%), antifibrinolytics (9%), unfractionated heparin (9%) and LMWH (5%) were less common. Barriers to using standard DIC guidelines at various institutions were identified.
Conclusion: This survey reveals variable practices among pediatricians who diagnose and manage DIC. Guidelines which standardize practice in adults are not widely accepted in pediatrics. Pediatric DIC guidelines can address barriers to standardizing practice.

Poster # 005

SAFETY AND EFFICACY OF LONG-TERM OPEN-LABEL DOSING OF SUBCUTANEOUS (SC) ROMIPLOSTIM IN CHILDREN WITH IMMUNE THROMBOCYTOPENIA (ITP)

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Background: Children with ITP for ≥6 months who completed a romiplostim phase 1/2 or 3 study could enroll in this extension study, as described in this encore abstract.
Objectives: To evaluate the safety and efficacy of long-term romiplostim in children with ITP.
Design/Method: All patients received SC romiplostim once weekly, starting at the parent study final dose or 1 µg/kg if previously receiving placebo, adjusted from 1−10 µg/kg to target platelet counts of 50−200×10-9/L. Incidence of adverse events (AEs) was the primary endpoint.
Results: As of 24 Feb 2016, 66 patients entered this study; 65 received romiplostim. At baseline, median (min–max) age was 11 (3–18) years; 56% were female; 61% were white, 14% African American, 14% Hispanic/Latino, 9% Asian, and 3% other; 9.1% had prior splenectomy. Median (min–max) baseline platelet count was 27.5 (2–458)×10-9/L. Median (min–max) treatment duration was 100 (5–321) weeks. Median (min–max) average weekly romiplostim dose was 4.8 (0.1–10.0) µg/kg. All 65 patients received their doses per protocol >90% of the time. Reasons for discontinuing treatment (n=22, 33%) included consent withdrawn (n=8), required other therapy (n=4), noncompliance (n=3), administrative decision (n=3), per protocol (n=1), and AE (n=2) (asthenia, headache, dehydration, and vomiting in one patient and anxiety in the other, none treatment related); 43 (65%) patients continued. Fifty-two serious AEs occurred in 17 patients, 3 treatment-related (anemia, epistaxis, and thrombocytopenia). Bleeding AEs occurred in 56 patients; 5 treatment related (gingival bleeding, petechiae, injection site bruising, injection site hematoma, and epistaxis). No thrombotic events were reported. There were no peripheral blood abnormalities to warrant a bone marrow examination. No patients had anti-TPO neutralizing

antibodies.From week 2 on, median platelet counts remained >50×10-9/L and were generally >100×10-9/L. Nearly all (94%, 61/65) patients had a platelet response (monthly median platelet count ≥50×10-9/L). Nine (14%) patients entered remission, defined here as platelet counts ≥50×10-9/L for 24 weeks with no ITP treatments, for ≤1.9 years; these patients, none with prior splenectomy, had ITP for a median (min–max) of 5 (2–10) years, 1–5 past ITP treatments, and had received romiplostim for a median (min–max) of 1.6 (0.7–6.2) years. Twenty-three (35%) patients received rescue medications.
Conclusion: Over 6 years of data from this ongoing open-label extension of romiplostim in children with ITP show that >90% of children achieved a platelet response with romiplostim. The safety profile was overall tolerable, similar to that in past studies. Supported by Amgen Inc.

Poster # 006

HEMORRHAGIC AND ISCHEMIC STROKE IN CHILDREN WITH BRAIN TUMORS: A SINGLE-CENTER RETROSPECTIVE STUDY

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Background: Children with brain tumors are at increased risk for both ischemic and hemorrhagic stroke. Possible mechanisms include surgical disruption of normal vascular architecture, and exposure to radiation and anti-angiogenic therapies. Data in children with brain tumors are limited and likely underestimate the true prevalence of hemorrhagic and ischemic events in this population.
Objectives: To describe the frequency and characteristics of hemorrhagic and ischemic stroke in children with brain tumors.
Design/Method: We conducted a retrospective chart review of all pediatric patients with central nervous system (CNS) neoplasms who experienced an arterial ischemic or hemorrhagic stroke over a 5-year period in a large academic medical center. Cases were identified utilizing radiology data mining software (MONTAGE™ Search and Analytics). The radiology reports and medical charts of all potential cases were reviewed to identify true events. Relevant data were collected in a secure web-based database created using Research Electronic Data Capture (REDCap) application. Data are presented using descriptive statistics.
Results: A total of 287 children with brain tumors were treated at our institution from 2009 to 2013. Fifty-seven (19.8%) patients (median age 6.5 year, 31 males) experienced a CNS hemorrhage (43 patients; 14.9%) or arterial ischemic stroke (14 patients; 4.9%). Most events were diagnosed in patients with primary tumors, most frequently low grade gliomas (12 patients; 21%) and ependymomas (8 patients; 14%). Tumor locations in children who experienced a stroke were diverse, with 26% within the cortex, 26% suprasellar, and 12% in the posterior fossa. Events were more common in the early post-operative period. The mean duration of ICU stay in patients who experienced an event was 6 days (range 0-50 days). In children who developed CNS hemorrhage, 10 patients (18%) required prolonged hospitalization and 6 patients (11%) required surgical intervention to restore hemostasis. CNS hemorrhages were intratumoral and intraparenchymal in 50% and 36% of patients, respectively. Forty-one (72%) patients were not exposed to focal or craniospinal radiation at the time of event, and 36 (63%) patients had not received chemotherapy.

Conclusion: Children treated for brain tumors are at increased risk for stroke which can lead to significant morbidity. CNS bleeding was more commonly encountered than ischemic events, and was most likely to occur within tumors or surgical resection beds located in the cerebral cortex and suprasellar regions. Large prospective studies are needed to define the true incidence and identify risk factors predisposing to stroke in children with brain tumors.

Poster # 007

A SINGLE-ARM, OPEN-LABEL, LONG-TERM EFFICACY AND SAFETY STUDY OF SUBCUTANEOUS ROMIPLOSTIM IN CHILDREN WITH IMMUNE THROMBOCYTOPENIA (ITP)

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Background: Children with ITP will receive open-label subcutaneous investigational romiplostim for ≤3 years as described in this encore abstract.
Objectives: To assess platelet responses in children with ITP receiving romiplostim.
Design/Method: Eligible children had ITP for ≥6 months, ≥1 prior ITP therapy, and platelet counts ≤30×10-9/L. Weekly subcutaneous dosing was adjusted 1-10 µg/kg to target platelet counts of 50-200×10-9/L. The primary endpoint was the % time in the first 6 months with a platelet response [response=platelet count ≥50×10-9/L without rescue medications in the past 4 weeks].
Results: As of 15 Mar 2016, 145 patients received romiplostim. At baseline, median (min-max) age was 10 (2-17) years, ITP duration 1.9 (0.5-12.3) years, and platelet count 13 (2-168)×10-9/L; 4% had prior splenectomy. The median (Q1,Q3) % of time with a platelet response in the first 6 months was 50% (0%,83.3%). Overall, 80% (114/143) of patients had ≥1 platelet response. Median (min-max) treatment duration to date was 25 (1-67) weeks; total exposure was 79 patient-years. Median (min-max) average weekly romiplostim dose over the course of the study was 6.1 (0.4-9.0) µg/kg. Thirty-two patients (22%) discontinued treatment for lack of efficacy (n=17), required other therapy (n=5), patient request (n=4), noncompliance (n=2), adverse event (AE) (n=2) (interstitial lung disease and abdominal pain, vomiting, and headache), administrative decision (n=1), and investigator decision (n=1). Thirty-four (23%) patients received rescue medications. Fifteen (10.3%) patients had serious AEs (SAEs); abdominal pain was the one SAE deemed treatment-related. No grade 4-5 bleeding was observed. No neutralizing antibodies against romiplostim or TPO were identified.Of 30 patients with baseline bone marrow biopsies (obtained at European sites), all had modified Bauermeister scores of grade 0 (no reticulin) or 1 (fine fibers) and bone marrows typical for ITP. In year 1 on-study biopsies (n=21), there were no increases of ≥2 grades, collagen, or bone marrow abnormalities.
Conclusion: In this year 1 datacut of an ongoing open-label study of romiplostim in children with ITP, the proportion of time in the first 6 months with a platelet response was 50%, with 80% of children having a platelet response overall. The median romiplostim dose reached 10 µg/kg and there were no new safety signals. No effects of romiplostim on the bone marrow were observed in the subset of patients with bone marrow biopsies. Future datacuts for years 2 and 3

will provide more information on platelet response, dose requirements, and safety of romiplostim in children with ITP. Supported by Amgen Inc.

Poster # 008

THE EFFECT OF AGE AT DIAGNOSIS OF TYPE I VON WILLEBRAND DISEASE ON DIAGNOSTIC LAB VALUES: A PEDIATRIC PERSPECTIVE

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Background: The diagnosis of Type I von Willebrand disease (VWD) is determined based on bleeding symptoms and diagnostic lab values. U.S. guidelines recommend a von Willebrand antigen (VWF:Ag) and/or ristocetin cofactor (vWF:RCo) level of < 30 IU/dL for the diagnosis of type I VWD and 30-50 IU/dL for diagnosis of low von Willebrand factor. Prior studies have shown age affects vWF:Ag and vWF:RCo levels in healthy adults and those with type I VWD. Pediatric patients have not been included in prior studies.
Objectives: The primary aim of this study was to determine if age at diagnosis of type I VWD correlates with diagnostic lab values, including VWF:Ag level and VWF:RCo level in pediatric patients.
Design/Method: A retrospective database review was performed using the American Thrombosis and Hemostasis Network (ATHN) dataset. All patients with type I VWD, complete diagnostic lab records (vWF:Ag, vWF:RCo, Factor VIII level) and age at diagnosis were included in the study.
Results: Inclusion criteria was met by 1,570 patients. The patients were stratified into 5 groups based on age at diagnosis (stratum 1= 0-2 years, stratum 2= 3-10 years, stratum 3= 11-20 years, stratum 4= 21-30 years and stratum 5= 30+ years). An analysis of variance showed the mean vWF:Ag and vWF:RCo levels were not homogenous across the diagnosis age strata ($p<0.001$ and $p=0.001$ respectively). A post-hoc analysis showed the mean vWF:Ag in the 0-2 year strata was significantly less than the 3-10 year group (mean difference= 5.3, CI 2.0-8.6) and the 11-20 year strata (mean difference= 7.1, CI 3.6-10.5). However, the mean vWF:Ag in the 11-20 year strata was significantly higher than the 21-30 year strata (mean difference= 5.4, CI 1.0-11.8). The mean vWF:RCo in the 0-2 year strata was significantly less than the 3-10 year group (mean difference= 3.4 , CI 1.1-5.8) and the 0-2 year strata was significantly less than the 11-20 year strata (mean difference= 3.1, CI 0.7-5.6).
Conclusion: In pediatric patients with Type 1 VWD diagnostic VWF:Ag and VWF:RCo levels are directly related to age up through the adolescent age group .

Poster # 009

SAFETY AND EFFICACY OF ELTROMBOPAG (EPAG) AT DOSES UP TO 150 MG/DAY IN CHILDREN WITH CHRONIC IMMUNE THROMBOCYTOPENIA (cITP) WHO DID NOT ACHIEVE TARGET PLATELET COUNTS (PLTS) WITH 75 MG/DAY DOSE

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Background: Epag is an oral thrombopoietin-receptor-agonist that often increases Plts in cITP with a maximum licensed dose of 75 mg/day; however, some (even small) children do not respond to this dose. We report children with cITP on a double-blind, randomized-controlled study to determine if Epag, administered at doses up to 150 mg/day, can increase Plts in non-responders to 75 mg/day.
Objectives: To determine safety and efficacy of Epag at doses up to 150 mg/day in children with cITP not responding to 75 mg.
Design/Method: Children with cITP >1 and <22 years old with Plts <50,000/uL despite >3 weeks of Epag 75 mg/day were enrolled. The study comprises an 8-week double-blind phase (Part 1) followed by an open-label phase (Part 2); enrolled adults are not included here. Children were randomized 2:1 to receive Epag vs. placebo in Part 1. During Part 1, all patients received 75 mg/day of Epag and initially added 25 mg of study drug (Epag or placebo). Every 2 weeks, study drug increased by 25 mg/day up to 150 mg until either 8 weeks or Plts >100,000/uL. Part 2 allowed children randomized to Epag to continue treatment at their last dose at the end of Part 1. Children randomized to placebo received open-label escalated doses of Epag (recapitulating the 8-week dose escalation of Part 1) before initiating Part 2. Data analysis was descriptive. Imputation of Plts allowed omitting high Plts resulting from rescue therapy.
Results: Fifteen children aged 6-21 years (average 12), enrolled. Median Plts were higher in children on increased doses of Epag (n=10) compared to those on placebo (n=4) at week 4 (46,000 vs 36,000); week 6 (59,000 vs 22,000) and week 8 (65,000 vs 32,000). Three children on Epag and one on placebo (with an infection) met criteria to enter part 2 before reaching 8 weeks in part 1 because of Plts >100,000/uL. The average dose at the end of Part 1 was 2.6mg/kg; 6/10 children received >2mg/kg. All 15 children entered part 2. Four were disenrolled before 24 weeks: elevated transaminases (2) and no response (2). Two receiving other treatments were excluded from long-term analysis. Of nine children completing 24 weeks on open-label dosing, 70% had Plts >50,000/uL and 46% >100,000/uL. The child longest on study has participated for >3 years.
Conclusion: Doses of Epag >75 mg/day increased Plts in children with cITP not responding to 75 mg/day; special attention to monitoring transaminases is required.

Poster # 010

OUTCOMES AFTER OFF-LABEL USE OF RECOMBINANT FACTOR VIIa FOR SEVERE BLEEDING IN PEDIATRIC HEMATOLOGY/ONCOLOGY PATIENTS

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Background: Recombinant factor VIIa (rFVIIa) has been used off-label to treat severe bleeding after failure of conventional treatments. Data on off-label rFVIIa use in pediatrics remains sparse. Specifically, no report to date exclusively describes rFVIIa use in pediatric hematology/oncology patients.
Objectives: To examine the efficacy, outcomes and adverse effects of using rFVIIa off-label in

pediatric hematology/oncology patients during severe bleeding episodes.
Design/Method: Data was collected retrospectively and analyzed in all pediatric hematology/oncology patients who received rFVIIa off-label for severe bleeding at a single center, St. Jude Children's Research Hospital, from February 2006 to December 2014.
Results: Of 58 patients, 46 (79.3%) had received rFVIIa for treatment of bleeding and 12 (20.7%) prophylactically to prevent bleeding. Mean age was 10.7 years (SD 6.6), 60.3% were males. Thirty-seven (63.8%) patients had leukemia, 12 (20.7%) had solid tumors and 9 (15.5%) had non-malignant hematological conditions. Thirty-five (76.1%) and 6 (50.0%) patients had undergone bone marrow transplant in the treatment and prophylaxis groups, respectively. In the treatment group, 63.0% (29/46) of patients responded to rFVIIa, defined by bleeding stopped (23) or decreased (6). Seventeen (37.0%) patients, defined non-responders, had no change in bleeding. The use of fresh frozen plasma (FFP) and platelet transfusions was less during the first 24hrs after rFVIIa administration compared to 24hrs prior, but the difference was not significant (median 10.9 ml/kg (range 2.5-105.4) vs 14.6 ml/kg(3.4-101.9) and 10.6 ml/kg(2.8-98.6) vs 11.1 ml/kg(2.1-40.1), respectively). Three (6.5%) patients developed venous thromboembolism (VTE), at 24hrs post rFVIIa in 1 and more than 14 days after rFVIIa in 2 patients. The 28-day mortality rate was 41.3% overall, but only 17.2% (5/29) in responders compared to 82.4% (14/17) in non-responders ($P<0.0001$). Cause of death was bleeding in 52.6% (in 2/5 responders and 8/14 non-responders) and was never documented as related to rFVIIa administration. In the prophylaxis group, no patient died and 1 patient developed a VTE at 13 days post rFVIIa infusion.
Conclusion: Almost two thirds of patients of this pediatric hematology/oncology cohort, treated with off-label rFVIIa for severe bleeding, experienced improvement in bleeding. The rate of possibly related adverse events of VTE was low. Responders had lower mortality than non-responders, however, further analysis is required to explore the influence of rFVIIa dosing, concomitant use of FFP and platelet transfusions and other clinical factors.

Poster # 011

IMPACT ON HOSPITALIZATION RATE AND TREATMENT COST FOLLOWING THE INTRODUCTION OF A NEW PROTOCOL FOR THE CARE OF CHILDHOOD ACUTE ITP

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Background: Childhood immune thrombocytopenia is associated with low bleeding rate and high frequency of spontaneous remission. Although current guidelines suggest that patients be observed with no treatment, children still receive platelet-enhancing therapies by fear of bleeding or complications. In 2013 we introduced a standardized local protocol, based on a step-down approach, the protocol defining hospitalisation and treatment criteria.
Objectives: We hypothesized that the introduction of the new standardized protocol (SP) would help reduce hospitalization rate and may reduce cost of care of children diagnosed with acute ITP.
Design/Method: The protocol was introduced in January 2013. A retrospective chart review was

performed on all new cases of ITP at the CHU Sainte-Justine diagnosed pre-protocol (January 2010 to December 2012) and post-protocol (January 2013 and December 2014). Management and events of all acute ITP phase (first three months of disease) were recorded, including hospitalization, treatment regimen and complications. Chi-square test and t-test were used for statistical analysis.
Results: 91 patients were included in the study. Both cohorts were comparable by gender, age, platelet count and Buchanan bleeding score at presentation. The SP resulted in a 34% decrease in hospitalization rate ($p<0.001$) at diagnosis, as well as total mean hospitalization number over the first three months (1.4 vs 0.9, $p=0.017$). The overall percentage of treated patients did not change (80% vs 68%, $p=0.2250$). Furthermore, hospitalized patients were 4.7 times more likely to be treated. However, prednisone duration at diagnosis was significantly reduced (13.1 vs 5.8 days, $p=0.004$), as well as overall prednisone use during the first three months (15.2 vs 7.2 days, $p=0.008$). The effect was particularly striking in older children: those older than 3 years were 3.8 times less likely to be hospitalized (95% CI 1.94-7.61) and 2.3 times less likely to receive treatment (95% CI 1.2-4.3). There was no difference in the rate of persistent ITP (38% vs 30%, $p=0.43$), nor in serious bleeding complications (7% vs 5%, $p=0.70$).
Conclusion: The implementation of our management protocol of newly diagnosed ITP helped reduce the hospitalization rates and length of prednisone treatment without any increase of disease complications. The SP was successful at reducing the use of platelet-enhancing therapies in children older than three years old. A revised protocol discouraging the use of platelet-enhancing therapy in asymptomatic patients should further help to avoid unnecessary hospitalization and treatment in asymptomatic patients.

Poster # 012

USE OF PEDIATRIC BLEEDING SCORE AS A PRE-SURGICAL BLEEDING PREDICTOR IN PATIENTS WITH LOW LEVELS OF FACTOR SEVEN

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Background: Coagulation Factor VII (FVII) is an essential blood-clotting protein in the coagulation cascade functioning to maintain hemostasis. Individuals with low FVII activity level (FVII:C) may be at increased risk of bleeding; however, there is no established tool to assess bleeding risk in these patients. As the minimum level of FVII:C required for hemostasis is not known, patients with low FVII:C levels undergoing surgical procedures are often exposed to potentially unnecessary doses of fresh frozen plasma (FFP) or recombinant FVIIa (rFVIIa) to ensure adequate hemostasis. The Pediatric Bleeding Questionnaire (PBQ) is a simple, pediatric-specific bleeding questionnaire validated in Von Willebrand disease (VWD) where those with a PBQ score >2 are at increased risk of having VWD than the ones scoring <2. The application of PBQ as a bleeding risk screening tool in the pre-op setting has not previously been studied.
Objectives: To address the utilization of the PBQ as a bleeding risk predictor in patients with low factor VII activity level undergoing surgical procedures.
Design/Method: This was a single center, retrospective chart review of pediatric patients seen in our hematology clinic between October 2011 and November 2016. Patients with low FVII:C levels who underwent surgical challenges with a completed PBQ were eligible. Patient age,

gender, Factor VII activity level, PBQ score, surgery type, perioperative hemostatic measures, and perioperative bleeding severity were recorded.
Results: Thirty one patients with a mean age 10.7 [range 2.5 - 17.7] years were eligible. Mean factor VII activity level was 38.3 [range 2.2 - 49] %. All but one patient had a PBQ score < 2 [range -1 - 3]. Twenty different surgical procedures were performed: 18 (60%) involving the nasopharynx, 8 (26.7%) skeletal, 2 (6.6%) cardiac, and 2 (6.7%) gastrointestinal procedures. No perioperative bleeding prophylaxis was administered to 21 (70%) patients. Six (20%) received oral vitamin K, 2 (6.6%) received ≤ 2 doses of Aminocaproic acid, and 1 (3.4%) received recombinant activated factor VII (the patient with FVII:C 2.2%) preoperatively. None of the patients reported prolonged peri/ post-operative bleeding.
Conclusion: None of the pediatric patients with low FVII:C level and PBQ ≤ 2 had perioperative bleeding regardless of pre-operative intervention. Using PBQ questionnaire could prevent patients with low FVII:C levels from receiving unnecessary medications and exposure to their side effects with no added risk of bleeding. Further studies are needed to assess the optimal cut off point for PBQ score to predict bleed risk, while maximizing specificity.

Poster # 013

EMBOLIZATION HAS A PLACE IN THE MANAGEMENT OF SIROLIMUS AND CHEMOTHERAPY REFRACTORY KAPOSIFORM HEMANGIOENDOTHELIOMA

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Background: Kasabach-Merritt phenomenon (KMP) is a rare life-threatening, consumptive coagulopathy associated with kaposiform hemangioendothelioma (KHE) and prompt diagnosis and management is critical.
Objectives: To present a case series of four patients. Three patients with KMP associated with KHE demonstrated response to sirolimus combined with other medical therapies. One patient initially responded to medical therapy, but then required rescue with embolization with good response.
Design/Method: Case series of four patients.
Results: Three patients with KMP and KHE have been successfully treated with sirolimus. The first patient is a 4-year-old female with KHE of the head, neck, chest wall, and mediastinum who initially was started on vincristine and steroids, and eventually propranolol was added. The patient had progressive tumor growth with KMP, and 3 months later was started on sirolimus with improvement of disease, allowing for vincristine, steroids and propranolol to be weaned off. Sirolimus was discontinued after a total of 25 months of therapy and she is currently doing well 27 months off therapy. Our second patient is a 3-year-old male with KHE of the head and neck with KMP who responded well to sirolimus and steroids, recurred 3 months off therapy, with good response after being restarted on sirolimus. The third patient is a 7-month-old male with KHE of the head, neck, and upper thorax who was started on vincristine, steroids and sirolimus at diagnosis. Steroids and vincristine were discontinued within 3 months, and patient remains on sirolimus with resolution of KHE 6 months after initiation of therapy. One patient with sirolimus-resistant KMP and progressive tumor growth has achieved improvement of her coagulopathy and KHE after embolization. This patient is a 9-month-old female with KHE of the

left face and neck who had tumor growth, respiratory distress and worsening coagulopathy on vincristine, steroids, propranolol, and sirolimus. She subsequently underwent embolization and had a prolonged hospital course with complications secondary to pre-existing coagulopathy. Patient is now 3 months post-embolization, continues on sirolimus, with complete resolution of KMP and improvement in KHE.
Conclusion: Sirolimus with or without steroids are becoming first line therapies in the management of KHE with KMP. Many patients will respond rapidly and achieve complete response with these therapies. For the rare medically refractory cases, embolization remains a salvage modality directed at decreasing the tumor burden and potentiating antiangiogenic systemic agents. Given the rarity of KHE with KMP, collaborative studies are essential to further investigate treatment regimens and evaluate long-term outcomes.

Poster # 014

CORRELATION OF THE ISTH-BAT AND MCMDM-1 BLEEDING SCORE WITH LABORATORY BLEEDING PARAMETERS IN TYPE I VON WILLEBRAND PATIENTS

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Background: Bleeding is a key component in patients with von Willebrand disease, however, reporting and interpretation being subjective, bleeding assessment tools became necessary. In 2008, the European Molecular and Clinical Markers for the Diagnosis and Management of type 1 VWD (MCMDM-1 vWD) questionnaire was established and independently validated. Further, in 2010, the International Society on Thrombosis and Hemostasis – Bleeding Assessment Tool (ISTH-BAT) was developed and validated.
Objectives: Our aim was to administer ISTH-BAT and MCMDM-1 bleeding score questionnaire to the Omani type I vWD patients and obtain a bleeding score as well as correlate it with the laboratory diagnostic parameters.
Design/Method: Fifty-five Type I vWD index cases were enrolled in this prospective study. The diagnosis of Type I vWD was confirmed using the criteria recommended by the ISTH-SSC for vWD. These patients were personally interviewed and the ISTH-BAT and the MCMDM-1 bleeding score questionnaire was administered by a single investigator.
Results: The mean time to administer the two questionnaires was 13 minutes each, with a range from 8 to 39 minutes. Overall, bleeding from the oral cavity was the most predominant symptom [59%], but amongst the females, menorrhagia was the most prevalent symptom [94%]. The prevalence of other symptoms were epistaxis [44%], tooth extraction [44%], bleeding from minor wounds [37%], cutaneous bleeds [33%], bleeding at surgery [33%], GI bleeds [7%] and hematoma [7%]. No patient had haemarthrosis or CNS bleeds. The mean MCMDM-1 BS in this cohort was 4.74 with a range from 0 to 17. 15% of the patients had a BS of 0, whereas, another 26% had a BS below 4. However, the mean ISTH BAT BS amongst females was 7.1, but, in males it was 5.2 and in children it was 4.2. Although 7% of these patients had a BS of 0, 53% [n=8] of the females, 71% [n=5] of the males and 50% [n=3] of children were above the mean normal BS cut-off of 6, 4 and 3 respectively. The BS was negatively correlated with FVIII:C levels, vWF:Ag, vWF:RiCOF and vWF:CBA respectively and the Pearson's correlation

coefficient was respectively -0.11,-0.25,-0.29 and -0.28;p >0.05.
Conclusion: Both MCMDM-1 and ISTH BAT bleeding scores attempt to reflect the severity of bleeding amongst vWD patients. Hence, it is not surprising that it did not correlate significantly with the surrogate laboratory parameters, which are the backbone in the diagnosis of vWD patients, albeit, along with clinical, personal and family history of bleeding.

Poster # 015

A RARE CASE OF PAEDIATRIC KAPOSIFORM HAEMANGIOENDOTHELIOMA MIMICKING MALIGNANCY OF THE KIDNEY

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Background: Kaposiform Haemangioendothelioma(KHE) is a benign vascular tumour typically seen in childhood. Most cases of KHE involve superficial and deep tissues of the extremities, while visceral involvement is less common. It is aggressive locally and often associated with Kasabach-Merritt Phenomenon(KMP). We report a case of KHE occurring in the kidney in a 5 month old infant with associated KMP.
Objectives: To inform presentation of a rare case
Design/Method: Review of clinical presentation and management of a rare tumour
Results: A 5 month old girl presented with a ballotable mass over the left upper abdomen. Cardiac, respiratory and genital examinations were unremarkable. Her spine was normal and there was no hemihypertrophy or petechial rashes.MRI and CT abdomen had shown large enhancing lobulated mass, 3.9 x 6.4 x 5 cm in size, in the left retroperitoneum centered at the left renal hilum, which may represent a neuroblastoma or exophytic left Wilms'tumour. The blood tests had shown low Hb 8.2 g/dL and platelet 23,000. Bone marrow aspiration and trephine biopsy were done in view of possible bone marrow involvement of tumour and it was reported as normal marrow with no evidence of tumour infiltration. Tumour markers, AFP, beta hCG, urinary VMA and HVA were normal. Therefore, immune-mediated thromobocytopenia as paraneoplastic phenomenon was assumed and patient was given a trial of intravenous immunoglobulin (IVIG) and 3 doses of intravenous methylprednisolone. The likelihood of KMP was then considered as there is no satisfactory improvement of platelet count. The work up of consumptive coagulopathy had shown hypofibrinogenaemia [fibrinogen 0.40g/L (normal range 1.80-4.80g/L)] and elevated markers of coagulation activation [D dimers >32 mg/L (normal range 0.19-0.55 mg/L)] approving KMP.To get a safe platelet level for surgery, platelet concentrate was transfused repeatedly before operation. And nephroureterectomy was performed under the cover of continuous platelet and cryoprecipitate transfusions using intraoperative rotational thromboelastometry (ROTEMTM) to guide the transfusion of blood products. The histopathology and immunophenotype were in keeping with that of KHE.
Conclusion: KHE of the kidney is extremely rare. There is one case report of 4 year old girl with KHE involving the kidney. She received neoadjuvant vincristine and actinomycin, subsequent nephrectomy and post-op interferon-alpha administration. In our case, the patient was successfully treated with surgery without any chemotherapy and follow-up imaging had shown

no local recurrence at one year post- surgery. To conclude, key radiological and haematological features aided in the diagnosis of this case and influenced subsequent management.

Poster # 016

CASE REPORT OF POOR SUBCUTANEOUS ABSORPTION OF PROTEIN C CONCENTRATE COINCIDING WITH PUBERTY

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Background: Protein C deficiency is a rare, inherited coagulopathy with variable clotting that can lead to life-threatening conditions, such as purpura fulminans, in severe cases. The condition is inherited in homozygous or compound heterozygous mutations of the protein C gene.
Objectives: We describe here the case of two patients, sister and brother, who presented with purpura fulminans at birth, and were diagnosed with protein C deficiency based on factor activity levels of 0% and family history.
Design/Method: Data on patients were obtained through chart review and during clinical visits of the patients.
Results: Within 24 hours of birth, both siblings were treated with fresh frozen plasma and anticoagulation with low molecular weight heparin. They received protein C concentrate (Ceprotin [Bacter, Deerfield, IL]) through compassionate use or a clinical trial soon after. Following closure of the trial, the sister was placed on warfarin until protein C concentrate was commercially available. Genetic testing revealed compound heterozygous protein C deficiency, heterozygous Factor V Leiden mutation, and heterozygous MTHFR. Paternal history included multiple deep venous thrombi and laboratory confirmed protein C deficiency with baseline activity of 36%. Their mother was asymptomatic but had baseline activity of 68%. Both the maternal and paternal grandmother's obstetric histories revealed stillbirths. Patients were maintained, with minimal complications, on therapeutic protein C concentration levels via subcutaneous administration with doses adjusted to obtain prophylactic levels (trough >20%). At the age of 11, the older female sibling presented with increasing dosage needs, recurrent thromboembolisms, and purpura which coincided with puberty. After hospitalization and determination of medication compliance, she was transitioned to intravenous concentrate administration where the same dose produced a dramatic response in protein C activity level (>200%). Another trial of subcutaneous treatment was attempted but deemed unsuccessful after protein C activity levels at 1 hour prior and 4 hours after subcutaneous administration were found to be largely unchanged from trough levels (25% and 18%, respectively). Due to the poor subcutaneous absorption, permanent intravenous access was obtained and she remains on intravenous protein C concentrate. The only identifiable change in her clinical course has been the start of puberty. Her brother has been able to continue subcutaneous infusions without difficulty during this time.
Conclusion: We present this case series to illustrate the need for further research evaluating the effect of puberty on the response to subcutaneous administration of protein C concentrate.

Poster # 017

THE CHALLENGING JOURNEY OF A COMPLEX LYMPHATIC-VENOUS MALFORMATION PATIENT

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Background: Vascular anomalies encompass a wide range of malformations of arteries, capillaries, veins, lymphatic channels and combined lesions. While mostly benign, the malformations can cause significant morbidity and mortality related to deformation and impairment of vital structures or through significant thrombocytopenia and coagulopathies related to Kasabach-Merritt Syndrome (presumed to occur via platelet trapping/activation by abnormally proliferating endothelium within the vascular malformation with subsequent consumption of clotting factors). While hemangiomas of infancy have been amenable to medical therapy, effective management of the other malformations has been challenging. Recent reports have illustrated the utility of the mTOR inhibitor Sirolimus in treatment of various vascular anomalies. The proposed mechanism of action is through inhibition of the signaling pathway leading to angiogenesis.
Objectives: Demonstrate the effective use of mTOR inhibitor for Lymphatic-Venous Malformations (LVM).
Design/Method: We present one patient with a LVM of the left thigh, treated with multiple modalities including embolization, Sirolimus and surgery with peri-operative anticoagulation.
Results: M.S is a 3 year old female who was born with a large left thigh mass. She presented to our Vascular Anomalies clinic at 14 months of age. MRI/MRV/MRA showed a 15 x 10 cm complex mass consistent with a LVM. This was associated with a consumptive coagulopathy with fibrinogen consistently < 60 and elevated d-Dimer. She underwent twelve embolization procedures over eighteen months, with slight decrease in the size of the mass after each procedure and no change in coagulation profile. She received cryoprecipitate prior to each procedure. Two attempts at surgical resection failed due to excessive intraoperative bleeding. Perioperative anticoagulation with Enoxaparin enabled normalization of the coagulation profile prior to each surgical attempt. Patient was started on Sirolimus 0.8 mg/m2/dose BID, with trough goal 5-10 ng/mL and coagulopathy corrected within 3 months.
Conclusion: LVMs are difficult to treat and often require multiple treatment modalities. Our patient had minimal response to multiple embolization procedures however, after initiation of Sirolimus, there was rapid correction of coagulopathy with decrease in size of the mass indicating a significant therapeutic benefit of mTOR inhibitors in LVM. She will continue on this modality for a few more months before further surgical intervention will be attempted. This case emphasizes the importance of a multidisciplinary approach in successful management of complex vascular malformations.

Poster # 018

RIVAROXABAN PROPHYLAXIS IN SEVERE CONGENITAL PROTEIN C DEFICIENCY: CASE REPORT

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Background: No well-defined general guidelines are available for the treatment of symptomatic patients with severe congenital protein C deficiency. Current treatment for this condition focuses on Protein C replacement or long term anticoagulation with warfarin or low molecular weight heparin.
Objectives: To describe the use of Rivaroxaban prophylaxis and assess safety and effectiveness in a patient with severe Protein C deficiency.
Design/Method: Chart and literature review.
Results: A 17 year old male, ex 33 week-premature first twin baby from Thailand, diagnosed with severe Protein C Deficiency after presenting to a local hospital with an acute manifestation of bilateral leg swelling and purpura fulminans when he was 2 years old. His Protein C activity was 2%. His twin brother had severe neurologic involvement due to stroke at birth. He was initially treated with FFP replacement 10-15ml/kg weekly and LMWH and later warfarin. MRI done at that time showed prior ischemic events. Upon arrival to the US at 16 years of age his treatment with warfarin was continued. During the following year, he presented several times with complications including deep venous thrombosis and skin necrosis. He was started on rivaroxaban – a direct thrombin inhibitor- 20mg orally daily at 17 years of age. For the following two years he did well and had no other acute thrombotic, bleeding events or medication side effects. Follow up brain MRI showed no new areas of infarct. Physical exam was entirely normal. He was able to complete high school without issues and has is doing well in college. Monthly blood counts and liver function tests were done during that period showed no adverse effects. Later, the test period interval was extended to 2 and then 3 months.
Conclusion: This case demonstrates an autosomal recessive Protein C deficiency successfully managed with the use of direct Xa inhibitor- rivaroxaban- given orally on a daily basis. This treatment approach appears to be safe and effective and could be studied in prospective large cohorts patients with Protein C deficiency.

Poster # 019

CONSERVATIVE MANAGEMENT IS SAFE IN ISOLATED SKELETAL CYSTIC LYMPHANGIOMATOSIS

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Background: Cystic lymphangiomatosis (CLA), one of the entities now encompassed by the term generalized lymphatic anomaly (GLA), is uncommon in children. Incidence is difficult to estimate, as the majority of disease descriptions are limited to case reports and small case series. CLA may involve the bone, spleen, liver, mediastinum or lung. We present a unique case of CLA limited to the bone in a 12-year-old girl. Isolated bony CLA is exceedingly rare, and treatment algorithms are not well established. A few case reports and small case series have reported treating these patients with bisphosphonates, propranolol, steroids, or alpha interferon.
Objectives: To provide evidence that isolated skeletal cystic lymphangiomatosis may be safely observed without additional therapeutic intervention.

Design/Method: We present a 12-year-old girl who initially presented to the emergency room after sustaining a concussion from a fall. She underwent cranial MRI and CT and was incidentally found to have multiple cystic lesions of the frontal, bilateral parietal, and right occipital bones, suspicious for LCH. Biopsy of the frontal bone lesion revealed scattered dilated vascular channels, staining positive for CD34 and D240. Focal areas of dilated lymphatic structures were also observed, suggesting a lymphatic malformation. CD68 staining revealed scattered histiocytes. Langerhans cell histiocytosis was excluded based on negative staining for S100 and CD1a. Further imaging with a skeletal survey identified additional lesions in her several ribs and bilateral femora. No visceral involvement was noted on CT.
Results: This patient has been followed with serial whole body MRI every 6 months for 3 years, with no significant progression of disease. No additional bony lesions have arisen, and no visceral involvement has developed. She has never received therapy directed at these lesions. She is growing and developing well, is active in sports, and is asymptomatic. Likely incidental to her CLA, she developed Type I Diabetes Mellitus one year after diagnosis and is now stable on insulin.
Conclusion: Cystic lymphangiomatosis isolated to the bone is exceedingly rare, and established treatment standards are not available. We present a unique case of isolated skeletal CLA in a child and suggest that cases such as this may be treated conservatively with careful observation in the absence of visceral involvement, pain, or other symptoms.

Poster # 020

SUCCESSFUL TREATMENT OF LUPUS ANTICOAGULANT HYPOPROTHROMBINEMIA SYNDROME WITH ANTI CD20 ANTIBODY, RITUXIMAB

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Background: Lupus anticoagulant-hypoprothrombinemia syndrome (LAHPS) is a rare acquired disorder caused by prothrombin antibodies in presence of lupus anticoagulant which can predispose to severe life threatening bleeding. The disease is most common in the pediatric age group and common associations are SLE and viral infection. There is no standardized mode of treatment nonetheless some form of immunosuppression has been traditionally used in different cases with corticosteroid being the most commonly used agent.
Objectives: To describe a case of LAHPS in a teenage girl, who responded to immunosuppression with monoclonal anti-CD20antibody, rituximab.
Design/Method: Case report.
Results: The patient was a 13 yr. old girl who presented with severe menorrhagia with prolonged PT/INR and aPTT giving rise to severe anemia. She was found to be positive for presence of lupus anticoagulant, as well as for IgM and IgG antibodies for β2 glycoprotein and cardiolipin. She did not display any evidence of thrombosis and continued with heavy menstrual bleeding. She then developed facial rash and arthropathy, and was diagnosed with SLE. She was started on high dose steroid and underwent renal biopsy to monitor for lupus nephritis, which resulted in excessive bleeding and formation of perinephric hematoma. She also developed a left femoral DVT. Interaction of the lupus anticoagulant made it difficult to measure factor levels. However,

prothrombin level was found to be 14, and did not correct with serial dilutions. She was thus diagnosed with LAHPS. The patient was started on rituximab 375mg/m2. After four weekly doses of rituximab her prothrombin level started normalizing, menstrual bleeding resolved and she has not had any thrombotic event since. Prothrombin level normalized 4weeks into treatment with rituximab.
Conclusion: This report discusses a case of LAHPS. It is a rare disorder and there is no well-established treatment protocol. There are a few case reports where Rituximab has been used in LAPHS – most of them have not shown any clear efficacy and none of them were pediatric patients. In our case while the patient continued to have low prothrombin level as well as clinically evident deranged bleeding and coagulation status while being on corticosteroid and hydroxychloroquine, it improved with institution of Rituximab. Rituximab can be used as a second line treatment of LAHPS in pediatrics with good efficacy.

Poster # 021

USE OF CT ANGIOGRAPHY FOR 3D RENDERING TO FACILITATE RESECTION OF A COMPLICATED MASSIVE CONGENITAL HEMANGIOMA: A CASE REPORT

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Background: Congenital hemangiomas are categorized by their clinic behavior as being either rapidly involuting congenital hemangiomas (RICH), or noninvoluting congenital hemangiomas (NICH). Some congenital hemangiomas may require active intervention in the postnatal period when complications arise.
Objectives: We describe the case of an infant born at 34 weeks gestation with a massive congenital hemangioma of the lateral upper thigh that developed ulceration and failed to involute, causing morbidity that necessitated surgical removal for management of a consumptive coagulopathy (anemia/thrombocytopenia) and high output cardiac failure.
Design/Method: The lesion was best imaged with 3-dimensional computed tomography angiography (CTA). Information from this scan allowed for surgical mapping, and with multidisciplinary involvement a comprehensive care plan was made. The coagulopathy and anemia were aggressively managed by the hematology and critical care teams. Particulate embolization of the proximal two-thirds of the lesion was performed by the interventional radiologist to help reduce intraoperative bleeding. The pediatric surgeon placed vessel loops around the iliac artery and vein to further control bleeding.
Results: Successful excision of the vascular lesion (measuring 9.2 x 8.4 x 2.4 cm) with Integra closure was performed by pediatric and plastic surgery with minimal blood loss. Correction of coagulopathy and improvement of high output cardiac failure followed. Three weeks following surgery, the patient required wound debridement and split-thickness skin grafting from the lower thigh. At 6 weeks post-surgery, the graft and donor site both demonstrated excellent healing.
Conclusion: Complicated congenital hemangiomas can be successfully excised with careful planning and utilization of sophisticated imaging modalities when a coordinated multidisciplinary team approach is utilized.

Poster # 022

ACQUIRED FACTOR VIII INHIBITOR IN A PATIENT WITH DUCHENNE MUSCULAR DYSTROPHY

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Background: Acquired Factor VIII (FVIII) inhibitors are only rarely seen in the pediatric population with an estimated incidence of 0.045 per million/year in children younger than 16 years old. Approximately 50% of cases are associated with underlying comorbidities including malignancies, infections, or other autoimmune diseases. There is no consensus in the pediatric hematology community about the appropriate treatment for patient s with acquired FVIII inhibitors.
Objectives: This case report details an 11 year old patient with Duchenne Muscular Dystrophy (DMD) and no significant past bleeding history initially referred to Pediatric Hematology for a prolonged PTT noted on screening labs.
Design/Method: At the time, this patient had routine labs while participating in a clinical trial for a novel oligonucleotide to treat DMD. At the time of consultation, he was noted to have recent easy bruising and prolonged bleeding after losing a tooth. Further lab work revealed the presence of a FVIII inhibitor, known to be acquired because of previously normal bloodwork. This was not a previously described adverse effect associated with his DMD drug. Initial FVIII activity was <1% while initial FVIII inhibitor screen was 294 Bethesda units.
Results: He went on to have multiple episodes of clinically significant bleeding, including wrist and calf soft tissue bleeds, necessitating hospitalization and treatment with Factor VIIa (FVIIa). After the second bleeding episode, the decision was made to attempt inhibitor elimination with oral steroids and cyclophosphamide.
Conclusion: He was successfully treated using this regimen after a total of 8 months of treatment, although he remains on a lower dose of corticosteroids for treatment of his underlying DMD. His most recent FVIII activity was 143% and FVIII inhibitor was undetectable.

Poster # 023

RESPONSE TO MTOR INHIBITION (RAPAMYCIN) IN MULTIFOCAL LYMPHANGIOENDOTHELIOMATOSIS WITH THROMBOCYTOPENIA (MLT)/CUTANEOVISCERAL ANGIOMATOSIS WITH THROMBOCYTOPENIA (CAT)

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Background: Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT) or cutaneovisceral angiomatosis with thrombocytopenia (CAT) both refer to a rare vascular tumor that primarily affects children. The clinical presentation is variable and typically involves thrombocytopenia with vascular lesions in the skin, lungs, gastrointestinal tract, and bones. Life-

threatening hemorrhage from the lungs and gastrointestinal tract can occur. Diagnosis is established by characteristic findings on biopsy. The clinical course and response to treatment are not well-established in the medical literature.
Objectives: To increase awareness of MLT/CAT and to report the response to MTOR inhibition (rapamycin or Sirolimus) in children diagnosed with MLT/CAT.
Design/Method: Clinical information, treatment, and outcome data were obtained from a retrospective chart review of 3 MLT/CAT cases treated with rapamycin and compared to published reports obtained from a literature review performed using the keywords multifocal lymphangioendotheliomatosis with thrombocytopenia, cutaneovisceral angiomatosis with thrombocytopenia, and rapamycin.
Results: Patient 1: 18 month-old male with fatigue, hemoptysis, and lower extremity pain, with thrombocytopenia, who on imaging had pulmonary nodules and bony lytic abnormalities. Tissue from a lung wedge resection was consistent with MLT/CAT. He was started on steroids and a 6 month course of Sirolimus. He had significant clinical improvement on Sirolimus that was terminated due to severe anorexia, a known side effect, which resolved after drug cessation. Patient 2: 6 year-old female born with skin lesions who, at 1 month of age, developed gastrointestinal bleeding, and thrombocytopenia, and on endoscopy was found to have angiomata suggestive of MLT/CAT. She also had hypoalbuminemia, hypogammaglobulinemia, hyposplenism, hyperammonemia, and short stature. She was unresponsive to Vincristine and sub-therapeutic doses of Sirolimus, and remained transfusion-dependent until she was started on Thalidomide with steroids.Patient 3: 2.5 year-old male who, at 2 weeks of life, developed hemoptysis, gastrointestinal bleeding, and thrombocytopenia, and was found at laparotomy to have angiomata that were indicative of MLT/CAT. He was started on Sirolimus in combination with steroids in infancy with significant clinical improvement and was ultimately weaned off of steroids.
Conclusion: In 2 of 3 cases of MLT/CAT, patients responded well to MTOR inhibition, and the non-responder did not reach therapeutic troughs before stopping the drug. Sirolimus should be considered first-line therapy for these complex vascular lesions. Due to the rarity of this diagnosis, there is no standard of care, and randomized trials are very unlikely, therefore we propose the development of a single arm, open label treatment protocol to establish the efficacy of Sirolimus in MLT/CAT.

Poster # 024

MESOAORTIC COMPRESSION OF A LEFT SIDED INFERIOR VENA CAVA (IVC) PRESENTING AS RECURRENT, UNPROVOKED SUB-MASSIVE PULMONARY EMBOLISM (PE) - A NOVEL ANATOMIC THROMBOPHILIA?

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Background: Left sided IVC, a rare, often benign anatomic variant has estimated prevalence of 0.2-0.5%. To our knowledge, there are no reported cases of recurrent PE/deep vein thrombosis resulting from a left sided IVC.
Objectives: To describe a pediatric patient who presented to our tertiary care children’s hospital with recurrent sub-massive PE resulting from mesoaortic compression or nutcracker syndrome of

a left sided IVC.
Design/Method: Case report with review of literature
Results: A previously healthy, 13 year old male presented to our center with substernal chest pain, dyspnea and syncope. Computed tomography pulmonary angiogram (CTPA) was positive for bilateral pulmonary emboli with right heart strain. An echocardiogram confirmed the right heart strain. Doppler sonograms of bilateral lower and upper extremities were negative for thrombus. An ultrasound of his abdomen revealed a left sided IVC, but no other anomalies. He was treated with catheter-directed thrombolysis followed by 6-months of therapeutic anticoagulation. Thrombophilia testing was negative for congenital and acquired thrombophilias. A 3-month repeat CTPA and echocardiogram were negative for residual thrombus/right heart strain respectively. Four days after interruption of anticoagulation, the patient presented to the ED with recurrent chest discomfort and palpitations. Repeat CTPA was positive for recurrent bilateral PE with evidence of right heart strain, again confirmed on echocardiogram. Patient was treated with catheter-directed thrombolysis followed by anticoagulation. A contrast enhanced CT scan of his abdomen and pelvis demonstrated an enlarged left IVC (megacava), marked dilation and ectasia of the iliac veins, and residual thrombus within the dilated left internal iliac vein. A conventional venogram with pullback pressures obtained from the right atrium to the iliac system showed hemodynamically significant compression of the left IVC as it passed from left to right between the aorta and superior mesenteric artery with stasis and turbulent flow within the IVC and dilated pelvic veins.
Conclusion: Pulmonary embolism (PE) is rare in pediatrics with an estimated prevalence of 0.14-0.9 cases/100,000 children. Left sided IVCs are also rare – most cases are benign and cause no complications. Herein, we describe a pediatric patient with mesoaortic compression or nutcracker syndrome of a left-sided IVC who presented with recurrent PE. No consensus exists for long-term management of these patients given the multiple PE's. Our patient is currently on long term anticoagulation with low molecular weight heparin as we explore potentially therapeutic interventional approaches.

Poster # 025

UNDERSTANDING THE ROLE OF SIROLIMUS IN CLOVES SYNDROME

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Background: Background: In recent years, the parallel discovery of PIK3CA mutations and completion of a phase 2 study of sirolimus in patients with vascular anomalies has enabled discussion of sirolimus for overgrowth disorders caused by PIK3CA mutations. The most extreme of these overgrowth syndromes is CLOVES (congenital lipomatous overgrowth, vascular anomalies, epidermal nevi and skeletal anomalies).
Objectives: Objective: To describe responses to sirolimus therapy in 19 patients with CLOVES
Design/Method: Methods: This is a retrospective cohort study. We identified 19 patients with CLOVES syndrome treated with sirolimus for at least 6 months through the Lymphatic Anomalies Registry. Patients were treated initially with 0.8 mg/m2 PO BID and titrated to 12 hour sirolimus trough levels of 7-13 ng/ml. Unless allergic, all patients received trimethoprim-sulfamethoxazole prophylaxis. Prior to sirolimus initiation, goals of therapy were agreed upon by

patients/parents and clinicians with emphasis on quality of life and disease complications over physical changes in overgrown tissues. Functional outcomes were measured by Karnofsky/Lansky score and patient/parent report and quality of life was measured by patient/parent report.
Results: Results: Age at initiation ranged from infancy to 24 years. Length of therapy ranged from 6 to 46 months. Nine patients reported no adverse events. The most common adverse event was mucositis and others included fatigue, acne, diarrhea, constipation, increased cholesterol, neutropenia and decreased appetite. No patients had increased infections, disease progression or worsened quality of life. Of 10 patients with the goal to improve lymphatic complications (infection, swelling, leaking vesicles), 9 (90%) achieved this goal. Of 5 patients with goals to improve function and QOL, 4 (80%) achieved this goal. Of 12 patients aiming to decrease tissue bulk, 7 (58.3%) had improved size of their vascular anomaly and 3 (25%) had improvement in the size of fatty lesions, while 4 (33.3%) saw no change in tissue bulk. Of 15 patients with known current status, 10 are still on therapy.
Conclusion: Conclusion: Sirolimus improves lymphatic complications, overall function and quality of life in CLOVES. The role of sirolimus in other PIK3CA overgrowth disorders requires further study.

Poster # 026

TREATMENT DOSING OF ENOXAPARIN IN AN OBESE PEDIATRIC POPULATION

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Background: Practice guidelines recommend weight-based dosing of enoxaparin at 1mg/kg every 12 hours. Despite obesity being an independent risk factor for thrombotic events, there are no guidelines for dosing in an obese pediatric population and no recommendations for a maximum therapeutic dose. Given the obesity epidemic, guidelines are greatly needed to safely and effectively anticoagulate this at-risk population.
Objectives: To determine whether traditional weight-based enoxaparin dosing is appropriate for an obese pediatric population.
Design/Method: We conducted a retrospective chart review of all patients aged 1-18 years with a weight greater than the 98th percentile for age treated at our institution for a thrombotic event from 2007 to 2015. Actual (mg) and by weight (mg/kg) enoxaparin doses, anti-Xa levels, number of dose adjustments required to obtain a therapeutic anti-Xa (0.5 to 1.0) and adverse events were obtained for each patient.
Results: We had 21 evaluable patients. Two patients were less than 5 years of age, twelve were 5-15 years and seven were greater than 15 years of age. Patient weight ranged from 19.5kg to 112.3kg. Ten patients were started with an enoxaparin dose of 1mg/kg (0.95-1.01mg/kg). Their initial anti-Xa ranged from 0.45 to 1.1, with seven of these patients (70%) within the appropriate therapeutic range. Two patients with a dose of 100mg were above range. Nine patients received an initial enoxaparin dose that was below 1mg/kg (0.78-0.93mg/kg). These patients had an anti-Xa ranging from 0.35 to 1.17, with six patients (67%) in the therapeutic range. Two patients were above target, with a dose of 100mg (0.89mg/kg) and 80mg (0.92mg/kg). Two patients had a starting dose above 1mg/kg (1.08-1.13mg/kg), both with a supratherapeutic anti-Xa level (1.08-

1.13). No patients required more than two dose adjustments to obtain an appropriate therapeutic anti-Xa. Three patients (14%) had minor bleeding including menorrhagia, mild hematuria and small amounts of blood in the stool. One patient had enoxaparin held for 4 days due to bleeding. Bleeding was not associated with an elevated anti-Xa. No patients had thrombus progression.
Conclusion: Weight-based dosing of enoxaparin at 1mg/kg every 12 hours in obese pediatric patients appears appropriate, with no evidence of thrombus progression or significant bleeding. While some patients dosed above 80mg in our study had supratherapeutic anti-Xa levels, this was not associated with bleeding. However, anti-Xa monitoring with dose adjustments based on levels may be beneficial in this population.

Poster # 027

EVALUATING THE UTILITY OF THE EPISTAXIS SEVERITY SCORE AND CURACAO CRITERIA FOR PEDIATRIC PATIENTS PRESENTING FOR HEREDITARY HEMORRHAGIC TELANGIECTASIA EVALUATION

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Background: Hereditary hemorrhagic telangiectasia (HHT) is a vascular disorder characterized by epistaxis, telangiectasias and arteriovenous malformations (AVMs) The Curacao criteria can be used to clinically diagnose a patient with HHT based on four criteria: patient history of epistaxis, AVMs, telangiectasias and family history. Patients with three or four criteria are diagnosed with HHT, whereas two criteria have possible HHT, and one or none of the criteria are unlikely to have HHT. This criteria is challenging to apply to the pediatric population, as AVMs and telangiectasias may not develop until late adolescence or adulthood. Epistaxis is usually the first manifestation of HHT, but it is also a common presentation of other bleeding disorders. The Epistaxis Severity Score (ESS) is a standardized measure used to evaluate the severity of a patient's nose bleeds.
Objectives: To report our experience at Texas Children's Hematology Center utilizing the Curacao criteria and ESS in conjunction with molecular testing for pediatric patients referred for HHT evaluation.
Design/Method: An analysis of patients with suspected HHT using molecular testing for HHT, ESS and Curacao criteria.
Results: Personal history of severe epistaxis or a family history of HHT are the most common reasons pediatric patients (ages 2-19) are referred to the Texas Children's Hospital Vascular Anomalies Clinic for HHT evaluation. Twelve patients had molecular testing for HHT, including sequencing and deletion/duplication of ENG, ACVRL, SAMD4, RASA1, and GDF2. All patients positive for an HHT mutation (n=6) had a positive family history. These patients presented at a younger age (mean 9.5 years) and had a Curacao criteria score (1.8) – which would otherwise place them in the "unlikely to have HHT category", and ESS (4.86 – moderate severity). The patients who tested negative for an HHT mutation (n=6) were older (mean 12 years), less likely to have HHT by Curacao criteria (1.4), had a lower ESS (4.28), and a negative family history.
Conclusion: Family history is the most reliable criteria for clinical diagnosis and molecular testing for HHT in the pediatric setting. We recommend collaboration with local adult HHT

providers to ensure pediatric referrals occur at earlier ages. ESS may be a valuable way to assess epistaxis in the pediatric population and an additional study of a larger pediatric patient cohort is necessary.

Poster # 028

RISK OF THROMBOSIS WITH SMALL CALIBER TUNNELED CENTRAL LINES VIA THE INTERNAL JUGULAR VEIN WITH SINGLE-INCISION TECHNIQUE IN CHILDREN LESS THAN 2 YEARS OLD

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Background: The use of peripherally inserted central catheters (PICCs) is common in children requiring long-term central venous access, but there's a high risk of thrombosis in small diameter vessels.
Objectives: Our goal was to determine the incidence of catheter-related thrombosis in children less than 2-years-old by accessing a larger diameter vessel via tunneled jugular small caliber central lines with single-incision technique.
Design/Method: IRB approved retrospective review from August 2014 to August 2015 (1-year review) revealed 58 tunneled jugular small caliber central lines placed with a single-incision technique in 48 patients (21 females, and 27 males). All these catheters were placed in the Interventional Radiology suite under General Anesthesia with sonographic and fluoroscopic guidance via the right internal jugular vein (n=53), or left internal jugular vein (n=5). The primary indication was long-term IV access for total parenteral nutrition (TPN), antimicrobials, chemotherapy, or multiple drips.
Results: The mean age was 325.6 days, mean weight was 8.6 kilograms, and mean time with central line in place was 41.5 days (with one catheter still in place). No procedure-related complications were observed. The symptomatic thrombosis rate was 1.7% (n=1), and the over-all thrombosis rate was 5.2% (n= 3). All thrombi were non-occlusive and identified on ultrasound. Furthermore, 2 of 3 patients with thrombosis had a previous history of venous thromboembolism. Follow-up ultrasound was available in 2 of 3 patients showing resolution of thrombus.
Conclusion: Our study sample demonstrates symptomatic thrombus in 1.7% of single-incision IJV central lines in children less than 2 years of age. We would like to share our experience of 100 patients by the time of the meeting/presentation.

Poster # 029

SUCCESSFUL USE OF SIROLIMUS AND ZOLEDRONIC ACID IN A 6-YEAR OLD BOY WITH MULTIOSTEOTIC PSEUDOMYOGENIC HEMANGIOENDOTHELIOMA: CASE REPORT AND REVIEW

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Background: Pseudomyogenic hemangioendothelioma (PMH) is a rare neoplasm with vascular and sarcomatous elements, unpredictable course, and uncommon metastatic or fatal potential. While systemic chemotherapy has been reported with variable success, generally accepted treatment is aggressive surgery with wide margins. Evidence based treatment options are lacking. We report the successful use of sirolimus (SIR) and zoledronic acid ZA) to induce a sustained remission and avoidance of amputation in a 6 year old.
Objectives: Our objective is to report our experience and to review the literature for systemic chemotherapy of PMH. Case: A 6-year old boy presented with multifocal PMH of the bones of the right leg. Amputation was recommended. After second opinions, the family chose a recommended course of monthly ZA (2.3mg/m2, 4mg max) and SIR (3mg/m2/day; level 8-12ng/ml) with the goal of avoiding amputation. We report clinical sustained clinical remission 15 months as documented by PET-CT. Treatment was associated with mild/manageable side effects: mild/occasional bone pain, fever, mucositis, all of which resolved spontaneously, were treated conservatively and did not require dose modifications. The patient has now received 14 dose of ZA. SIR trough levels have been within target goals of 8-12 ng/ml. The mother and patient report normal mobility/activity, resolution of swelling and pain.
Design/Method: PubMed/Google Scholar search using terms: “pseudomyogenic hemangioendothelioma,” “epithelioid sarcoma-like hemangioendothelioma” selected for patients under 40 and English language.
Results: We found case reports of 20 pediatric and young adult patients with PMH. Variable responses to conventional cytotoxic chemotherapy in young adults is described in several cases. A contemporary case describes salvage of conventional chemotherapy with everolimus with reported outcome. No cases comparable to ours were identified.
Conclusion: Systemic therapy has an unclear role in treatment of PMH. In select cases it may reduce or eliminate the need for radical surgery, with particular relevance to pediatric patients. Increasing knowledge and identifying non-surgical successful strategies for PMH and possible correlates of tumor response will allow for development of robust treatment protocols.

Poster # 030

ETIOLOGY OF THROMBOSIS IN CHILDREN: AN INSTITUTIONAL STUDY

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Background: Thromboembolism (TE) is a rare event in childhood, occurring significantly less frequently than in adults. Not only is it associated with an increase in the length of hospital stay and medical costs, it is also associated with substantially increased morbidity and mortality in children and, more importantly, rates have been steadily increasing in the pediatric population. The increase can be attributed in large part to medical advances resulting in more frequent use of central venous catheters (CVC), and improved survival rates of the seriously ill.
Objectives: This study aims to analyze the contributing factors to TEs in the pediatric population at Ochsner Medical Center (OMC), with the hope of affecting future management, including the use of prophylactic treatment that is currently not standardized in children.
Design/Method: The international Classification of Diseases, Ninth Revision codes was used to

identify patients aged 0-21 years, admitted between July 1, 2009 and September 30, 3013 who were diagnosed with a thromboembolic event during their treatment stay. 340 identified patients have been reviewed, with 73 meeting study parameters.
Results: 22 patients (30%) were found to be on some form of prophylaxis when the thromboembolic event occurred (aspirin, heparin/LMWH, warfarin, IVC filter). Population risk factors identified were age (<1year or >16 years), gender (male>female), smoke exposure, genetic predispositions (e.g. Factor V Leiden), congenital anomalies (e.g. congenital heart disease), prolonged immobility, prematurity, asphyxia, and sepsis. Estimated thrombosis rate at OMC was 0.83-2.06%.
Conclusion: Currently there is no national standard regarding the prophylactic treatment of TE in the pediatric population due to the lack of high-quality evidence-based studies. According to our data, the current Ochsner pediatric thrombosis rate is within the national average. While our institution falls in the lower end of the national average, due to the morbidity associated with TE, we propose that better strategies for prevention and treatment for pediatric thromboembolism should be implemented for the pediatric cohort at Ochsner Medical Center to inform clinical decision-making and for better care of our patients.

Poster # 031

PREVALENCE OF HYPERTENSION (HTN) AND CARDIOVASCULAR RISK FACTORS IN A PEDIATRIC HEMOPHILIA POPULATION

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Background: Improved life expectancy in hemophilia has led to a greater interest in age-related disorders. Cardiovascular disease has been increasingly reported in the hemophilia adult population. Several studies have reported higher prevalence of hypertension (HTN) in adults with severe hemophilia when compared with their unaffected counterpart. However, the characteristics of atherosclerotic risk factors among this population are not yet well established. To date, there is very limited information regarding the prevalence of HTN and cardiovascular disease in the pediatric hemophilia population.
Objectives: To determine the prevalence of HTN and associated cardiovascular risk factors in the pediatric hemophilia population in comparison to general pediatric population.
Design/Method: We conducted a cross-sectional study from the National 2012 Health Cost and Utilization Project database. We reviewed information from patients between the ages of 0 to 21 years. We used ICD-9 codes to define hemophilia, hypertension, obesity, hypercholesterolemia and/or lipid disorders, and diabetes. We compared the prevalence of hypertension between the hemophilic group and an age and gender matched control group that did not have hemophilia.
Results: The prevalence of HTN was significantly higher in children with hemophilia (CWH) in comparison to the general pediatric population (1.71% vs 1.02%, p-value=0.005). When adjusting the analysis for gender, the prevalence of HTN in the hemophilia cohort remained higher, although not statistically significant, when compared to unaffected children (1.52% vs 1.22%, p-value=0.2568). We subsequently examined whether the presence of one or more

cardiovascular risk factors could explain the higher prevalence of HTN in CWH. There was a higher concomitant prevalence of obesity in the hypertensive hemophilia cohort (2.64% vs 1.32%, p-value <0.0001). Interestingly, non-hemophilic males had a much higher prevalence of diabetes mellitus (DM) than did their hemophiliac counterpart (1.47% vs 0.56%, p-value=0.0015). An abnormal lipid profile did not appear to have a significant contribution towards hypertension in CWH (0.06% vs 0.27%, p-value 0.0822).
Conclusion: Pediatric patients with hemophilia have a significantly higher prevalence of HTN in comparison to the general pediatric population. This subpopulation is also impacted by higher rates of obesity but interestingly, a lower prevalence of DM. This data suggests that blood pressure and cardiovascular risk factors need to be closely monitored in CWH, and a better preventive strategy is likely needed to identify those hemophilic patients with higher risk of developing cardiovascular disease in adulthood. Further research is needed to determine if there is an association difference between cardiovascular disease and hemophilia depending on disease severity.

Poster # 032

OBESITY, SEDENTARY LIFESTYLE, AND VIDEO GAMES: THE NEW THROMBOPHILIA COCKTAIL IN ADOLESCENT MALES

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Background: Pediatric venous thromboembolism (VTE) is rare with an incidence rate of 0.7-4.9 per 100,000 person-years. Two peaks in incidence are noted: one in infants <1 year and the second in adolescents. Over the last two decades, an increase in pediatric VTE attributable to improved diagnostic techniques, clinical awareness, and increasing risk factors—higher complexity of care, central venous catheters, obesity, and increased use of oral contraceptive pills (OCP)—has been reported. Notably, between 1980-2012 obesity has more than doubled in children aged 6-11 (7% to 18%) and quadrupled in adolescents aged 12-19 (5% to 21%). Given the direct mortality rate of 2% and risk for post-thrombotic syndrome of 26%, it is important to understand underlying modifiable risk factors.
Objectives: To identify evolving modifiable risk factors for thrombosis in adolescents males.
Design/Method: Case series and literature review.
Results: Case 1: An 18-year-old obese male (BMI 37 kg/m2) presented with bilateral pulmonary emboli (PE) and an associated right lower lobe infarction. Thrombophilia testing revealed factor V Leiden heterozygosity. He also had a very sedentary lifestyle, spending 8+ consecutive hours playing video games per day. Case 2: A 17-year-old obese male (BMI 39 kg/m2) developed bilateral basilar PE and pulmonary infarctions in the setting of a left femoral deep venous thrombosis. Thrombophilia testing identified factor V Leiden heterozygosity and vascular imaging revealed May-Thurner syndrome. He conceded being sedentary for hours on end playing video games prior to the VTE occurrence. Case 3: A 13-year-old obese male (BMI 56 kg/m2) developed a left lower lobe PE in the setting of 3-week immobility secondary to Guillain-Barre syndrome. He also had occlusive thromboses in bilateral cephalic veins and in the right saphenous vein. Thrombophilia testing and family history for thromboses were negative.
Conclusion: With the rising incidence of VTE in the adolescents, it is important to identify

modifiable risk factors associated with this increase. Akin to OCP use in females, the combination of sedentary lifestyle and the growing popularity of electronic gaming in adolescent boys; especially “extreme gamers” playing up to 48.5 hours/week, may pose excessive VTE risk in the setting of obesity. Recognizing this emerging epidemic by medical providers is crucial. Identifying prolonged video game/electronic use and immobility in the setting of obesity may be essential in risk assessment. Encouraging patients to have a more active lifestyle and to minimize screen time may reduce the risk of VTE in adolescent boys.

Poster # 033

THROMBIN GENERATION IN PATIENTS WITH SEVERE HEMOPHILIA A IS VARIABLE AND MAY BE PREDICTIVE OF RESPONSE TO TREATMENT

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Background: Patients with severe hemophilia A may have variable bleeding phenotypes despite having equivalently low factor (FVIII) levels of <1%. The basis for this heterogeneity in the clinical expression of severe hemophilia is poorly understood. Recent evidence indicates that global assays of coagulation may be better predictors of the coagulation capacity and hemostasis compared with traditional coagulation tests. Current prophylaxis goals in patients with hemophilia minimize time spent at baseline. Thus, we hypothesized that evaluating Endogenous Thrombin Potential (ETP) at baseline, 10% and 40% FVIII correction levels will be better reflective of real-world scenarios and the effects of treatment.
Objectives: Our objective was to study thrombin generation parameters (ETP, peak thrombin and lag time) at baseline, 10% and 40% factor correction levels in patients with severe hemophilia A. Additionally we aimed to determine if the baseline ETP was predictive of response at the spiked levels.
Design/Method: Our study was a single institution cross-sectional study. Baseline plasma samples at trough FVIII were obtained from patients with severe hemophilia A and thrombin generation was evaluated using a standard calibrated automated thrombogram (CAT). Full-length recombinant FVIII was added to trough patient plasma for final factor concentrations of 0.1 U/dl and 0.4 U/dl. Data regarding bleeding phenotype, FVIII mutation severity, factor replacement product, any history of thrombosis or risk factors for thrombosis were collected.
Results: Samples from 57 patients with severe HA without inhibitors were evaluated. CAT mean lag times were 6.37 minutes (SD 6.36), mean ETP was 808.87 nM/minute (SD 369.64) and mean peak thrombin levels were 87.45 nM (SD 62.87). Marked variability in responses were noted among patients at baseline, 10% and 40% FVIII levels. Results were divided into quartiles for ETPs at baseline, 10% and 40%. 64.9% of patients remained in the same quartile ranges when ETPs at baseline FVIII levels were compared to ETPs at corrections to 10% or 40%.
Conclusion: Our results indicate variability in thrombin generation among patients with severe hemophilia A (FVIII<1%) at baseline as well as different correction levels. Since phenotypic heterogeneity is observed in patients with severe hemophilia (FVIII<1%), this may suggest that ETP better correlates with bleeding severity as compared to factor levels. Additionally, baseline ETPs appear to be responsive to treatment at 10% and 40% factor correction levels. Given that

the standard of care for patients today is prophylaxis, ETP at different potential trough FVIII levels may be useful in guiding treatment decisions.

Poster # 034

ORAL ANTICOAGULANT THERAPY IN YOUNG CHILDREN UTILIZING AN EXTEMPORANEOUS LIQUID WARFARIN FORMULATION: EVALUATION OF ANTICOAGULATION QUALITY, EFFICACY, AND SAFETY OUTCOMES

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Background: Warfarin is the most commonly used oral anticoagulant in children. Prior studies have reported poor anticoagulation (AC) control in infants and young children receiving warfarin. In this population, warfarin tablets are crushed and dissolved in water which could lead to inconsistent dosing and variable AC. A liquid warfarin formulation (1 mg/mL) can be extemporaneously prepared which could allow for uniform dosing leading to more stable AC. However, AC outcome data on the use of this formulation in children is not available.
Objectives: To report AC quality, efficacy, and safety of liquid warfarin in young children.
Design/Method: We conducted a retrospective study of all patients who received warfarin at our center since 2013 with a target International Normalized Ratio (INR) of 2.0-3.0. We compared patients who received liquid warfarin to those who received uncrushed warfarin tablets. Outcome measures included percentage time in therapeutic range (%TIR), percentage of INR values within target therapeutic range (%ITTR), % time with INR <1.5, % time with INR >4.0, AC failure, and AC-related bleeding.
Results: Twenty patients were included. Liquid warfarin was prescribed to 8 patients. Patients who received liquid warfarin were significantly younger [median age 3.8 years (range 2.1-6.2)] than patients who received warfarin tablets [median age 13.3 years (10.7-18)] (P=0.003). The median duration of AC was 10 months (3-30) for patients on liquid warfarin and 22 months (5-29) for patients on warfarin tablets (P= 0.3). For target INR of 2.0-3.0, the mean %TIR was 70.8% (58.2-92.1) in patients on liquid warfarin and 80.4% (72.6-97.8) in patients on warfarin tablets (P= 0.05) while the mean %ITTR was 62.3% (45.5-77.8) and 70% (53.8-88.9) (P=0.28), respectively. For target INR of 1.8-3.2, the respective mean %TIR values were 85.2% (79.4-96.9) and 89.3% (79.7-100) (P=0.08) while the respective mean %ITTR values were 76.2 (63.6-88.9) and 81.3 (61.5-100) (P=0.21). The mean % time with an INR <1.5 was 0.3% (0-1.9) in patients on liquid warfarin and 0.7% in patients on warfarin tablets (0-5.2) (P=0.6) while the mean % time with an INR >4 was 1.3% (0-4.9) and 0.5% (0-1.5) (P=0.9), respectively. AC failure was observed in 1 patient receiving liquid warfarin and 2 patients receiving warfarin tablets (P=1.0). AC-related bleeding occurred in 1 patient in each group (P=1.0).
Conclusion: Our study suggests that, in young children, oral AC with an extemporaneous liquid warfarin formulation is effective, safe, and leads to improved AC control in this cohort compared to previous reports.

Poster # 035

FACTOR DOSING IN HEMOPHILIA PATIENTS USING IDEAL BODY WEIGHT VERSUS ACTUAL BODY WEIGHT

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Background: Current factor dosing in Hemophilia patients is based on actual body weight (AW). However, given the obesity epidemic in the United States and the high cost of factor replacement, should patients be dosed based on AW or is there a role for dosing factor based on ideal body weight (IBW). Nearly half of the patients in a demographic study of the United States hemophilia population were considered either overweight or obese based on their body mass index (BMI). (Curtis et al 2015) Estimation of dosing based on IBW could cut expenses by almost 50 percent; an annual savings of approximately $136,000. (Graham et al 2014)
Objectives: To figure out a cost effective way of dosing factor in obese hemophilia patients.
Design/Method: We began a retrospective review of patient recovery studies of factor VIII and factor IX at our center to determine the effect of factor dosing based on AW versus that based on IBW. Information collected included: height, weight, IBW, BMI, dosage of factor infused, and the 1 hour recovery. Factor recovery was calculated by comparing the incremental increase in the pre-infusion factor activity and the 1-hour post infusion activity. Data was analyzed with student's t-test and regression analysis to determine if there were any differences between Dose Discrepancy and Factor Discrepancy. DOSE DISCREPANCY, which is the difference between the factor dose given based on AW and calculated factor dose based on IBW. FACTOR DISCREPANCY, which is the difference between rise in factor activity based on AW and predicted rise in factor activity based on IBW.
Results: Our database included 38 males and 2 females, age range of 13 to 70 years, and BMIs ranging between 16.9 and 42.1. Patients were then stratified by BMI comparing BMIs below 25 (normal, n =23) versus greater than 25 (overweight or obese, n=17). Patients with a BMI below 25 had a high correlation between the Factor Discrepancy or Dose Discrepancy. Pearson correlation coefficient of 0.789 ($p<0.05$). However, in patients with BMIs above 25 there was no correlation between Dose Discrepancy and Factor Discrepancy. Pearson correlation coefficient of 0.240 ($p=0.322$).
Conclusion: These results suggest that IBW is an effective way to dose patients who are at a normal BMI of 25 or less but in patients who are overweight or obese (BMI >25) IBW does not provide a reliable method to predict post-infusion factor activities. Prospective studies of overweight and obese patients will need to be studied.

Poster # 036

PROPHYLACTIC ENOXAPARIN DOSING IN AN OBESE PEDIATRIC POPULATION

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Background: Pediatric obesity is an independent risk factor for thrombotic events. Consequently, this population would benefit from thromboprophylaxis in high risk situations.

Despite this, there are only two small case reports examining prophylactic enoxaparin dosing in an obese pediatric population, with no formal dosing recommendations.
Objectives: To determine whether traditional weight-based enoxaparin dosing of 0.5mg/kg every 12 hours is appropriate for an obese pediatric population.
Design/Method: We conducted a retrospective chart review of patients aged 1-18 years with a weight greater than the 98th percentile for age given enoxaparin to prevent a thrombotic event at our institution from 2007 to 2015. Actual (mg) and by weight (mg/kg) enoxaparin doses, anti-Xa levels, number of dose adjustments required to obtain a prophylactic anti-Xa (0.1 to 0.3) and adverse events were obtained for each patient.
Results: We had 26 evaluable patients. Three patients were less than 5 years of age, eighteen were 5-15 years and five were greater than 15 years of age. Patient weight ranged from 17.4kg to 130kg. Fifteen patients were started with an enoxaparin dose of 0.5mg/kg (0.47-0.55mg/kg). Their initial anti-Xa ranged from <0.1 to 0.62, with eleven (73%) within the appropriate prophylactic range. Three patients were supratherapeutic (anti-Xa 0.37-0.55). One patient was subtherapeutic (anti-Xa <0.1). Eleven patients received an initial enoxaparin dose below 0.5mg/kg (0.25-0.44mg/kg). Their anti-Xa ranged from <0.1 to 0.33, with six (55%) of these patients having an anti-Xa in the prophylactic range. Four patients were subtherapeutic (anti-Xa <0.1) and one patient was supratherapeutic (anti-Xa 0.51). No patients required more than two dose adjustments. Two patients (7.7%) had minor bleeding including epistaxis and a small amount of blood in the stool. Bleeding was not associated with an elevated anti-Xa level (0.21-0.25). Three patients (11.5%) developed a thrombus while on enoxaparin prophylaxis. Two developed a line-associated thrombus during an acute infection, and one individual with spina bifida developed an inferior vena cava thrombus following a bowel resection. None of these individuals had a subtherapeutic anti-Xa (0.15-0.33).
Conclusion: A prophylactic enoxaparin dose of 0.5mg/kg every 12 hours with no maximum dose appears to be safe in an obese pediatric population, with most individuals having appropriate prophylactic anti-Xa levels. Although minor bleeding and thrombus development occurred infrequently, it happened in individuals with appropriate prophylactic anti-Xa levels.

Poster # 037

PRELIMINARY RESULTS FROM A GLOBAL COMPARATIVE LABORATORY FIELD STUDY WITH BAY 94-9027, A SITE-SPECIFICALLY PEGYLATED RECOMBINANT FACTOR VIII PRODUCT

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Background: Accurate measurement of factor VIII (FVIII) activity in patients with hemophilia A is important for patient monitoring and treatment decisions. Discrepancies in results using different assays or reagents to measure prolonged–half-life factor products have been recognized. BAY 94-9027 is a prolonged–half-life FVIII product site-specifically conjugated with a 60-kDa polyethylene glycol molecule (2×30 kDa branched).
Objectives: A global field study was conducted to assess the ability of clinical laboratories to measure BAY 94-9027 activity in spiked hemophilic plasma samples using their in-house or

specific assays.
Design/Method: In this 2-part study, laboratories received sample sets (3–4 per laboratory) of 26 blinded samples in randomized order for analysis. Each set consisted of triplicate test samples of BAY 94-9027 or a comparator (antihemophilic factor [recombinant] plasma/albumin-free method [rAHF-PFM (Advate®); Shire]) spiked at low (<10 IU/dL), medium (10–50 IU/dL), and high (50–100 IU/dL) concentrations in pooled hemophilic plasma. Normal control plasma and unspiked hemophilic plasma in triplicate were positive and negative controls, respectively. Two additional blinded samples matching 2 of the other 24 samples in the set were included in each set to decrease the predictability of each set. Laboratories analyzed test samples using their in-house assays (one-stage, chromogenic, or both), reagents, and standards (part 1). In part 2, all laboratories tested 2 additional sample sets using 2 activated partial thromboplastin time kits (Pathromtin® and HemosIL® SynthASil) previously shown to accurately measure BAY 94-9027 and full-length FVIII. FVIII recovery and FVIII levels were primary and secondary endpoints, respectively.
Results: Fifty-two laboratories in North America, Europe, and Israel participated in the study. In part 1, 49 laboratories tested samples using the one-stage assay, 16 used the chromogenic assay, and 13 used both assays. The reagents routinely used for measuring FVIII activity varied among participating laboratories. Mean FVIII recovery ranged from 75.1%–103.2% for BAY 94-9027 and 94.6%–114.7% for rAHF-PFM across all concentrations and reagents using the one-stage assay. As expected based on previously published data, the PTT-A and HemosIL® APTT-SP kits underestimated BAY 94-9027 at all concentrations. More accurate one-stage results were generated using the Pathromtin® and SynthASil kits, as shown in part 2 of the study. For the chromogenic assay, mean FVIII recovery ranged from 104.4%–117.1% for BAY 94-9027 and 87.7%–107.8% for rAHF-PFM across all concentrations.
Conclusion: BAY 94-9027 can be accurately monitored using the chromogenic assay and select commonly used one-stage assay kits without need of a conversion factor. This study was funded by Bayer AG (Leverkusen, Germany).

Poster # 038

FREQUENCY AND CHARACTERISTICS OF THROMBOSIS IN CHILDREN WITH BRAIN TUMORS

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Background: Thrombosis is a common morbidity in adult patients with brain neoplasms. Cancer-related hypercoagulable states have been well described in the adult literature, particularly in patients with malignant gliomas. Thrombotic risk factors often present in pediatric patients with brain tumors include prolonged immobility, indwelling vascular access devices, surgical disruption of normal vascular architecture, and exposure to radiation and anti-angiogenic therapies. Data in children with brain tumor are limited and likely underestimate the true prevalence of thrombotic events in this population.
Objectives: To describe the frequency and characteristics of thrombotic events in children with brain tumors.
Design/Method: We conducted a retrospective chart review of all pediatric patients with central

nervous system (CNS) neoplasms who experienced a thrombotic event over a 5-year period in a large academic medical center. Cases were identified utilizing radiology data mining software (MONTAGE™ Search and Analytics). The radiology reports and medical charts of all potential cases were reviewed to identify true thrombotic events. Relevant data were collected in a secure web-based database created using Research Electronic Data Capture (REDCap) application. Data are presented using descriptive statistics.
Results: A total of 287 children with brain tumors were primarily treated at our institution from 2009 to 2013. Twelve (3.8%) patients (median age 14 years, 7 females) experienced thrombotic events. Most events were diagnosed in patients with primary tumors, most frequently ependymomas (25%) and medulloblastomas (17%). Of the 12 thrombotic events, 10 (83%) occurred following a subtotal resection. Thrombotic events were diagnosed at a median duration of 7.5 months after tumor diagnosis (range, 0-80.8 months). Only 1 patient had a thrombotic event at presentation. Nine (75%) patients had not been exposed to focal or craniospinal radiation at the time of event, and 4 (42%) had not received chemotherapy. All 12 events were deep vein thromboses (DVTs) with 8 (67%) catheter-related DVTs and 4 (33%) non-catheter-related DVTs. Affected venous segments included lower extremity veins (6 patients), upper extremity/neck veins (5 patients), and both (1 patient). The majority (83%) of thrombotic events were symptomatic at presentation. None of the 12 patients experienced clinically evident pulmonary embolism. A thrombophilic state was identified in 2 cases (17%).
Conclusion: Our study suggests a higher frequency of venous thrombotic events in children with brain tumors than previous reports. The majority of thrombotic events were symptomatic, catheter-related DVTs. Large prospective studies are needed to define true incidence and identify risk factors predisposing to thrombosis in children with brain tumors.

Poster # 039

MULTI-MODAL IMMUNE TOLERANCE FOR HEMOPHILIA B

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Background: Inhibitor formation is a serious complication in hemophilia that is much more common in Factor VIII deficiency than Factor IX deficiency. In the latter, immune tolerance (IT) is less successful and also fraught with complications such as anaphylaxis and proteinuria.
Objectives: We discuss a unique case of a young boy with inhibitors to Factor IX who was successfully treated with IT using plasma-derived Factor IX (IXpd) product, desensitization to Factor IX, and rituximab.
Design/Method: This is a single case report from retrospective review of the patient's electronic medical record. Literature search was conducted via PubMed using the following search terms: Factor IX inhibitors, Hemophilia B, immune tolerance.
Results: A twelve year old boy was diagnosed with Factor IX deficiency at birth. Both he and his older brother had Factor IX levels of <1% and >50bp large gene deletions (c.Exon1_Exon8del) per CDC testing on HIRS study). He did well with recombinant factor IX (IXr) replacement until three years of age when he developed an inhibitor. At two years of age an inhibitor titer of 2.6 BU was detected. IT was started with IXr, but resulted in anaphylaxis. He

was then treated episodically with maintained on recombinant factor VIIa (rFVIIa) infusions. His course was complicated by recurrent joint bleeds, port infections as well as mucosal and soft tissue bleeding. He was then diagnosed with platelet storage pool disorder (dense granuole defect of 1.6). Frequency of hospitalizations for joint bleeds increased and administration of rFVIIa failed to significantly correct whole blood coagulation as analyzed on thromboelastogram (TEG). FEIBA was introduced which improved TEG results, but increased inhibitor titer to 11.8 BU. IT was then initiated with Rituximab (375mg/m2 x 4 doses) and desensitization to IX using plasma-derived IX (IXpd) over 10 days. Although initially successful, but approximately two into IT, an anaphylactic reaction again occurred. Desensitization was restarted. IT then proceeded uneventfully with 30 u/kg IXpd daily. Inhibitor was no longer detected six weeks into IT. Six months after the initiation of IT, factor IX recovery levels twelve hours after 30 units/kg were 34%.
Conclusion: IT may be successfully accomplished for Hemophilia B, but may require a multi-modal approach including immune modulation with rituximab, desensitization to IX, and use of a plasma derived product. The pathophysiology of inhibitor formation in hemophilia B is probably different from that of hemophilia A.

Poster # 040

CONTINUOUS LOW-DOSE HEPARIN INFUSION FOR CATHETER RELATED THROMBOSIS PROPHYLAXIS

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Background: Central venous catheters (CVC) are often required in critical care settings in order to provide life sustaining care. Their usage has improved the quality of care in pediatric patients by providing a secure point of access and minimizes the number of peripheral needle sticks. However, CVC usage is not without risks. Clinical studies identify CVC usage as the single most important risk factor for deep vein thrombosis (DVT) in children and the incidence of CVC-related thrombosis ranges from 3-45% depending on the characteristics of the population studied. Per unit protocol, the Penn State Health Children’s Hospital PICU (Hershey, PA) utilizes a low dose continuous infusion of unfractionated heparin (UFH) at 10 units/kg/hr as a standard of care for prophylaxis against CVC-related venous thromboembolic events (VTE) and to maintain line patency. The efficacy of this approach has never been evaluated.
Objectives: To determine if low dose continuous heparin infusion for prophylaxis results in lower incidence of CVC-related VTE, catheter dysfunction and central line associated blood stream infection (CLABSI).
Design/Method: To determine if the incidence of catheter related VTE is lower than published data a retrospective chart review was conducted utilizing the institutional electronic medical record for all patients in 2015, aged 0-17.99 years, who developed a CVC-related VTE during a PICU admission. Secondary objectives such as the incidence of catheter dysfunction, CLABSI, and any associated bleeding complications are also being analyzed.
Results: Interim analysis including 378 eligible patients (57% male, mean age 4.93 years, range 0-17.92) demonstrated that a total of 506 CVCs placed, comprised of predominantly non-tunneled CVCs (78.8%), followed by peripherally inserted central catheters (PICCs) (12%),

totally implantable venous access devices (4.74%) and tunneled CVCs (4.34%). Surprisingly, only 9 total CVC-related VTEs (1.8%) were identified. Eight CLABSIs (1.5%) were identified and occurred in a total of 5 patients. A total of 81 doses (16%) of tissue plasminogen activator were utilized.
Conclusion: Preliminary results suggest that prophylactic low dose UFH infusion may significantly decrease the occurrence of CVC-related VTE. Further analysis will compare another similar sized and acuity level PICU (Children's Hospital of Pittsburgh) which does not practice the same method to serve as a control for our study.

Poster # 041

BASELINE CHARACTERISTICS AND BLEEDING OUTCOMES IN PATIENTS WITH SEVERE HEMOPHILIA A ADMINISTERED BAY 94-9027 PROPHYLAXIS EVERY 5 OR EVERY 7 DAYS

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Background: BAY 94-9027 is a B-domain–deleted prolonged–half-life recombinant factor VIII product site-specifically conjugated with a single (dual-branched) 60-kDa polyethylene glycol molecule.
Objectives: Conduct a post hoc analysis to assess the relationship between baseline characteristics and bleeding outcomes in adolescents and adults with severe hemophilia A who received BAY 94-9027 prophylaxis every 5 or 7 days in the PROTECT VIII trial
Design/Method: In PROTECT VIII, a phase 2/3, partially randomized, open-label trial, previously treated males aged 12–65 years with severe hemophilia A received BAY 94-9027 for 36 weeks on demand or as prophylaxis at intervals determined following a 10-week run-in period of 25 IU/kg 2x/wk. Patients with ≤1 spontaneous bleed during the run-in were eligible for randomization to 45–60 IU/kg every-5th-day or 60 IU/kg every-7th-day prophylaxis for 26 weeks.
Results: Baseline mean±SD age was 33.7±13.0 years for every-5th-day (n=43) and 37.0±13.5 years for every-7th-day (n=43) groups. In the every-5th-day and every-7th-day groups, median (range) number of bleeds in the previous 12 months was 4.5 (0–69) and 3.0 (0–50), median number of target joints were 1.0 (0–6) and 2.0 (0–6), and 81.4% and 88.4% of patients were previously on prophylaxis, respectively. After randomization to every-5th-day and every-7th-day prophylaxis, median (quartile [Q]1;Q3) annualized bleeding rates were 1.9 (0;4.2) and 3.9 (0;6.5). All patients randomized to every-5th-day prophylaxis remained in this group, but 11/43 patients randomized to every-7th-day prophylaxis switched to more frequent dosing (every 5th day, n=8; 2x/wk, n=3). In those 11 patients, median (Q1;Q3) number of bleeds were reduced from 2.0 (2.0;6.0) to 1.0 (0.0;2.0) after changing to more frequent dosing. Median (Q1;Q3) number of bleeds in 32 patients who remained on every-7th-day prophylaxis was 0.5 (0.0;2.0). In patients who left versus remained in the every-7th-day group, median (range) number of target joints at baseline were 2.0 (0–4) versus 1.0 (0–6), respectively, and median number of bleeds in the previous 12 months were 3.5 (1–15; n=10) versus 3.0 (0–50).
Conclusion: Baseline characteristics were similar in patients randomized to receive BAY 94-9027 every 5th or 7th day. Compared with patients remaining in the every-7th-day group,

patients who switched to more frequent dosing tended to have more target joints at baseline and more bleeds in the previous 12 months. These data indicate that BAY 94-9027 prophylaxis dosing intervals can be extended to 5 or 7 days using an individualized approach based on patients' bleeding history and breakthrough bleeding pattern. Study funded by Bayer AG (Leverkusen, Germany).

Poster # 042

PEDIATRIC VENOUS THROMBOSIS ASSOCIATED WITH STAPHYLOCOCCAL INFECTIONS: SINGLE INSTITUTIONAL EXPERIENCE

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Background: Since the emergence of community-acquired methicillin-resistant S. aureus (MRSA), severe manifestations of infection are commonly encountered. An increasing incidence of deep vein thrombosis (DVT) associated with Methicillin-sensitive Staphylococcus aureus (MSSA) and Methicillin-resistant Staphylococcus aureus (MRSA) has been also described in several studies
Objectives: Review our institutional experience by evaluating characteristics and outcomes of children with VT and staphylococcal infections.
Design/Method: Retrospective clinical data from 16 pediatric patients with VT and staphylococcal infection over a 5 year period was obtained via medical record abstraction. Information extracted included demographics, date of presentation, presenting signs/symptoms, VT site, underlying risk factor(s) for VT, underlying infection, isolated organism, labs, imaging, anticoagulation treatment, and outcome.
Results: Sixteen patients with a median age at diagnosis of 8 years were included. The most common infection encountered was osteomyelitis (56%). The most common isolated organism was MRSA (63%). VT sites confirmed by Doppler US (DUS) were primarily upper/lower extremities, mostly deep venous thrombosis (DVT). Median time elapsed between infection and VT diagnosis was 5.5 days. Central venous catheters (CVC) were present in 50% of cases. All patients received anticoagulation with low molecular weight heparin (LMWH) except one patient with superficial VT who was managed conservatively. 50% patients had complete resolution of DVT by the end of treatment, 25% patient had early disappearance of the thrombus at 7-10 days. Only 2 patients (12.5%) had persistent thrombus at 6 months. Six patients (37.5%) were lost to follow up. No thrombosis or bleeding complications were noted.
Conclusion: Staphylococcal infections may increase the risk of VT in children. Therefore, a high index of suspicion for VT is warranted in children with Staphylococcal infections (particularly MRSA) to promptly diagnose and treat. This approach may improve outcomes and minimize complications. Prophylactic anticoagulation in presence of staphylococcal infection, particularly MRSA, may be considered in future studies.

Poster # 101

DIAGNOSTIC UTILITY OF NEXT-GENERATION SEQUENCING PANEL FOR COMMON HEMATOLOGIC INDICATIONS IN THE PEDIATRIC POPULATION

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Background: Next-generation sequencing (NGS) has been widely adopted in the clinical setting, and is advantageous for a reduction of time and cost in the diagnostic odyssey. NGS gene panels are recommended when evaluating patients for conditions of considerable heterogeneity and overlapping phenotypes, such as hematologic disorders. These panels result in fewer variants of uncertain significance and incidental findings than whole exome/genome sequencing, but are limited by gene selection and do not allow for gene discovery. Identifying the molecular etiology of a patient's hematologic symptoms is essential to confirm the diagnosis, predict future health problems, provide genetic counseling, and identify appropriate hematopoietic stem cell donors. NGS panel sequencing had a diagnostic rate of 38% in a previous report of patients with bone marrow failure.
Objectives: Analyze the diagnostic rate of a targeted NGS gene panel personalized for pediatric patients with common hematologic referral indications.
Design/Method: A retrospective chart review of the 46 pediatric patients recommended to have next generation sequencing targeted to their hematologic phenotype since September 2014.
Results: The NGS panel was performed in a CLIA-certified clinical laboratory on 39 patients. This testing was denied by the healthcare payer for five patients, and two patients declined testing due to high out of pocket cost. The most common indication was thrombocytopenia (n=19), followed by neutropenia (n=15). Other indications for testing were myelofibrosis, Fanconi anemia, aplastic anemia, and Diamond Blackfan anemia. The average number of genes on the panels were 32 for neutropenia and 30 for thrombocytopenia. The panel results were considered diagnostic for 10/39 (25.6%). The diagnostic rate for neutropenia specifically was 30%, comparable to previous research studies. The diagnostic rate for thrombocytopenia was 13.3%. In the diagnostic cohort, patients had fewer previous genetic tests. In non-diagnostic cohort, more patients had previous negative genetic testing and more were recommended to have additional genetic testing, which when performed, was also non-diagnostic.
Conclusion: The targeted NGS panel is feasible in the clinical pediatric hematology setting, as it is being approved by healthcare payers. As a first-line test, it has a high diagnostic rate for patients with neutropenia, and may be appropriate to rule out many genetic causes of thrombocytopenia.

Poster # 103

PERIFERAL EXPRESSION OF HEPCIDIN GENE IN EGYPTIAN β-THALASSEMIA MAJOR

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Background: Iron over load is the major cause of morbidity and mortality in transfusion dependent β-thalassemia major patients. There is a sophisticated balance of body iron metabolism of storage and transport which is regulated by several factors including the peptide hepcidin. Hepcidin is the main iron regulatory molecule; it is secreted mainly by the liver and other tissues including monocytes and lymphocytes, expression of hepcidin in such cells is unclear and has been studied in few reports with controverted result.
Objectives: to evaluate the peripheral expression of hepcidin mRNA in Egyptian β-thalassemia major patients to explore its diagnostic and future therapeutic roles which may help in management of patients.
Design/Method: Peripheral expression of hepcidin was measured using quantitative real time PCR (qRT-PCR) in 50 β-thalassemia major patients attending the hematology outpatient clinic of the children hospital of Cairo University (age range 11-36 years), in addition to 20 healthy volunteers as a control group. All patients were subjected to clinical evaluation including medical history, and clinical examination. Evaluation of cardiac siderosis using cardio-vascular magnetic resonance (CMR) relaxation time T*, T* was measured in milliseconds (ms), and liver iron concentration (LIC)measurements was measured using SDPA R2-MRI (FerriScan®).Aspartate and alanine aminotransferases(AST and ALT)were measured using Integra-400 (Roche),HCV antibodieswere tested using enzyme immunoassay (EIA) (COBAS-Amplicore),and estimation of serum ferritin level which was done using micro particleenzyme immunoassay (MEIA) (Abbott AxSYM System).
Results: Hepcidin levels in β-thalassemia major patients showed statistically significant decrease in comparison to the control group, and was correlated to cardiac iron stores (T2*). However, hepcidin level was not different among the patients according to the HCV status or whether splenectomized or not.
Conclusion: ; peripheral expression of hepcidin, in iron over loaded β-thalassemia major patients, is a reflection of hepatic expression. It can be used as a molecular predictor for the severity of cardiac iron overload and can be used as a future target for therapy in β-thalassemia major patients.

Poster # 105

HEMOGLOBIN C TRAIT ACCENTUATING ERYTHROCYTE DEHYDRATION IN A HEREDITARY XEROCYTOSIS CASE WITH A NOVEL MUTATION

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Background: Hereditary Xerocytosis is an autosomal dominant hemolytic anemia characterized by erythrocyte dehydration with decreased water and solute content. Typical phenotype is mild compensated hemolytic anemia with hemolytic and aplastic episodes, cholelithiasis, and thrombotic and hemochromatosis tendencies. Borderline thrombocytopenia and exercise-induced hemolysis also have been reported. Laboratory findings include increased erythrocyte mean corpuscular hemoglobin concentration (MCHC), decreased osmotic fragility, stomatocytes, and characteristic ektacytometry pattern. Most cases are due to mutations in PIEZO1, a mechanosensitive ion channel. Hemoglobin C is due to a glutamic acid to lysine substitution at codon 6 of the HBB gene. Erythrocytes of HbC carriers are also dehydrated with an elevated

MCHC and shortened survival. Inheritance of modifier genes is known to influence disease phenotype.
Objectives: Describe the case of a patient with both Hereditary Xerocytosis and Hemoglobin C trait.
Design/Method: Case report.
Results: A 17-year-old boy with Hemoglobin C trait presented with bleeding, petechiae, and severe thrombocytopenia thought to be ITP in the setting of EBV infection and was treated with IVIG. Several days later, he developed acute Coombs-negative hemolytic anemia with abundant spherocytes and stomatocytes on peripheral smear. After resolution of the thrombocytopenic and hemolytic episode, some stomatocytes persisted, his hemoglobin normalized but his erythrocytes continued to exhibit elevated MCHC. Erythrocytes from his mother and father also showed elevated MCHC. Osmotic gradient ektacytometry revealed a pattern consistent with erythrocyte dehydration in the patient and both parents, with the proband's erythrocytes more severely affected than either parent's. Whole exome sequencing of patient's blood-derived DNA identified a heterozygous Arg (CGC) to Cys (TGC) substitution at aa1955 in exon 5 of the PIEZO1 gene. This novel missense mutation is in a region highly conserved across vertebrates and is predicted to be pathogenic with a CADD phred score of 14.9. Sequencing genomic DNA from the parents revealed the proband inherited the PIEZO1 variant from his mother and hemoglobin C from his father.
Conclusion: Hemoglobin C trait accentuated the severity of Hereditary Xerocytosis. Hgb AC and PIEZO1 mutation in the proband resulted in increased erythrocyte dehydration compared to his mother who has only the PIEZO1 mutation and his father who only has Hgb AC. Thus, two variants associated with erythrocyte dehydration lead to more severe disease phenotype than either variant alone. Co-inheritance of two interrelated disorders and/or modifier alleles, which each by itself could be asymptomatic, should be considered in severe erythrocyte dehydration and clinically amplified cases.

Poster # 107

TRANSFUSION-DEPENDENT HEREDITARY SPHEROCYTOSIS AND RENAL TUBULAR ACIDOSIS DUE TO A NOVEL HOMOZYGOUS MUTATION IN BAND 3

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Background: Hereditary Spherocytosis (HS) is a disorder in which abnormalities of erythrocyte membrane proteins lead to loss of membrane surface area, resulting in spherical cells with altered deformability. HS mutations have been identified in genes encoding the membrane proteins spectrin, ankyrin, Band 4.2, and Band 3. Inheritance is usually autosomal dominant, but 25% of patients have recessive or de-novo mutations. A common cause of HS is deficiency of Band3/AE1, the anion exchanger encoded by SLC4A1. Full length AE1 forms the core of a macromolecular complex of membrane proteins. A N-terminal truncated form of Band 3, kAE1, is expressed in the α-intercalated cells of the renal collecting duct and facilitates urinary acid excretion. Deficiency of kAE1 leads to distal renal tubular acidosis (dRTA). Heterozygous mutations in Band 3 have been reported that variably impair trafficking or anion transport,

leading to HS or dRTA. Only a handful of patients exhibit both HS and dRTA. These patients have homozygous missense mutations in Band 3.
Objectives: Report a novel Band3/AE1/SLC4A1 mutation causing severe HS and dRTA.
Design/Method: Case study
Results: A 6-day-old male with parental consanguinity presented with tachypnea, splenomegaly, and severe anemia. Hemoglobin was normal at birth but was 6.6 g/dL on presentation with reticulocyte count 0.4%. Peripheral smear revealed uniform spherocytosis, osmotic fragility was positive, EMA showed significantly diminished Band 3 binding, and HS was diagnosed. Frequent transfusions were required and weight gain was poor. Further evaluation revealed non-gap acidosis, high urine pH, and nephrocalcinosis on ultrasound, diagnostic of dRTA. Each parent's RBC morphology, Hgb, retic, and urine pH were normal, while EMA binding was mildly decreased, consistent with compensated HS. SDS-PAGE of erythrocyte membranes revealed Band 3 protein was marked decreased in the proband and mildly decreased in each parent. Genetic testing of the proband identified a homozygous Ser (AGT) to Arg (CGT) substitution at codon 725 in exon 17 of SLC4A1, near the anion binding site. Parents were heterozygous for the mutation.
Conclusion: S725R is a novel mutation in Band3/AE1/SLC4A1 causing both severe HS and dRTA when homozygous. Decreased presence of this mutant protein in the RBC membrane is consistent with a trafficking defect leading to the HS phenotype. RTA also could be due to impaired trafficking of Band3/kAE1 in renal tubular cells. Alternatively, molecular modeling suggests that the location of S725R at the active site could affect anion binding and transport.

Poster # 109

ACANTHOCYTIC SPHEROCYTOSIS IN 3 SIBLINGS DUE TO NOVEL COMPOUND HETEROZYGOSITY IN THE ALPHA-SPECTRIN GENE CAUSING HEMOLYTIC ANEMIA

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Background: Hereditary hemolytic anemias include a variety of enzyme and membrane protein defects that may be difficult to diagnose. In addition, common polymorphisms are present in the population which cause hemolytic disease only when combined with other alleles. Next generation sequencing has been proposed as a method to further elucidate the variety of membrane defects that may occur in these anemias.
Objectives: We present a family of three children affected with a spherocytic anemia with acanthocytic features that appears more severe in infancy. The parents are unaffected. Next generation sequencing of the genes involved in the red blood cell membrane was informative in elucidating the inheritance patterns in order to provide accurate genetic counseling.
Design/Method: Case Report.
Results: The proband, a 2-month-old infant, presented with severe hemolytic anemia with acanthocytes and spherocytes, requiring transfusions at the age of 2-4 months. Evaluation included normal glucose-6-phosphate dehydrogenase and normal pyruvate kinase levels. The osmotic fragility test was abnormal. Both parents had normal CBCs and reticulocyte counts, while one of two older siblings has a similar hemolytic anemia. A fourth sibling was also found

to have acanthocytic spherocytosis starting at two months of age. Next generation sequencing of the proband's DNA revealed no mutations in the RBC membrane protein genes SPTB (beta spectrin), SLC4A1(band 3 protein), and ANK1 (ankyrin), but found 3 mutations in the SPTA1(alpha spectrin) gene, including a novel amino acid change sequence and a stop codon. **Conclusion:** These siblings exhibit a unique form of hemolytic anemia due to compound heterozygosity of mutations in the alpha spectrin genes. The anemia includes progressive acanthocytosis and anemia in the neonatal period that gradually improves to a more typical spherocytosis, with occasional acanthocytes, in childhood. Next generation sequencing was informative in revealing a novel autosomal recessive combination of spectrin mutations that are associated with this phenotype. Interestingly, only one of the mutations were thought to be pathogenic based on previous literature. Next generation sequencing of the gene in the family members allowed us to elucidate the reasons why three of the 4 siblings inherited a hemolytic anemia from unaffected parents.

Poster # 111

CDAR: THE FIRST REGISTRY FOR PATIENTS WITH CONGENITAL DYSERYTHROPOIETIC ANEMIA IN NORTH AMERICA

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Background: Congenital dyserythropoietic anemias (CDA) consist a heterogeneous group of rare genetic disorders characterized by ineffective erythropoiesis and multinuclear erythroid precursors in the bone marrow. Clinical findings include chronic anemia, frequently with evidence of hemolysis although with suboptimal reticulocytosis, and iron overload. The identification of several genetic defects underlying different subtypes of CDA provided insights into the pathogenesis but many gaps still exist in understanding the related molecular mechanisms and the natural history of the disease.
Objectives: To establish a Congenital Dyserythropoietic Anemia Registry (CDAR) in North America with the goal to collect long-term retrospective and prospective phenotypic data and create a bio-repository of de-identified patient specimens, as a tool for the investigation of natural history, epidemiology, and biology of CDA.
Design/Method: CDAR was initiated at Cincinnati Children's as a multicenter study based on collaboration with the treating physicians (ClinicalTrials.gov Identifier: NCT02964494). Patients of any age diagnosed with CDA and their family members are eligible to enroll. Data including demographic information, medical history, family pedigree and history, diagnostic test results, treatment and complications are entered in a confidential database with yearly updates. Bone marrow slides are centrally reviewed for confirmation of diagnosis. The patients may elect to consent to donation of blood, DNA, and bone marrow specimens to the CDAR biorepository and to generation of induced pluripotent stem cells and/or immortalized B-cells. For participants without a genetic diagnosis, Next-Gen sequencing for known CDA-associated genes is used to identify a mutation. If a causative mutation is not identified, whole exome sequencing may be performed to reveal candidate genes for further research of CDA pathogenesis.

Results: Since CDAR opened in August 2016, 10 individuals (7 affected and 3 family members, from five families) were enrolled. Two patients had pathogenic mutations in CDAN1 and KIF23 causing CDA-I and CD-III, respectively. One patient with apparent diagnosis of CDA-I was found to have a novel candidate gene variant in VPS4A, currently under validation studies. The last four patients had a pathologic diagnosis of CDA-II, presenting however with autosomal dominant inheritance in two different families, with negative results for known associated genes, and currently undergoing whole exome sequencing.
Conclusion: CDAR will provide a longitudinal database and associated biorepository to facilitate natural history studies and molecular pathways research in Congenital Dyserythropoietic Anemias. Such research is necessary to build-up knowledge for these rare diseases in order to guide diagnostic and therapeutic decisions and be a collaborative resource for patients, treating physicians, and investigators.

Poster # 113

VPS4A: A NEW CANDIDATE GENE FOR CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE I (CDA-I)

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Background: A 2 year old female patient with transfusion dependent anemia and the pathologic diagnosis of Congenital Dyserythropoietic Anemia type I (CDA-I) was enrolled in the CDA Registry of North America (CDAR; ClinicalTrials.gov Identifier: NCT02964494). Next Generation sequencing identified no mutations in the known CDA-associated genes, including CDAN1 and C15orf41, which are causative for CDA-I. Whole-exome sequencing for the patient and her parents (family-trio design) revealed a novel, de-novo VPS4A missense variant located at the last codon of exon 8, potentially affecting splicing. VPS4A is an ATPase, which in association with the endosomal sorting complex required for transport (ESCRT), has been shown to play critical role in cell division of HeLa cells in vitro, concentrating at spindle poles during mitosis and midbodies during cytokinesis.
Objectives: To validate the pathogenetic role of the VPS4A variant for CDA and further investigate the role of VPS4A in erythroblast mitosis and cytokinesis.
Design/Method: The level of VPS4A mRNA expression in patients versus control reticulocytes was evaluated by qRT-PCR. Immunofluorescence staining for VPS4A in erythroblasts proliferating in ex vivo erythropoiesis culture from normal CD34+ cells was performed and visualized by Imaging Flow Cytometry (IFC ImageStream). Induced pluripotent stem cells (iPSCs) were generated from patient's peripheral blood mononuclear cells (PBMNCs), after family's consent per CDAR protocol. The role of VPS4A will be further studied in ex vivo erythropoiesis after knockdown by shRNA in normal CD34+ cells. Ex vivo erythropoiesis will be performed in patient's IPCs derived CD34+ cells with and without VPS4A rescue to validate gene function.
Results: VPS4A gene expression in the patient's reticulocytes was decreased by 55-70% compared to control using three different set of primers. IFC studies in normal dividing

erythroblasts showed that VPS4A was localized at the spindle poles during mitosis and at midbodies during cytokinesis. In addition, flow cytometry and IFC, after labeling of transferrin receptor (CD71) with anti-CD71 antibody and of RNA with Thiazole Orange (TO), demonstrated a unique cell population in the patient's red blood cells being TO negative but CD71 positive, implying that VPS4A is also involved in reticulocyte maturation, likely by participating in vesicle formation and the sorting of CD71 through the exosomal pathway. iPSCs have been successfully generated from patient's and control PBMNCs and VPS4A shRNA carrying lentivirus has been produced for ex vivo erythropoiesis studies.
Conclusion: VPS4A appears to play a critical role in erythroblast mitosis, cytokinesis and erythrocyte maturation. Therefore, it is a promising candidate gene for a CDA-I-like disease.

Poster # 115

EVALUATION OF A PROTOCOL USING INTRANASAL FENTANYL FOR TREATMENT OF ACUTE PAIN CRISIS IN SICKLE CELL PATIENTS IN THE EMERGENCY DEPARTMENT. THE SATISFI - SICKLE CELL ANALGESIC TREATMENT WITH IN FENTANYL SOLUTION FOR FAST TRACK INTERVENTION - STUDY

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Background: Sickle cell vaso-occlusive crisis (VOC) is one of the most frequent causes of emergency visit and admission in children with this condition. Intranasal (IN) fentanyl has been used increasingly for pain treatment in the emergency department (ED), including for patient with sickle cell disease (SCD).
Objectives: We aim to evaluate whether the use of a new pain management pathway using IN fentanyl from triage as first line therapy for patient with SCD in VOC will lead to improved care of SCD, translated by a decrease in time to first opiate dose, aiming to meet quality of care indicators. We also aim to prospectively evaluate patient and parent satisfaction with the use of IN Fentanyl.
Design/Method: Retrospective chart review of patients with SCD who presented to the ED with VOC, in the period pre (Jan-June 2014) and post (Oct-June 2016) implementation of the protocol. Patients in pre received oral or intravenous (IV) opiates as per previous management pathway. Patients in post received IN fentanyl if their pain was moderate-to-severe. Time to first opiate was evaluated pre and post implementation. Patient and parent satisfaction questionnaires were filled prospectively if patient presented during research nurse working hours, and median scores were calculated.
Results: Over the two periods, a total of 107 ED patients (56 pre, 51 post) were included respectively, and 14/51 patients filled out the satisfaction questionnaire. There was a significant difference of -45.8 min (95% CI -61.1, -31.9) in the opiate administration time, now meeting quality of care indicators. There was a significant increase of 45.7% (95% CI 29.0, 59.0) in the use of pain scales at triage evaluation. There was an increase in the number of patient treated with a non-IV opiate as 1st opiate dose: a difference of 43.8% (95% CI 26.7, 57.4). There was no difference in the number of patients without IV treatment: a difference of 15.8 (95% CI -1.4,

32.1). There was no difference in the hospitalization rates: a difference of 12.6 (95% CI -6.2, 30.1). Patient and parent satisfaction with IN treatment was 3.5/5 and 2/5 for the 14 patients evaluated prospectively.
Conclusion: This study validates the use of our protocol using IN fentanyl for the treatment of VOC in the ED by significantly reducing the time to 1st opiate dose. However, our protocol did not decrease the number of IVs.

Poster # 117

HEALTH CARE UTILIZATION, PATIENT TRUST, AND SATISFACTION WITH CARE IN ADULTS WITH SICKLE CELL DISEASE

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Background: Transition from pediatric to adult centered care for emerging adults with sickle cell disease (SCD) has previously been unsuccessful due to lack of connection to adult providers with experience with SCD, physician mistrust, poor patient preparation, and difficulty navigating the adult health care system. The resulting gaps in medical care lead to decreased out-patient visits and increased Emergency Department (ED) visits and hospitalizations, contributing to fragmented care and poor outcomes.
Objectives: To assess barriers that adults with SCD face when accessing adult care, satisfaction and trust with medical providers, and health care utilization.
Design/Method: Adult patients with SCD previously seen at Children's Hospital Los Angeles were contacted to participate in a mixed-methods telephone survey with items addressing connection with as well as satisfaction and trust in adult primary care providers (PCP) and hematologists, frequency of ED and hospital visits, and perception regarding transition experience. The Physician Trust Scale and items from the Patient Satisfaction Questionnaire Short-Form (PSQ-18) were utilized to assess patient trust and satisfaction respectively.
Results: Only 62% of the 34 survey participants, ages 22-39 years, identified having an adult PCP and/or hematologist. Patients' general satisfaction with care increased as their trust increased in both their adult hematologist ($p=0.001$) and PCP ($p<0.001$). Patients had greater trust in their hematologist (mean score 79.4 vs 65.1, $p = 0.0376$) and trended towards improved general satisfaction with care (mean score 3.8 vs 3.2, $p=0.128$) when compared to their PCP. For complications related to SCD, 62% of all participants had been to the ED and 50% had been hospitalized in the previous 6 months. Of those utilizing the ED, 60% had negative comments regarding their care, including delays and sub-optimal dosing in pain management and lack of provider experience with SCD. Regarding their transition experience, 50% were dissatisfied and more than 50% reported they were not prepared for adult care.
Conclusion: Almost 40% of patients are not receiving regular medical care for their SCD with a significant portion relying on emergency departments, which can lead to fragmented medical care. There was a higher level of trust and general satisfaction with adult hematologists, which may reflect patients' confidence in their specialists' ability to manage their disease. Based on participant feedback, medical care improved when their adult provider was involved in their

hospital care, indicating the importance of the connection with an adult provider familiar with their disease, which can lead to improved long-term outcomes.

Poster # 119

COMPARISON OF CHRONIC TRANSFUSION VOLUME PROTOCOLS FOR CHILDREN WITH SICKLE CELL ANEMIA

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Background: Chronic transfusion therapy (CTT) for sickle cell anemia (SCA) reduces the risk of stroke by diluting hemoglobin S (HbS) with HbA red blood cells and suppressing erythropoiesis. The goal of a CTT regimen is to maintain pre-transfusion HbS <30% while avoiding hyperviscosity; however established protocols for transfusion volumes are lacking.
Objectives: To compare HbS, reticulocytosis, and total blood transfusion volumes between 2 CTT protocols that use higher vs. lower transfusion volume parameters for pediatric SCA patients.
Design/Method: Children with SCA ages 3-20 years on CTT were enrolled in a 12-month prospective observational study at 3 transfusion centers at Children's Healthcare of Atlanta (CHOA). All centers used transfusion volume protocols that are based on pre-transfusion Hb. The higher volume (HV) protocol was used at 2 centers and the lower volume (LV) protocol was used at 1 center. Per the HV protocol: for pre-Hb range <8.0 – 10.0 g/dL, transfuse 13 – 17 ml/kg; for pre-Hb 10.1 – 11.0 g/dL, transfuse 8 – 12 ml/kg. Per the LV protocol: for pre-Hb <8.0 –9.0 g/dL, transfuse 15 ml/kg; for pre-Hb 9.1 – 10.0 g/dL, transfuse 12.5 ml/kg; for pre-Hb 10.1 – 10.5 g/dL, transfuse 10 ml/kg; for pre-Hb 10.6 – 11.0 g/dL, transfuse 7.5 ml/kg. For all transfusions, the volume, transfusion interval, and pre-transfusion Hb, reticulocytes, and HbS were recorded. Transfusions were excluded if transfusion interval (TI) >40 days, patient was on hydroxyurea, or there was partial manual exchange (PME).
Results: There were 82 patients (63 HV, 19 LV protocol, 1 LV/HV) who were followed for 1042 transfusion episodes. Excluding 167 PME and transfusions with TI >40 days, there were 571 HV and 205 LV transfusions. For HV transfusions, there was higher mean transfusion volume (13.3 vs. 12.1 ml/kg, $p<0.0001$), longer TI (29.9 vs. 27.7 days, $p<0.0001$), higher Hb (9.74 vs. 9.38 g/dL, $p<0.0001$), but higher mean HbS (22.4 vs. 20.6%, $p=0.034$). There was no significant difference in reticulocytes (9.64 vs. 9.09%, $p=0.11$) or frequency of HbS >30% (21.5% of HV vs. 17.1% of LV transfusions, $p=0.18$). Including all transfusions, the mean total blood volume per 365 days was 172.4 ml/kg for HV and 168.6 ml/kg for LV transfusions ($p=0.58$).
Conclusion: The HV transfusion protocol allowed higher Hb and did not increase the total blood volume received per year; however HbS suppression was greater with the LV protocol. This study did not examine hyperviscosity, which may be a potential concern with higher transfusion volumes.

Poster # 121

EFFECT OF HYDROXYUREA ON MICROALBUMINURIA IN PATIENTS WITH SICKLE CELL DISEASE

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Background: Renal involvement in children with sickle cell disease (Hemoglobin SS) is a serious complication that starts in childhood and may progress to end stage renal disease. Microalbuminuria is an early clinical marker of renal involvement before the appearance of clinically significant proteinuria. In several studies it is shown that hydroxyurea decreases the incidence of microalbuminuria in children with SS disease as compared to those without treatment or on chronic transfusion therapy.
Objectives: To evaluate the effect of hydroxyurea (HU) therapy on the development or resolution of microalbuminuria/Proteinuria in children with sickle cell disease
Design/Method: This is a cross sectional retrospective cohort study to find out the incidence of Microalbuminuria (Albumin/creatinine ratio >30 – 299 mg/gm) and Proteinuria (urine protein/creatinine ratio >200 mg/gm) before and after hydroxyurea therapy in SS disease. Cases were selected from the sickle cell database and only those who had at least one value reported of urine microalbumin and urine protein pre therapy and post therapy were included in the study.
Results: Out of 60 patients with SS disease on Hydroxyurea therapy, data was available in 48 patients. The mean age was 13.7±5.3 years and 45.8% were male. The mean duration of HU therapy in the cohort was 60.5 ±37 months. There was increase in mean hemoglobin level and decrease in LDH level post HU therapy but this was not statistically significant. The decrease in reticulocyte count post HU therapy was significant. ($p<0.001$). There were 4(8.3%) patients who developed microalbuminuria, 2(4.1%) with prior microalbuminuria resolved post HU therapy and 4(8.3%) had persistent proteinuria despite HU therapy.
Conclusion: Prior to HU therapy, the incidence of MA was 12.5% and after treatment, it is 16.7%. Four patients developed MA while on HU and in 2 patients, MA resolved. Previous reports suggest that HU may slow the development of MA in sickle cell patients but our data suggest that we still need to be cautious and continue to monitor for MA in these patients. Hemolysis has been shown to be a risk factor for the development of MA in previous studies and the noted reduction in the reticulocyte count could suggest a reduction of hemolysis. However this did not seem to have an effect in our patient cohort. Factors that enable resolution of MA can be explored in larger samples.

Poster # 123

NECESSITY OF PREOPERATIVE TRANSFUSIONS FOR PATIENTS WITH SICKLE CELL DISEASE UNDERGOING MINOR PROCEDURES

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Background: Patients with sickle cell disease (SCD) have an increased risk of post-operative complications including acute chest syndrome (ACS) and pain crisis. The standard of care is to

transfuse to hemoglobin (Hb) > 10 g/dL pre-operatively to reduce these risks. There is limited data on minor procedures, and it is unclear if the same stringent transfusion guidelines are necessary.
Objectives: To determine if a pre-operative transfusion goal of Hb >10g/dL is necessary in patients with SCD undergoing minor procedures.
Design/Method: A retrospective review was conducted from June 2012 to May 2016 of patients with SCD who underwent tonsillectomy and adenoidectomy (T&A) or myringotomy. Demographic and clinical characteristics were compared between patients who received pre-operative transfusions and those who did not. Specific data collected included sickle cell type, age, sex, baseline Hb, hydroxyurea therapy and complications in the 30 day post-operative period. Statistical analyses were completed using Fisher's exact test for categorical variables and t-test for continuous variables.
Results: A total of 20 patients with SCD that had T&A or myringotomy were identified. Five patients had hemoglobin SC disease (HbSC) with pre-operative Hb > 10 g/dL. They were not transfused pre-operatively per published guidelines and had no post-operative complications. Fifteen patients had Hemoglobin SS disease (HbSS). One patient with HbSS had T&A and amputation of digit and was therefore excluded. One patient with HbSS had a pre-operative Hb of 10 g/dL, and per published guidelines was not transfused. Of the 13 patients with pre-operative Hb < 10 g/dL, seven were transfused and six were not. The mean age was 6.7 years with male:female ratio of 1:2.25. In comparing the transfused versus non-transfused group, the mean baseline hemoglobin was 7.5 g/dl vs 8.9 g/dl (p= 0.01) and 43% of transfused patients were on hydroxyurea compared to 33% of non-transfused patients. Post operatively 2/6 patients in the non-transfused group developed complications compared to 0/7 in the transfused group (p=0.36). Complications included ACS on post-operative day 1 and pain crisis on post-operative day 5.
Conclusion: Thirty three percent of patients with HbSS disease not transfused prior to minor procedures developed post-operative complications compared to zero patients in the transfused group. Although the p-value is not significant, this study is limited by size, and given the trend toward complications in the non-transfused group, we would advocate for a pre-operative Hb goal of > 10g/dL in SCD patients prior to minor procedures.

Poster # 125

THE EFFECTS OF IRON STATUS ON PULMONARY HYPERTENISION IN PATIENTS WITH SICKLE CELL DISEASE

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Background: Pulmonary hypertension (PH) could develop in chronic hemolytic anemia, including sickle cell disease and thalassemia. Among described markers associated with PH are increased systolic blood pressure, low hemoglobin, hemolysis and low transferrin levels. Clinical significance of iron status remains unclear. In patients with thalassemia iron overload has been reported in association with PH. In patients with sickle cell disease it was proposed that iron deficiency could lead to decreased hemolysis, which is one of the described factors, increasing the risk of PH. However there is no sufficient data to support clinical benefits.

Objectives: To evaluate possible relationship between pulmonary hypertension measured by Tricuspid Regurgitation Jet Velocity (TrJet), iron status and other laboratory markers.
Design/Method: Retrospective chart review of 53 patients with homozygous HbS disease followed at St. Christopher's Hospital for Children, Philadelphia. We collected data on demographics, systolic blood pressure, laboratory and echocardiographic data. Multiple regression analysis of each marker as independent variable and TrJet as dependent variable was conducted to determine a correlation.
Results: From 53 patient 26 were females and 27 males. Fifteen patients previously underwent splenectomy. For all patients: TrJet is significantly positively correlated with age, history of splenectomy ($p=.039$) and negatively correlated with HgbF and ProBNP. A moderate correlation ($p<.01$) was found between Trjet and Ferritin (+), Reticylocyte count (+) and Hemoglobin (-).Patients with splenectomy had positive correlations of TRJet with TIBC, SBP, and negative with proBNP, and MCHC. In a multiple linear regression analysis after controlling for age and splenectomy status TIBC remains independently significant ($p=0.039$).
Conclusion: The role of iron status for development of pulmonary hypertension remains unclear. Further studies, including more patients with iron deficiency are indicated.

Poster # 127

ASSOCIATION OF BIOMARKERS WITH BMI AND METABOLIC SYNDROME IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Patients with sickle cell disease (SCD) usually have lower BMI compared to standard growth curves. Diminished growth among children with SCD is secondary to hemolysis, chronic anemia and high metabolic rate. With advancements in therapies and improved nutritional status, the prevalence of obesity is increasing, placing them at greater risk of metabolic syndrome (MS).(1) Considering that MS is associated with an increased risk of cardiovascular disease in adults and other associated co-morbidities, early identification of risk factors is important.(2)
Objectives: We aimed to evaluate the association between biomarkers, BMI and presence of MS in pediatric patients with SCD.
Design/Method: We performed a retrospective chart review of patients with SCD followed at Marian Anderson Center at St. Christopher's Hospital for Children, ages 10-22 years old. A total of 139 patients met inclusion criteria. Data collected included BMI, blood pressure, markers of metabolic syndrome, hemolysis, inflammation and cardiac markers. Analysis of variance tests were performed to examine biomarker differences between obese and non-obese patients, patients of various weight categories, and patients with MS versus those without MS. Pearson correlations were calculated to evaluate for associations between biomarkers, BMI and MS.
Results: Of the 139 patients that met inclusion criteria, 17 (12%) were obese with 5 patients having metabolic syndrome as defined by the International Diabetes Federation.(3) The systolic blood pressure was significantly higher in obese patients ($p = 0.026$). Additionally, systolic and diastolic blood pressures were significantly higher with the presence of MS (both $p = 0.001$).

Hemoglobin and hematocrit were statistically different between weight groups (underweight, normal weight, overweight, obese), with higher mean values being seen in the overweight and obese groups ($p = 0.006$ and 0.007, respectively). BMI percentile was positively correlated with hemoglobin and hematocrit (both $p < 0.001$) and negatively correlated with platelets ($p = 0.018$). No other correlations were found between cardiac biomarkers, BMI and MS.
Conclusion: Increased BMI and the presence of MS correlated with increased blood pressure. Higher mean values of hemoglobin and hematocrit were seen in patients with higher BMIs, suggesting a correlation between disease severity and BMI. No significant correlation was found between inflammatory markers and BMI or MS. Further prospective studies and larger sample size are needed to elucidate this association.

References:1. Chawla et al., Pediatrics, 20132. Bediako et al., Blood, 2015 3. Alberti et al., International Diabetes Federation, 2007

Poster # 129

A RETROSPECTIVE ASSESSMENT OF URINE CONCENTRATING ABILITY AMONG PATIENTS WITH SICKLE CELL

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Background: Sickle Cell Disease (SCD) is a complicated, multi-system illness for which there are few approved therapies. Improvements in early childhood have led to increased average lifespan of affected individuals. As life expectancy increases, however, these individuals incur ongoing organ damage due to prolonged exposure of repeat sickling episodes. Renal damage is one of the complications frequently seen in patients with SCD.
Objectives: Evaluate the effect of different preventive therapies on urine concentrating ability using an established patient database from the Medical University of South Carolina's Lifespan Comprehensive Sickle Cell Center.
Design/Method: This was a retrospective cohort study of 554 individuals with previously diagnosed SCD. Chart review was utilized to record the age, gender, body mass index, urine pH, urine specific gravity, blood pressure and hemoglobin genotype as well as current disease management classified as: no therapy, Hydroxyurea, or chronic transfusion therapy. Multiple linear regression was utilized to assess the significance of recorded variables on urine specific gravity.
Results: There were 344 individuals, 172 of each gender with sufficient data for analysis. Mean age was 16 years (range 4 - 38). Mean body mass index was 21.39 (range 13.02 - 48.85). Aggregate urine pH was 6.39 (+/-1.72) and MAP mean value were 81.86 (+/-8.70) respectively. Aggregate urine specific gravity mean was 1.011 (+/- 0.002). The most prevalent genotype was hbSS (204 individuals). Multiple linear regression was conducted controlling for genotype to reduce confounding by therapy indication. Transfusions, age, mean arterial pressure, and urine pH with corresponding p values <0.0001, 0.0026, 0.0023, and 0.0073 respectively were all significant for individuals with hbSS disease (for specific gravity).
Conclusion: Interpretation of these results suggests that when compared to individuals without preventive therapy, utilization of transfusions improved urine concentrating ability by 0.002.

More specifically, an individual's urine concentrating ability decreases 0.001 for every 11 years of life. Every increase of 15.4 in MAP and 2.0 in average urine pH is associated with a 0.001 increase and 0.0016 increase in urine specific gravity. Preventive therapies for SCD have made significant strides in improving and extending the lifespan of these individuals. Chronic renal damage is highly prevalent within this demographic and is indicated by albuminuria and hyposthenuria, an inability to concentrate urine. This study suggests that patients undergoing chronic transfusion therapy have a greater ability to concentrate urine suggesting a disease modifying effect on the kidneys.

Poster # 131

SIGNIFICANCE OF LOWER AIRWAY OBSTRUCTION AND VITAMIN D DEFICIENCY IN SICKLE CELL DISEASE

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Background: Severity of sickle cell disease (SCD) depends on multiple factors including genotype, fetal hemoglobin level, severity of hemolysis, anemia, inflammation, and endothelial activation. Among various co-morbidities, respiratory conditions such as asthma, lower airway obstruction (LAO) and chronic lung disease are prevalent in 20 to 48 percent of SCD patients and are known to increase mortality in this population. Vitamin D deficiency has been associated with asthma and decreased pulmonary function. Additionally, vitamin D deficiency has been associated with chronic pain, stroke, and cardiovascular diseases. Given the high prevalence of vitamin D deficiency and lower airway obstruction (LAO) in African American children, early identification of these comorbidities may be a useful predictor of clinical course of SCD.
Objectives: To evaluate the prevalence of vitamin D deficiency in patients with sickle cell disease and lower airway obstruction (LAO) and its association with disease severity.
Design/Method: Retrospective chart review of patients with SCD followed at St. Christopher's Hospital for Children, Philadelphia were performed. We collected data on demographics, complications, pulmonary function, and laboratory data. Multiple regression analysis was conducted to determine correlations.
Results: Chart review revealed 44 patients with vitamin D levels and pulmonary function test performed within a year. Vitamin D insufficiency (32 to 20 ng/ml) and deficiency (<20 ng/ml) were present in 43% and 47% of patients, respectively. Although 85% of patients had a diagnosis of asthma, 27.1 % of patients were classified with LAO defined as percent predicted FEV1/FVC less 95%. There was no significant association between vitamin D status and the prevalence of LAO and percent predicted FEV1/FVC (%) ($p= 0.12$, $p= 0.84$ respectively). This population study had the following comorbidities diagnoses: pulmonary hypertension (14.3%), sleep apnea (8.8%), cerebrovascular disease (8.8%), and acute chest syndrome (2.3%), which were not significantly correlated to either vitamin D or LAO status. Analysis of laboratory markers revealed significant association between vitamin D levels and platelet count, WBC, and LDH ($p= 0.02$, $p= 0.008$ and $p= 0.01$ respectively).
Conclusion: We have not identified significant correlations between vitamin D status and LAO in patients with SCD. Association between vitamin D status and markers of hemolysis require additional evaluation. Additional studies with larger study population need to be performed to

better establish a possible association, if any, between individual or concomitant presence of vitamin D deficiency and LAO and SCD morbidity.

Poster # 133

SICKLE CELL TRAIT: THE RISKS FOR ATHLETIC PARTICIPATION

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Background: Sickle cell trait (SCT) is an inherited blood disorder that affects 1 to 3 million people in the United States and more than 100 million people worldwide. Previous studies have suggested that having sickle cell trait increases one's risk of exertional rhabdomyolysis and subsequent death. A number of these cases highlighting several high-profile deaths have been reported in both television and newspaper media and attributed death to SCT. A recent study published in the New England Journal of Medicine reported that SCT was not associated with a higher risk of death than absence of the trait. None of the medical experts in the National Institutes of Health (NIH), American Academy of Pediatrics (AAP), or Centers for Disease Control and Prevention (CDC) advise against participation in competitive sports. We performed a retrospective review of both newspaper and television media to determine if television and newspaper media opinion used evidence-based guidelines in accurately depicting the risks associated with SCT.
Objectives: To highlight the discrepancy between the evidence-based guidelines in the medical community with the depiction of SCT-associated risks in national television and newspaper media.
Design/Method: Sixteen media outlets were included in this review. This included the 6 most viewed television news networks based on the 2015 Nielsen ratings and the top 10 newspaper outlets according to circulation in the United States. The search engines on each of the respective media websites were used to identify stories reporting about sickle cell trait, whether these stories quoted evidence-based guidelines and whether they quoted the NCAA policy pertaining to athletic participation.
Results: Three of the 6 television networks and 9 of the 10 newspaper outlets reported stories relating to SCT, however 1 of the 6 television networks and 3 of the 10 newspaper outlets referenced evidence-based guidelines. Additionally just 1 of the 6 television networks and 2 of the 10 newspaper outlets quoted the NCAA policy pertaining to athletic participation.
Conclusion: The absolute risks of SCT are known to be low, but not well described by the mainstream media. More accurate risk estimates are needed, as well as continued research into contributing factors. Widespread dissemination of universal precautions for exertion-related illness and a consistent positive message of SCT participation in athletics may lead to less discrimination of SCT individuals and an overall reduction morbidity and mortality.

Poster # 135

RISK FACTORS FOR VENOUS THROMBO-EMBOLISM (VTE) IN CHILDREN WITH SICKLE CELL DISEASE (SCD): A MULTICENTER COHORT STUDY

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Background: A hypercoagulable state resulting in increased VTE has been described in adults with SCD. Similar data for children is lacking. Previously, in a single-institution, retrospective study of 414 pediatric patients with SCD followed at Nationwide Children's Hospital, we identified central venous catheters (CVC) as an independent risk factor for VTE [OR (± 95%CI): 10.3 (1.1-92.2)]. 12/414 (2.9%) subjects developed VTE over the course of the study.
Objectives: The objective of this retrospective, multicenter cohort study was to describe risk factors associated with VTE in children with SCD across children's hospitals in the United States (US).
Design/Method: Data for this study was obtained through PHIS, an administrative database that contains clinical and resource utilization data for 49 free standing children's hospitals in the US. ICD-9-CM codes were used to identify subjects. Eligible subjects were <21 years of age, were admitted to one of the PHIS hospitals between 01/01/2009 and 12/31/2013 and had at least 2 SCD specific ICD-9 discharge codes. VTE and comorbid conditions of interest (congenital heart disease, cancer, chronic renal disease (CRD), obesity, inflammatory bowel disease etc) were also identified using ICD-9 codes. Supply codes were used to identify CVC placement and pharmaceutical billing codes to identify oral contraceptive use. Logistic regression analysis was used to study association between unique patient characteristics and VTE. Variables found to be significant (p-value < 0.05) on univariate analysis were entered into a multivariate model.
Results: A total of 8966 unique subjects (4359 female) met inclusion criteria with a mean age (±SD) of 10.3 (±6.4) years. 160 subjects (96 female) developed VTE during the study period. Mean age (±95%CI) at VTE diagnosis was 14.8 (±5.9) years. On multivariate analysis, CRD [OR (±95%CI): 5.2 (2.5-11.1)], any CVC placement [4.2 (3.1-5.9)]; history of stroke [2.5 (1.5-4.1)]; female gender [1.6 (1.1-2.2); and older age at admission [1.1 (1.06-1.12)] were identified as risk factors associated with VTE diagnosis. There was a positive correlation between the number of CVCs placed/1000 patients and the number of VTE diagnosed/1000 patients (p=0.02).
Conclusion: Rate of VTE in children with SCD admitted to children's hospital in the US is around 1.8%. CVC use is associated with a nearly 4-fold increased risk of VTE diagnosis. Additionally, CRD, history of stroke, female gender and older age at admission were also associated with VTE diagnosis. Prospective cohort studies are needed to confirm these findings and develop risk prediction models for VTE in children with SCD.

Poster # 137

VITAMIN D STATUS OF A CANADIAN COHORT OF CHILDREN WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) can lead to multiple complications, including bone complications and pain crisis. Vitamin D has been reported to have multiple skeletal and extra-skeletal effects, which might help prevent those complications.
Objectives: The objectives of our study were to 1) evaluate the clinical practice at the Sainte-Justine University Hospital Center (UHC) regarding the assessment of vitamin D status in children with SCD, and 2) document the prevalence of vitamin D deficiency, vitamin D intakes and compliance to vitamin D supplementation in our cohort. A secondary objective of our study was to determine if vitamin D deficiency is associated with SCD complications.
Design/Method: Children from our population of patients with SCD (n = 307) whom had a vitamin D level drawn within the year prior to data collection were included. Serum 25-OH-vitamin D and SCD-related complications were extracted from medical charts. Vitamin D deficiency was defined as 25-OH vitamin D less than 30 nmol/l and vitamin D insufficiency as 25-OH vitamin D less than 50 nmol/l. Vitamin D intakes and adherence to supplementation were also assessed for 46 of those patients.
Results: Our study population included 116 SCD patients, 53% girls; median age at the time of the evaluation of 11.2 years (range 1.3 to 18.4); 49% were Haitians, 49% Africans and 2% of other ethnicities, genotype was 65% HbSS, 27% HbSC and 8% other genotypes. Characteristics of the study population were representative of the entire cohort followed up at our center. Vitamin D status was then assessed in 38% of SCD children followed up in our clinic. Amongst those, 67% of children were vitamin D insufficient while 33% were deficient. Vitamin D intakes were also insufficient (352.59 +/- 234 IU) and were correlated to serum 25-OH-vitamin D levels ($p = 0.005$). Moreover, 17% of patients took vitamin D supplements, but only 50% were adherent to their supplementation. Finally, 28.6% of insufficient patients had renal complications, compared to 8.3% for non-insufficient patients ($p=0.025$) while 18.9% of deficient patients tended to have gall-bladder complications compared to 7.2% for non-deficient patients ($p= 0.071$).
Conclusion: Given the high prevalence of vitamin D deficiency and its potential association with SCD complications, vitamin D supplementation and effective compliance strategies should be considered in Canadian children with SCD. These results highlight the need for randomized double blind placebo controlled trials to test the impact of optimal vitamin D supplementation on clinically important outcomes in children with SCD.

Poster # 139

QUALITY OF LIFE AND SCHOOL ABSENCES IN CHILDREN WITH SICKLE CELL DISEASE WITH AND WITHOUT ASTHMA

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Background: Children with Sickle Cell Disease (SCD) often experience pain, fatigue, and a host of other stressors that could affect their quality of life. A subset of the population will also manage a second chronic illness; the most prevalent comorbid chronic disease is asthma (15-28% of youth with SCD).
Objectives: We compared children with SCD only to children with comorbid SCD and asthma to explore differences in quality of life and academic disruption.

Design/Method: Data were extracted from sixty-four children with SCD ages 7-16 (M=10.58, SD=2.87, 42.2% Male) enrolled in a cognitive training study. Caregivers reported the child's age, ethnicity, gender, asthma status, missed school days, and family resources (food, housing, finances). Children and caregivers each completed the Pediatric Quality of Life Inventory-Sickle Cell Disease Module (PedsQL-SCD) to rate perceptions of the child's health-related quality of life. Children also completed the Wechsler Intelligence Scale for Children-Fifth Edition, a standard measure of intelligence (IQ).
Results: Nineteen children (30%) had SCD and asthma. When comparing caregiver-rated PedsQL-SCD Total Scores, the SCD and asthma group demonstrated lower quality of life (M=55.04, SD=21.34) than the SCD-only group (M=71.00, SD=20.54), t(46)=2.47, p=0.017. The SCD and asthma group had more problems with pain-related functional impairment, pain management, anxiety, and communication with medical providers (p's=0.010-0.030). The SCD and asthma group also missed significantly more days of school (M=20.42, SD=26.89) than the SCD-only group (M=10.52, SD=10.76), t(57)=-2.03, p= 0.047. Higher IQ was associated with better child-rated quality of life for children with SCD and asthma (r=0.467, p=0.019) but not for those with SCD only. Better parent-rated child quality of life was also correlated with having more material resources in the SCD and asthma group (r=0.463, p=0.035) but not in the SCD-only group.
Conclusion: Caregivers of children with SCD and asthma feel their children experience poorer quality of life compared to children with SCD only. Adding to evidence of increased functional impairment, children with SCD and asthma also missed more days of school. Child IQ and family resources were associated with quality of life for children with SCD and asthma but not for children with SCD only, suggesting that cognitive and family resources may have a heightened role in moderating disease outcomes on quality of life among children with multiple chronic conditions. Results highlight the increased complexity of managing multiple chronic conditions, but could also reflect cumulative physiological factors influencing disease severity. Youth with SCD and asthma may benefit from disease self-management interventions.

Poster # 141

COMPLEMENTARY AND ALTERNATIVE MEDICINE: A SURVEY OF ITS USE BY PEDIATRIC SICKLE CELL PATIENTS INPATIENT VERSUS OUTPATIENT WITH COMPARISON OF PHYSICIAN DISCLOSURE RATE AND TYPE OF COMPLEMENTARY AN ALTERNATIVE MEDICINE USE VARIATION IN BOTH SETTINGS

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Background: NIH research indicates 11.6% of Children use Complementary and Alternative Medicine (CAM). The percentage of patients rises to 50 %, when they have chronic, recurrent, or incurable medical conditions. Sickle cell disease is chronic in nature and causes debilitating pain. However, little data is available to assess pediatric sickle cell CAM use. Most of the studies that have been done have assessed limited numbers of patients in nations with less access to healthcare. There is evidence that CAM use is higher due to limited access to medical care in less

industrialized nations. One study done in Mississippi demonstrates 63% of sickle cell patients using CAM 1.
Objectives: This study is designed to test the hypothesis that sickle cell patients are using CAM both at home and in the hospital without disclosing CAM use to physicians.
Design/Method: Patients at Arkansas Children's Hospital were identified by a chart review to confirm eligibility. Eligibility included a diagnosis of sickle cell disease, admission to the hospital after January 1, 2013, and age less than 18 years of age. Type of sickle cell and physician/APRN documentation of CAM use were also noted. Verbal consent was obtained at their hematology clinic visit and an anonymous survey was administered.
Results: 65 patients were surveyed out of 80 eligible patients. 46.2 % used CAM at home and 40% in the hospital. When CAM therapy was used at home, physicians were made aware of CAM use 40% of the time and in the hospital 53.8% of the time. However, physicians/APRNs only documented CAM use 4.6% of the time. The percentage of using ingestible CAM therapies was 23.1% at home and 4.6% inpatient. Physicians were made aware of ingestible CAM use at home 33.3% of the time and in the hospital 66.7% of the time. Physicians/APRNs documented CAM use 4.6% of the time. Ingested CAM included alkalinized water, cannabis, special diets, garlic, ginseng, peppermint, turmeric, melatonin, multivitamins, and supplements.
Conclusion: Pediatric sickle cell patients use CAM both at home and in the hospital without the documented knowledge of their physicians. This data demonstrates patients are also ingesting CAM products while inpatient without physician knowledge. These products, particularly when ingested, may cause side effects/interference with medical treatment.1. Sanchez, H, et al, J of Alt and Comp Med, 2015.

Poster # 143

PEDIATRIC SICKLE CELL ACTION PLAN: DECREASING ACUTE CARE UTILIZATION FOR VASO OCCLUSIVE CRISIS

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Background: Vaso occlusive crisis (VOC) is the most common reason for hospital admissions and emergency room visits in sickle cell disease (SCD). Multi-modal approaches suggest that education of patients, caregivers, and the healthcare team are a key factor in reducing readmission rates following hospitalization for children with VOC. There is a paucity of data on parental understanding of pain medications on hospital discharge, a confusing and intense time for families. This quality improvement (QI) project addresses staff and patient/parent knowledge gaps by incorporating a sickle cell pain action plan (SPAP) into the discharge process.
Objectives: The global aim is to decrease 7 and 30-day readmission rates for VOC by 15% in a pediatric sickle cell population in one year.
Design/Method: A multi-disciplinary team initiated a QI project at a single institution in April 2016. The key drivers comprised of pharmacy, nursing, pediatric residents, patient representatives and pediatric hematologists. The SPAP was implemented upon discharge. The SPAP was modeled on the success of the asthma action plan and provides a tool for patients to

use for decision making on their own pain management. The QI leader performed monthly educational modules and sent weekly email reminders to leaders of inpatient team. PDSA cycles were performed with pharmacy consults, and resident and nursing champions encouraging the utilization the SPAP. Monthly run charts were created to assess 7 and 30-day readmissions. Process measures were the number of pharmacy consults completed and surveys (5 point Likert scale) of patient understanding post discharge. Pareto charts showed pharmacy consults were not performed due to staffing and a new electronic medical record.
Results: Thirty-day readmission rates from April-July 2016 had a 36% reduction compared to 2015 data. August 2016 had staffing changes and rise of readmissions, but with implementation of new team champions the subsequent months had 54% reduction in readmissions. Seven-day readmissions have not changed. Of the patients/parents surveyed 86% and 91% strongly agreed they knew which pain medications to administer and how to escalate care compared to 56% and 47% prior to the project. Ninety percent of the surveyed families agreed that the SPAP: helped them understand their pain medications, remember the medication names, and that this was an easy tool to understand and would be used again in the future.
Conclusion: VOC readmission rate can be decreased by using a teaching tool to enforce medication understanding upon discharge.

Poster # 145

MANAGEMENT OF VASO-OCCLUSIVE EPISODE IN THE EMERGENCY DEPARTMENT VERSUS HEMATOLOGY/ONCOLOGY DAY HOSPITAL OF A CHILDREN'S QUATERNARY CARE CENTER

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Background: Acute vaso-occlusive episodes (VOE) are a major manifestation of sickle cell disease (SCD), accounting for the majority of morbidity and hospital admissions. Consensus of the American Pain Society and National Institutes for Health recommendations is to administer the first dose of analgesics (an opioid and NSAID) within thirty minutes of triage with pain reassessment every fifteen minutes.
Objectives: The goal of the present study is to compare the admission rate for VOE from our institution's Pediatric Ambulatory Chemotherapy and Transfusion Center (PACT) versus ED and to determine which factors influence this outcome.
Design/Method: All PACT and ED patient visits for VOE were analyzed for the period of February 2014 – May 2015. All patients through age 21 years were included, as well as the following sickle cell disease genotypes: HbSS, HbSC, HbS β thal+, and HbS βthal0. Variables assessed were timing from triage to administration of the first analgesic, choice and dosage of the first analgesic, time to pain reassessment, and disposition. Statistical analysis was completed using a combination of a univariable analysis comparing baseline data and a multivariable analysis to control for differences in the latter.
Results: A total of 370 visits involving 140 children with SCD with a mean age of 10.9 ± 5.5 years (50% female) were evaluated for VOE during this time period. There were no differences in demographic data between those coming to the PACT versus ED. In 66% of PACT visits and 41% of ED visits, the children received previous treatment at home with oral oxycodone and

ibuprofen (p=0.07). The initial pain score was lower in those coming to the PACT versus ED (median=6 vs 7, respectively, p = 0.04). The timing from triage to the first analgesic was significantly different between the PACT and the ED (median=32 minutes in the PACT versus 70 minutes in the ED, p<0.0001). The admission rate from the ED (57%) was significantly higher than the PACT (29%) even when accounting for differences in baseline variables (p=0.0004). Other variables influencing the rate of admission were fever at presentation and initial pain score.
Conclusion: Even when accounting for the difference in the initial pain score upon presentation, the rate of admission for VOE from the ED was significantly higher than admission from the PACT. Improving the time to the administration of the primary analgesic may alter this outcome. We are working with the ED to improve timely administration of analgesics.

Poster # 147

OPTIMIZING ELECTRONIC DOCUMENTATION OF VACCINE ADMINISTRATION TO IMPROVE SICKLE CELL HEALTHCARE

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Background: People suffering from Sickle Cell Disease (SCD) have poor splenic function making them prone to infections from encapsulated bacteria, such as Streptococcus Pneumoniae, Haemophilus Influenza Type b (HiB), and Neisseria Meningitides. At Children's Hospital of Orange County (CHOC), concern for our SCD patients not having updated vaccine documentation was noted after recent Pediatric Intensive Care Unit (PICU) admissions for treatment of the sepsis from encapsulated bacterial organisms.
Objectives: This project was initiated to put safety devices into place to ensure proper documentation of receipt of the vaccinations as well as reconcile immunizations that were given to our sickle cell patients at outside facilities, but not adequately documented.
Design/Method: From 8/12/15 to 12/12/16 health care providers and Information Technology (IT) were involved in reviewing the original electronic medical records (EMR) of 44 sickle cell patients at our institution. Issues noted upon analysis of the Cerner Electronic Medical System included the lack of vaccine documentation, inability to automatically transfer immunization records from the California Immunization Registry (CAIR) to a Cerner affiliated database, and misinterpretation by medical providers in deciphering the status of the immune record for these patients.
Results: Initial EMR overview of the vaccine records for our 44 active patients showed 0 of 44 patients had updated vaccine records. Further analysis showed only 1 of 44 patients had documentation of the HiB vaccine, 5 of 44 patients had documentation of the 23-valent pneumo vaccine, and 11 of 44 patients had documentation of the meningococcal vaccine. Upgrades were then made to our Cerner EMR to implement an easy to use interface to upload vaccine records and provide an easy visual display of the vaccinations to minimize any misinterpretation. Upon completion of the upgrades, 41 of 44 SCD patients now had confirmed and updated vaccine records. Moreover, of the 41 updated files, we noted that 100% had received their HiB vaccine, 68% had received the 23-valent pneumococcal vaccine, and 88% had received the meningococcal vaccine.

Conclusion: EMR documentation that is accurate, complete, and easily decipherable has helped CHOC identify which SCD patients require vaccinations. Moreover, the upgrades have minimized the PICU admissions due to sepsis from encapsulated organisms for our SCD patients during the time frame that this project was performed. This upgraded vaccine documentation system will soon be used for people with immune deficiency or a history of bone marrow transplant being treated at CHOC.

Poster # 149

SICKLE TREATMENT AND OUTCOMES RESEARCH IN THE MIDWEST (STORM) - A REGIONAL NETWORK FOR IMPROVING THE MANAGEMENT OF SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD), which affects the red blood cell, is the most common genetic disorder in the United States. There are approximately 100,000 patients with SCD in the United States and approximately 15,000 in the Midwest. Sickle Cell Treatment and Outcomes Research in the Midwest (STORM) is a six-state regional learning network funded by Health Resources and Services Administration (HRSA) to improve outcomes for individuals with SCD in Indiana, Illinois, Ohio, Michigan, Minnesota and Wisconsin. Led by the Cincinnati Comprehensive Sickle Cell Center in collaboration with the James M. Anderson Center for Health Systems Excellence, STORM brings together pediatric and adult providers to collaborate with patients and families to 1) address the lack of provider's knowledgeable evidence-based management of SCD and 2) improve under-utilization of hydroxyurea by using provider education strategies and quality improvement methods.
Objectives: STORM's global aim is to build a sustainable network to improve outcomes and care for patients with SCD in the Midwest. Our current smart aim is to improve health for patients with SCD, as measured by a 20% increase in the eligible number of patients prescribed hydroxyurea, based on recommendations in the NHLBI Evidence-Based Management of SCD guidelines.
Design/Method: STORM is utilizing the Institute for Healthcare Improvement Breakthrough Series model to guide quality improvement work and engage all six sites in monthly Action Period calls, localized Plan-Do-Study-Act (PDSA) cycles, and semi-annual "learning sessions". "STORM is also using patient-level data focused on process and outcomes measures, including hospitalizations, emergency department visits, pneumococcal vaccinations, as well as offering and prescribing hydroxyurea. States enter data into REDCap and receive monthly run charts to track both local and regional progress. The STORM network is guided by a Key Driver Diagram to lead regional interventions to improve access to care; engage patients, families and healthcare providers; and focus on appropriate medical management.
Results: Sites received training in QI methods and are now conducting site-specific QI projects to address local needs. Regional data collection efforts are ongoing; currently, there have been over 300 patients and 1700 patient encountered entered into REDCap. Preliminary results show that the number of eligible patients prescribed hydroxyurea has increased 20% over time, and

100% of eligible patients have been offered hydroxyurea in the STORM network.
Conclusion: Preliminary data suggests that improvements will continue as sites become more experienced in QI methods. More regional patient-level data will also become useful in guiding future regional quality improvement efforts.

Poster # 151

INTRODUCING PREVENTATIVE CARE FOR CHILDREN WITH SICKLE CELL DISEASE (SCD) IN NORTHERN HAITI

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Background: Hôpital Sacré Coeur in Milot is a 150-bed referral hospital in Northern Haiti, a region with approximately 1 million inhabitants whose per capita income is roughly $800 US/year. SCD prevalence in this region is estimated at 15%. Many with this disease die undiagnosed and untreated. Given limited resources and the high prevalence of SCD, a program of prevention was undertaken by a staff pediatrician in the hospital, with support from a pediatric hematologist and a pediatric intensivist both based in the US, initiating prophylactic penicillin (PCN), and hydroxyurea (HU) according to guidelines.
Objectives: To introduce PCN and HU to selected children with SCD and to monitor tolerability, toxicity, efficacy, and acceptability clinically and, for patients on HU therapy, laboratory tests, with clinical guidance from the US based pediatric hematologist and medicines supplied by Yale-New Haven Hospital.
Design/Method: Medications for this project (PCN 250 mg and HU 500mg, tablets) were made available through an (ongoing) generous donation from Yale-New Haven Hospital. Beginning in 2015, the Medical Director of the Pediatric Sickle Cell Clinic at Hôpital du Sacré-Coeur identified candidates for therapy during their SCD clinic appointments or hospital admissions. Patients were eligible for PCN if they had a diagnosis of SCD and for HU if they had HbSS disease on hemoglobin electrophoresis and were able to tolerate HU in capsule form. Scripted, verbal explanations of the medications, their effects, potential benefits and side effects were given to parents prior to enrollment in the two programs. Verbal consent was obtained for each. The PCN was dosed at 125 mg bid < 2 years and 250 mg bid > 2 < 5 years of age. The HU was dosed at 20 mg/kg/day rounded to the nearest whole capsule and complete blood counts with differential and liver enzyme studies were monitored q 3 months.
Results: To date 27 patients have been identified with SCD. Seventeen patients have been started on PCN. All five of those offered HU agreed to take it and be monitored. There have been no side effects leading to discontinuation of the drugs. All continue to take the medicines at this time.
Conclusion: Under careful, controlled circumstances and under the supervision of knowledgeable, dedicated providers, PCN and HU can be introduced into a resource poor community. With very limited resources (personnel and supplies) in an area such as Milot, preventing complications of SCD is paramount to improving both quality of life and disease survival.

Poster # 153

SEVERE LOSS OF CIRCULATING DENDRITIC CELL SUBSETS IN SPLENECTOMISED CHILDREN WITH SICKLE CELL DISEASE

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Background: Splenectomy is the mainstay of long-term management of sickle cell disease (SCD) patients with frequent splenic sequestration crisis. However, it exposes patients to increased risk of infections, which remain major concern for both patients and clinicians. Dendritic cells (DC) play a key role in priming immune responses against infections. To date, limited information is available about DC subsets and their clinical relevance in splenectomised children with SCD.
Objectives: To characterize the distribution of circulating DC subsets in relation to B cell subsets and markers of SCD severity in well-defined group of splenectomised children with SCD.
Design/Method: A total of 57 SCD children who underwent open splenectomy were prospectively enrolled. Twenty eight age- and sex-matched healthy children were recruited as controls. The indication of splenectomy was based on the history of patients, clinical examination, hematological and radiological findings. The circulating DC subsets including plasmacytoid DC (pDC) and myeloid DC (mDC) were phenotypically identified by the expression of HLA-DR, CD123, CD11c, Lin and CD1d surface markers using 8-color flow cytometry. The B cell subsets were characterized by the positive staining with CD19, CD24 and CD38 surface markers. Comparisons among study groups were performed using unpaired t test, while the Spearman's correlation was used to assess associations.
Results: Compared to healthy controls, splenectomised children exhibited significantly lower levels of pDC (P=0.02). Similarly, levels of mDC were significantly reduced in splenectomised children compared to healthy controls (0.009). Interestingly, levels of pDC expressing CD1d, a non-classical molecule that is critical for generating cytokines from innate cells, were significantly reduced in splenectomised children compared to healthy controls (P<0.001). Levels of memory B cells, but not total and naïve B cells, were also significantly lower in splenectomised children compared to healthy controls (P=0.02). The levels of pDC and mDC were weakly associated with memory B cells (r=0.41, P=0.04), but not with age, total hemoglobin levels at phlebotomy, baseline haemoglobin F, time since splenectomy, hydroxyurea therapy and clinical severity.
Conclusion: Collectively, these findings show the existence of significant abnormalities in the distribution of DC subsets, along with memory B cells, in splenectomised children, and this could reflect a potentially altered responsiveness of these cells to mount a protective immune response against pathogens seen in splenectomised children with SCD.

Poster # 155

HYDROXYUREA IMPROVES FEV1/FVC IN CHILDREN WITH SICKLE CELL ANEMIA

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Background: Pulmonary function abnormalities are prevalent in children with sickle cell anemia (SCA) and correlate strongly with pulmonary complications. Hydroxyurea and transfusion therapy decrease the risk of acute chest syndrome and other sickle cell complications but their effect on pulmonary function test results has not previously been established. We sought to describe the evolution of pulmonary function test results in our patients, and elucidate whether hydroxyurea had any beneficial effects on pulmonary function over time.
Objectives: To compare at least 3 consecutive PFT results of patients on hydroxyurea with those on no therapy, and to correlate PFT abnormalities with laboratory markers of SCD.
Design/Method: We performed a retrospective cohort study reviewing charts of patients between the ages of 11 and 21 years who had undergone three or more consecutive PFTs at least one year apart. We reviewed charts of patients who remained on Hydroxyurea (6 patients) for the duration of consecutive PFTs as well as charts of patients on no therapy (6 patients) during that period. We collected PFT parameters (FEV1, FVC, FEV/FVC, FEF25-75), laboratory results obtained within 6 months of each PFT (white cell count, hemoglobin, reticulocyte count, hemoglobin F, LDH) as well as clinical data (acute chest episodes, ICU admissions and intubations, pulmonary hypertension on echo). We then analyzed each of the PFT outcomes measures using a repeated measures analysis of variance (RMANOVA) models with a mixed models approach.
Results: Compared to control subjects, hydroxyurea subjects had lower baseline percent predicted FEV1 (70.5 vs 72.8), FEF25 - 75 (59.7 vs 63.3) and FEV1/FVC scores (92.7 vs 95.8) at T1. Significant improvements in FEV1/FVC (95.5 vs 95.4) were seen in the hydroxyurea cohort by the third measurement T3. FEV1 (75.7 vs 78.9) and FEF25-75 (71.9 vs 80.9) were also improved at T3.
Conclusion: Our preliminary findings include a statistically significant association between hydroxyurea therapy and increased FEV1/FVC ($p = 0.0069$) over time in patients with SCA. In addition, although not statistically significant, FEV1 and FEF25-75% also increase over time in these patients. Of note, these three parameters are related to obstructive pulmonary disease, suggesting that hydroxyurea therapy may have a mitigating effect on the obstructive lung disease in this patient population. The improvement in lung function does not seem to occur until after at least 4 years following initiation of therapy. Data collection is ongoing, and further analysis is required to establish and explore this association.

Poster # 157

ASSOCIATION OF METHYLTETRAHYDROFOLATE REDUCTASE A1298C AND C677T POLYMORPHISM WITH VASO-OCCLUSIVE CRISIS IN SICKLE CELL DISEASE

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Background: Vaso-occlusion is a determinant for most signs and symptoms of sickle-cell anemia (SCA). There is evidence that SCA and other chronic hemolytic anemia are characterized by a hypercoagulable state with increased thrombin and fibrin generation as well as platelet activation with an augmented risk for thromboembolic complications. Homocysteine is a sulfur amino acid and a normal intermediate in methionine metabolism which when elevated, contributes to thrombosis. Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme, which regulates homocysteine metabolism.
Objectives: The aim of the study was to assess the association between the C677T and A1298C polymorphisms and the frequency of vaso-occlusive crisis (VOC) and the level of Homocysteine and its relation to VOC in SCA.
Design/Method: A case- control study was carried over a period of one year at the Hematology clinic, children hospital of Cairo University including 50 sickle cell disease patients in a steady state (mean age; 6.2± 2.55 years) together with 30 age, and sex matched apparently healthy controls. Venous blood sample was aspirated from both groups to estimate complete blood picture, Hb electrophoresis, serum homocysteine (by chromatography) and folic acid by ELISA. C677T and A1298C polymorphism identification was done through tetra primer ARMS PCR. Statistical analysis was done, using the student T-test, Pearson correlation analysis and $\chi 2$test.
Results: Homocysteine level was significantly higher while folic acid level was lower in the patients group compared with control group with P value > 0.01 and 0.02 respectively. A significantly negative correlation was observed between Homocysteine level and folic acid level (P= 0.04). The correlation between the SCD genotypes and the occurrence of vaso-occlusive event was significant (p = 0.04), with the majority of the cases occurring in patients with the Hb SS genotype. Moreover, a strong positive correlation between homocysteine level and the frequency of vaso-occlusive crisis was found (P= 0.04). Association between vaso-occlusive events and polymorphism frequency showed no significant difference for both the C677T and the A1298C polymorphisms P = 0.9 and P= 0.42 respectively.
Conclusion: (Homocysteine is elevated in SCA patients and is positively correlated with the frequency of VOC while neither C677T nor A1298C MTHFR gene polymorphism are risk factors for VOC in the studied group of patients. Further studies with larger number of patients are recommended.

Poster # 159

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY (TCD), ORGAN FUNCTION, METABOLIC AND NUTRITIONAL STATUS IN CHILDREN WITH SICKLE CELL ANEMIA: BASELINE DATA FROM THE EXTEND TRIAL

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Background: Limited data are available on the efficacy of hydroxyurea in reducing neurological risks of sickle cell anemia (SCA) in resource-limited countries like Jamaica, where the burden of malnutrition, infectious co-morbidity and organ dysfunction is high.
Objectives: Expanding Treatment for Existing Neurological Disease (EXTEND, NCT02556099) is a phase 2 clinical trial that investigates the efficacy of hydroxyurea treatment in reducing transcranial Doppler (TCD) velocities in Jamaica.
Design/Method: Eligibility includes children with SCA, who were ≥ 2 and <17 years, with either conditional (170-199cm/sec) or abnormal (≥200cm/sec) TCD velocities, or previous clinical stroke. Hydroxyurea is escalated to maximum tolerated dose (MTD) during an 18-month treatment phase. The primary endpoint is TCD velocity, while secondary endpoints include brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), clinical and laboratory parameters, growth, protein metabolism, and pulmonary function. At baseline children were screened with TCD, hematology testing, brain MRI/MRA, anthropometry, pulmonary function testing, and protein oxidation assessed with 13-C phenylalanine tracer.
Results: EXTEND enrollment was completed in April 2016. A total of 43 children (27 females, 16 males) were 7.7±2.6 years at enrollment and 36% (n=15) were malnourished (BMI-age z score <-1). Children with prior stroke (N=10) had significantly higher TCD velocities (211±58 vs 177±21 cm/sec, $p<0.03$), with lower hemoglobin concentration (7.4±0.9 vs 8.5±1.2, $p<0.03$) than the conditional TCD group (N=27) or the abnormal TCD group (N=6), but there were no significant differences in %HbF or white blood cell count. All 10 children with stroke had abnormal MRI/MRA with infarction and vasculopathy, and 8 had Moya-Moya, compared to only ~24% (N=8) of children with abnormal MRI/MRA in the abnormal and conditional TCD group combined. The proportion of phenylalanine dose oxidized was 19.9±4.7% on mean intakes of protein 2.2 g/kg/d and energy 55 kcal/kg/d. Among 33 children completing lung function testing, 8 had restrictive lung disease, 3 had obstructive or mixed lung function pattern, and 3 demonstrated bronchial hyper-reactivity. Diffusing capacity was decreased in five of 21 children completing that test.
Conclusion: EXTEND participants in Jamaica with SCA and neurological disease have frequent co-morbidities of malnutrition and lung dysfunction. Children with prior stroke have more severe baseline neurological and hematological disease, compared to those with abnormal or conditional TCD. The effects of hydroxyurea therapy on TCD velocity and stroke risk will be compared to changes in anemia, protein metabolism, and lung dysfunction at study exit with long-term follow-up.

Poster # 161

GENETIC MODIFIERS OF IRON OVERLOAD IN SICKLE CELL DISEASE

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Background: Chronic transfusion therapy is used in sickle cell disease (SCD) for primary and secondary stroke prevention. Chronically transfused patients accumulate iron at a rate of 0.3 to 0.4 mg/kg/day, with a large degree of interpersonal variability, both in serum ferritin [1] and in liver iron concentration (LIC) [2-4]. Genetic modifiers could play a role in this variability, but they have not been sufficiently investigated. Several candidate genes were found to be significantly over or under expressed in a group of SCD patients with high LIC in comparison with those with low LIC including GSTM1 (glutathione S transferase M1), elF5A, CCND1, GNMT, and CCL18 genes [5]. GSTM1 plays an important role in detoxification of carcinogens, therapeutic drugs and products of oxidative stress, by conjugation with glutathione. Importantly, GSTM1 deletion has been noted to be associated with increased cardiac iron in thalassemia major [6] and increased SCD severity [7]. However, prior studies of GSTM-1 in SCD were not well controlled for iron chelation exposure and transfusion burden.
Objectives: To investigate the association of GSTM1 genotype and LIC among patients with SCD and transfusional iron overload.
Design/Method: We compared LIC in children with SCD with a history of > 12 lifetime erythrocyte transfusions stratified by GSTM-1 genotype. Baseline LIC was obtained within 3 months prior to starting chelation using R2*MRI and then again after initiation of iron chelation with deferasirox or desferal (mean 21.02 months from baseline). A real time PCR was performed to determine GSTM1 genotype. The primary outcome of LIC was controlled by the lifetime cumulative transfusion burden corrected by weight (mL/kg).
Results: Thirty-three children with SCD (HbSS) with median age of 7.58 years (range 3.47-18.12) were included. The GSTM-1 genotypes were: homozygous deletion (7), heterozygous (15), and wild type (WT) (11). The overall LIC was 9.3 mg/g dry liver weight. Baseline LIC, when controlled for transfusion burden, was lower for GSTM1 null genotype as compared to wild and heterozygous genotypes [means: 8.3 (SD: 6.6), 8.2 (SD: 3.5), and 12.4 (SD: 6.3) mg/g respectively, p-value=0.041)]. After chelation was initiated, patients with GSTM1 deletion unloaded iron more slowly as compared to wild type and heterozygous genotypes: (GSTM-1 mean change: null= -0.17; heterozygous= -1.9; WT: -3.29 mg/g, p= 0.036).
Conclusion: Our findings suggest that although homozygous deletion of GSTM1 does not seem to affect iron loading, it may reduce iron chelator effect during iron unloading phase. These findings need to be confirmed in a larger cohort.

Poster # 163

INSTITUTIONAL ANALYSIS OF OBSTRUCTIVE PULMONARY DISEASE INTERVENTION AS POTENTIAL ADJUVANT THERAPY FOR VASO-OCCLUSIVE CRISIS

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Background: Asthma is a common comorbid condition in patients with sickle cell disease. It has been well reported that patients with sickle cell and asthma have increased risk of morbidity and mortality in regards to acute chest syndrome; however, limited research has been done to establish the role of asthma in vaso-occlusive crisis. Prior work by this group demonstrated a

positive but incompletely characterized association between patients with comorbid asthma and increased severity and frequency of pain.
Objectives: This study was designed to further identify and risk-stratify patients at increased likelihood of vaso-occlusive complications with specific attention to smoke exposure and pulmonary function testing (PFT) results.
Design/Method: After updating the existing institutional database, patients were identified with sickle cell disease and asthma ages 6 to 12 years of age. An additional subset was identified as phenotypic and age-matched controls. Rates of hospital presentations, frequency of pain crises, presence of respiratory symptoms, and use of asthma medications, smoke exposure status, and PFT results were retrospectively analyzed over a 5-year period. Data collection and interpretation were accompanied by review of existing literature.
Results: A positive association was identified between patients with comorbid asthma and increased vaso-occlusive crises, although a temporal relationship between respiratory symptoms and pain onset could not be defined. A statistically significant association was seen between use of asthma controller medications and decreased pain presentations ($p<0.05$). Smoke exposure was not found to affect these relationships. Evaluation of PFT results indicated that not all patients with a clinical diagnosis of asthma demonstrated obstructive disease but had other abnormalities including restrictive patterns.
Conclusion: Respiratory-driven interventions may have a role in the management of sickle cell vaso-occlusive crisis as evidenced by more frequent pain presentations in patients with asthma. The data was not confounded by exposure to tobacco smoke. While pulmonary function testing suggested that patients may have a multifactorial etiology of their lung disease, they still appear to benefit from treatment with traditional asthma medications. Further study of the use of asthma management as adjuvant therapy for with sickle cell is in progress with the intent to improve pain management and decrease hospital encounters.

Poster # 165

TYPE 1 DIABETES MELLITUS AND SICKLE CELL DISEASE: A CASE SERIES OF PEDIATRIC PATIENTS AT RAINBOW BABIES & CHILDREN'S HOSPITAL

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Background: Type 1 Diabetes (DM1) is rarely described in conjunction with sickle cell disease (SCD). The few published case reports infrequently report testing for antibody-positive (Glutamic Acid Decarboxylase (GAD65), Insulinoma Antigen 2 (IA2)) disease. Furthermore, the presence of SCD affects HbA1c measurements and provides an additional challenge in DM1 management. Fructosamine, a validated surrogate marker of short term blood glucose control, must be used for monitoring.
Objectives: To identify pediatric patients with both DM1 and SCD cared for at UH Rainbow Babies & Children's Hospital.
Design/Method: A retrospective chart review of pediatric patients with a diagnosis of SCD, any genotype, and DM1 was performed over a 3-year time period.
Results: From April 2013 to November 2016, approximately 1200 patients were followed for DM1. About 250 children were followed routinely for SCD. We identified three African

American males with SCD and DM1, all of whom presented in DKA at their initial DM1 diagnosis. Patient 1: 9-year-old with SS disease complicated by dactylitis, vaso-occlusive crises (VOC), acute chest syndrome (ACS), and splenic sequestration; diagnosed with DM1 at 4 years of age; GAD65 positive (IA2 not tested).Patient 2: 9-year-old with SS disease complicated by pneumococcal sepsis, dactylitis, VOC, splenic sequestration, cholecystitis, and iron overload secondary to chronic transfusions for an abnormal transcranial doppler (TCD); diagnosed with DM1 at 9 years of age; GAD65 and IA2 positive. Of note, this patient has had previous HLA typing significant for DRB1*13:01 and DQB1*06:09, a combination that may be associated with DM1.Patient 3: 5-year-old with SC disease without significant complications; diagnosed with DM1 at 4 years of age; GAD65 and IA2 negative. All three patients have had persistently elevated fructosamine levels despite being on adequate doses of insulin.
Conclusion: SCD poses potential management difficulties in DM1 evaluation and treatment. Fructosamine levels in our patients remained elevated on insulin, either reflecting compliance issues or lack of an established reference range in the SCD population. Moreover, the combination of SCD and DM1 is less common in our population than would be expected based on population data. It is possible that the inheritance of protective HLA haplotypes prevents SCD patients from developing DM1, which is tightly associated with certain class II HLA genes. It is also possible that protective structural alterations to the red blood cells might offer increased resistance to environmental exposures and decreased autoimmune dysregulation, both of which have been implicated in the pathogenesis of DM1.

Poster # 167

THE NEW ENGLAND PEDIATRIC SICKLE CELL CONSORTIUM (NEPSCC): A SUCCESSFUL AND SUSTAINED COMMUNITY-PROVIDER PARTNERSHIP

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Background: Sickle cell disease (SCD) affects approximately 100,000 individuals in the US. Efforts have been directed towards improving the management of complications that individuals with SCD experience: penicillin (PCN) prophylaxis study, the multi-center study of hydroxyurea (HU) and stroke prevention trials. Although the NIH has provided guidelines based on these, there remain significant gaps both in in best clinical practices and community support for children with SCD and a pressing current need to address aspects of health, equity and racial disparity in this population.
Objectives: For providers and support staff of children with SCD in the New England area to work together to develop practice guidelines, community based participatory research with an opportunity to share data, to share clinical experiences, and to provide community and provider support for affected children and their families.
Design/Method: In 1999 Dr. Michael Osband of Boston Medical Center, Boston MA conceived the idea of a regional consortium of pediatric SCD providers and reached out to the institutions in the six New England States (Massachusetts, Rhode Island, Connecticut, New Hampshire, Maine and Vermont) that provided care to children with SCD, to constitute membership. Dr. Osband passed away in 2001 but his consortium continues, actively celebrating its 18th birthday in 2017.

Results: Over time the NEPSCC has added members, including an American Red Cross staff member, adult primary care and hematology providers, community based organizations, and an institution outside New England: Wyckoff Hospital, Brooklyn, New York. Research from the consortium includes one paper on obesity in SCD and a number of abstracts presented at national meetings. There is currently a study across the consortium on the impact of HU in children. In addition, through public-private partnerships, NEPSCC has held seven, annual, daylong symposia, free of charge, for members and the greater regional SCD community. Topics presented include pain management, describing conventional and alternative approaches, indications for HU therapy, transition from pediatric to adult care, sickle cell trait, clinical trials, and transplantation. NEPSCC has published handbooks for patients and their families and made available social, legal and medical resources for the community both online and in print.
Conclusion: With a passion for improving the wellbeing of patients and a willingness to devote time and energy (membership is entirely voluntary), it is possible to bring together a group of likeminded providers and SCD community-based organizations to work at a regional level for the betterment of children and families affected by SCD.

Poster # 202

GROWING UP WITH FANCONI ANEMIA: ADULT PATIENTS SOCIOECONOMIC STATUS AND PERCEPTIONS OF THE IMPACT OF FANCONI ANEMIA ON THEIR LIVES

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Background: Children with Fanconi Anemia (FA) face bone marrow failure in the first decade of life and most need bone marrow transplant to survive. Improved transplant techniques mean that most FA children now survive, and adult challenges are a more pressing issue. We hypothesized that the constant uncertainty of future medical events, and recent changes in outcomes might change life choices for patients with FA.
Objectives: Our goal was to define social, educational and economic achievement of adults with FA, and describe the influence of a diagnosis of FA on stress, risk-taking and personal goals.
Design/Method: We designed a twenty question electronic survey in multiple-choice and free text format. The FA family support group (Fanconi Anemia Research Fund) identified approximately 200 adults with FA and distributed the questionnaire via email.
Results: Sixty FA adults (median age 29 years, range 18-64) responded to the questionnaire. Overall, the group is well-educated, with all but 2 having at least some college, and 8 completed graduate school. 56% of respondents were married or in a long-term relationship. 41% reported thinking about FA at least daily when growing up, and more than 50% currently think about FA daily. 60% of respondents reported that growing up, peers did not understand the impact of FA on their lives. 30% of respondents acknowledged reckless life choices, with one reporting, “After I survived, I wanted to live to the edge of the world”. When asked “How big of an impact did FA have on shaping you into the person you are today?” 60% agreed that they never took a minute for granted. Additional questions addressed regrets, advice to their younger selves, and impact of changed prognosis, current anxieties and life priorities. 50% answered yes to the question “Would there be something that you would change if you knew that life expectancy for people

with FA would increase dramatically within your lifetime?" Respondents would have studied more, paid more attention to relationships and worried less. When asked about current priorities, 50% selected family and friends over academics and work. 50% reported some regrets about past choices, and when asked about current philosophy of life many reported living each moment to the fullest.
Conclusion: These data indicate that FA had a profound influence on the majority of FA adults. Despite this, the successful lives and achievements of most FA adults are important for providers to share with parents raising children with FA.

Poster # 204

MULTICENTER COHORT STUDY EVALUATING INPATIENT MANAGEMENT OF YOUNG WOMEN WITH HEAVY MENSTRUAL BLEEDING AND IRON DEFICIENCY ANEMIA

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Background: Under recognition of heavy menstrual bleeding (HMB) and resultant iron deficiency anemia (IDA) can lead to emergent medical care and inpatient hospitalization. Limited evidence describes the scope of this problem.
Objectives: To assess the frequency, clinical severity, and management of young women presenting with IDA and HMB who require inpatient hospitalization.
Design/Method: This retrospective multicenter cohort study utilized the Pediatric Health Information Systems (PHIS) administrative database. Subjects were 8 to 18 years of age, admitted to a PHIS hospital between October 1, 2012 and September 30, 2015 with both HMB and anemia as either a primary or secondary diagnosis code. International Classification of Disease, Ninth Revision (ICD-9), Clinical Modification Code discharge codes confirmed the presence of both conditions during admission. Patients with cancer, immune thrombocytopenic purpura, and aplastic anemia were excluded. Pharmaceutical billing codes were assessed for iron (intravenous and oral preparations), all hormone therapies, and all coagulants.
Results: A total of 1189 unique patients met inclusion criteria (median age of 14 years, range 8 to 18) for a total of 1239 admissions. Intensive care unit utilization occurred in 4.8% (n=60) of admissions, and 68.4% (n=847) involved transfusions. Assessment for a primary bleeding disorder was inconsistent, with complete blood counts, partial thromboplastin times (PTT), and prothrombin times (PT) being the most commonly evaluated measures, occurring in 85%, 76.1%, and 70.5% of admissions, respectively. Other hematologic assessments included factor levels (61.2%), von Willebrand ristocetin cofactor (57.6%), fibrinogen (27.4%), and platelet studies (platelet function analyzer and platelet aggregation, 15.7%). Laboratory iron measures including serum ferritin, serum iron, and total iron binding capacity (TIBC) were assessed in 34.1%, 31.2%, and 26.2%. Hormonal therapies utilized included combined oral contraceptives in 62.6% (n=776), conjugated estrogen or estradiol in 35.6% (n=440), and/or progestin therapy (medroxyprogesterone, norethindrone, megestrol, levonorgestrel intrauterine device) in 14.2% (n=176). Antifibrinolytics were administered in 8.2% (n=102). Iron therapy was prescribed in only 62.3%, with 3.6% receiving intravenous iron and 60.8% prescribed oral iron.
Conclusion: We found that hundreds of adolescent girls with combined HMB and IDA are

hospitalized at U.S. children's hospitals each year, with roughly 1 in 20 requiring ICU level care. Future management guidelines should include early detection, optimal treatment protocols to control acute bleeding, accurate diagnosis of primary bleeding disorders, appropriate iron replacement therapy, and consistent follow-up for these high-risk patients.

Poster # 206

GERMLINE AND SOMATIC GENETIC CHARACTERIZATION OF SHWACHMAN-DIAMOND SYNDROME

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Background: Shwachman-Diamond syndrome (SDS) is associated with exocrine pancreatic dysfunction, increased risk of leukemia, and biallelic SBDS mutations in the majority of individuals.
Objectives: Our objective was to characterize SBDS genotypes, somatic changes and associated hematologic phenotypes within the North American SDS Registry.
Design/Method: Median age of subjects was 12.3 years (range,0.7-53). SBDS genetic reports were available in 130 subjects.
Results: Eighty-two had biallelic SBDS mutations. Amongst those with biallelic SBDS mutations, cytopenias were noted in all but one. Intermittent neutropenia was the most frequent in 97% (n=70/72). Anemia and thrombocytopenia were seen in 53% (n=39/73) and 64% (n=48/75). In 81 of 82 patients harboring biallelic SBDS mutations, at least one mutant SBDS allele was the c.258+2T>C intron2 splice donor mutation. The mutation spectrum of the second SBDS allele included missense, splice site, and truncating mutations. One subject lacked the intron2 splice donor mutation, having c.183_184delTAinsCT and c.523 C>T mutations in SBDS confirmed to be in trans. This results in the combination of a truncating p.Lys62X mutation with a p.R175W missense mutation at a conserved residue predicted to be deleterious. This subject had neonatal severe aplastic anemia requiring platelet and red cell transfusions with profound neutropenia unresponsive to G-CSF and abnormal bone formation by morphology. The c.258+2T>C variant expresses a low level of SBDS protein, so absence of this hypomorphic allele may have contributed to this exceptionally severe phenotype.Marrow reports were available for 67 subjects with biallelic SBDS mutations. Hypocellularity was noted in 79% (n=49/62) and mild marrow dysmorphology in 58% (n=35/60). Clonal abnormalities developed in 36%, the most common being del20q in 19% (n=12/64). One had isochromosome 7. Three individuals developed AML. Twelve (15%) underwent hematopoietic stem cell transplantation (HSCT), 10 for MDS or AML and 2 for severe aplastic anemia. Median age of the cohort with del20q clones was 17 years (range, 10.8-29.3). Frequency of cytopenias was similar to that of non-del20q subjects. All 12 were noted to have marrow hypocellularity, and 10 mild marrow dysmorphology. In many the clone was persistent or grew over time, with longest duration of 14.4 years. Three with initially isolated del20q clones progressed to MDS with additional loss of

chromosome 7 (n=2), and progressive marrow dysplasia and falling blood counts (n=2). All three underwent HSCT.
Conclusion: These data suggest SDS patients with del20q clones remain at risk for clonal evolution. Higher patient numbers are needed to quantitate risk of MDS in SDS patients with del20q.

Poster # 208

ADDITION OF ELTROMBOPAG TO STANDARD EQUINE ATG-BASED IMMUNOSUPPRESSIVE THERAPY FOR PEDIATRIC IDIOPATHIC SEVERE APLASTIC ANEMIA

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Background: Aplastic anemia is a rare and life-threatening disorder, but treatment can result in greater than 90% long-term survival. Pediatric idiopathic severe aplastic anemia (SAA) is characterized by anemia, neutropenia, and thrombocytopenia, as well as a hypocellular bone marrow. Choice of initial therapy is based on the availability of an HLA-identical sibling. In the absence of a matched sibling donor, first line therapy consists of immunosuppressive therapy (IST) with horse anti-thymocyte globulin (ATG), cyclosporine, and a short course of corticosteroids, for the majority of patients. Eltrombopag is a synthetic non-peptide thrombopoeitin (TPO) mimetic, which non-competitively binds to an alternate site on the TPO receptor to promote hematopoietic stem cell growth in the bone marrow. It was originally developed for the treatment of chronic immune thrombocytopenia, but recently has been added to the standard IST regimen with encouraging results.
Objectives: Assess our institutional experience with the addition of eltrombopag to standard ATG-based IST for the treatment of patients with idiopathic severe aplastic anemia.
Design/Method: Retrospective chart review.
Results: Nine pediatric patients (median age 10, range 3-16 yo) with SAA were treated at our institution during the study period of November 2015 through January 2017. All 9 patients have 3 month follow-up data and 7 patients have 6 month follow-up data. All 9 patients met criteria for severe aplastic anemia. Treatment with IST and eltrombopag was started at a median of 35 days from diagnosis. At 3 months, of the 9 evaluable patients, one patient achieved complete remission (CR), 5 achieved partial remission (PR) denoted as transfusion independence, and 3 had no response (NR) giving a CR+PR response rate of 66.67%. Of the 7 evaluable patients at six months, one was in CR, 5 were in PR, and 1 had NR yielding a CR+PR response rate of 85.71%. Two of the NR patients at 3 months were PR at 6 months. Median time to achieve an ANC >500 was 14 days, ANC >1000 was 31 days, and platelet count >50K was 120 days. Median time to transfusion independence for both platelets and packed red blood cells was 54 days. No patients required hematopoietic stem cell transplant during the study period and one patient relapsed at 314 days post-IST.
Conclusion: The addition of eltrombopag to standard IST appears promising in our small cohort of pediatric patients with SAA, and is worth continued investigation.

Poster # 210

AUTOIMMUNE HEPATITIS-ASSOCIATED APLASTIC ANEMIA IN PEDIATRIC PATIENTS: A SEARCH FOR RISK FACTORS

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Background: Hepatitis-associated aplastic anemia is a well-recognized phenomenon. Aplastic anemia (AA) develops 2-3 months after the diagnosis of acute hepatitis, affecting young-aged males and is thought to be an immune-mediated process. However, no studies have looked into autoimmune hepatitis-associated aplastic anemia.
Objectives: To determine demographics, serological or pathological factors that can be used to predict the development of AA among patients with autoimmune hepatitis (AH).
Design/Method: Medical records of 0-18 years old patients from 2005-2015, found via ICD-9 code for AH (#571.42), were retrospectively reviewed. AH was defined as presence of autoantibodies or scores 10 or above using the Revised International AH Group Scoring System. AA was defined as bone marrow hypocellularity for age and absent malignant infiltrates or fibrosis. Continuous and categorical variables were compared between autoimmune hepatitis only group (AH group) and autoimmune hepatitis-associated aplastic anemia group (AHAA group).
Results: Forty-five medical charts were reviewed, 20 patients met criteria for AH and had data available for review. Fifteen patients (75%) did not develop AA while 5 patients (25%) did. Average age of AH diagnosis was 12.8 and 10.6 years in the AH and AHAA groups, respectively. Average alkaline phosphatase (AP), direct bilirubin (DB) and total bilirubin (TB) levels were 331.3unit/L, 7.6mg/dL, and 59.3mg/dL in the AH group versus 492unit/L, 11.3mg/dL and 17.2mg/dL in the AHAA group. All P-values <0.05. Comparison of other variables was not statistically significant. Average absolute neutrophil count, hemoglobin and platelets were comparable among both groups. Autoantibodies were present in 12 patients (80%) of the AH group and 1 patient (20%) of the AHAA group. Average number of days to normalization of liver enzymes after treatment is 110days in AH group and 58days in AHAA group. Average number of days from AH to diagnosis of AA is 60.8 days and average AST and ALT at that time were 24.4unit/L and 129.4unit/L.
Conclusion: Average age of onset of AH is in the late pre-adolescent period. Patients who develop AA are more likely to have higher AP, DB, and TB levels and absence of autoantibodies than those who do not develop AA. Bone marrow functions are normal at the time of diagnosis of AH for both groups. AA develops about 2 months after diagnosis of AH during which liver enzymes are normalizing and the normalization occurs sooner than patients who do not develop AA. Larger, multi-institutional prospective studies of this rare disease may show more statistically significant biomarkers that can be used to predict development of AA among AH patients.

Poster # 212

SIGNIFICANTLY DECREASED SKIN INTEGRITY IN PATIENTS WITH FANCONI ANEMIA

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Background: Fanconi Anemia (FA) is a rare inherited disorder involving defective DNA repair mechanisms that leads to bone marrow failure. Patients with FA are at risk of other cancers, particularly squamous cell carcinoma (SCC) of the head and neck and ano-genital region. SCCs originate from keratinocytes in the epidermis and we know skin barrier function is crucial for skin integrity. We hypothesized skin integrity is decreased in FA patients compared to controls, which may contribute to SCC development.
Objectives: We tested and compared skin integrity using time to skin blister formation in patients with FA and control subjects.
Design/Method: We used a negative pressure generating machine to form a small blister on the skin of subjects. The machine was applied at the same location (forearm) for all subjects. Standard operating procedures were used for all subjects, including generation of 200mmHg negative pressure on the skin surface. Time from negative pressure initiation to first appearance of skin blister was obtained for each subject.
Results: A total of 17 subjects were enrolled in the study. In the control group, there were 9 subjects (5 male and 4 female) with a median age of 18 years (13 to 22 years). The median time to blister formation for this group was 41 minutes (range 31 to 48 minutes).A total of 8 subjects with FA were evaluated. There were 5 female and 3 male subjects, with a median age of 18 years (12 to 25 years). The median time to blister formation was 21 minutes (range 19 to 24 minutes).The difference in time to blister formation was statistically different between the two groups ($p < 0.0001$).
Conclusion: There is a significantly reduced time to blister formation in patients with FA compared to control subjects. This may represent decreased skin barrier integrity in patients with FA, which may allow exposure to environmental antigens to deeper layers of the skin and may contribute to increased risk of SCC development. Further experiments are needed to confirm these findings and explore mechanistic pathology involved in defective skin integrity in patients with FA.

Poster # 214

USE OF ELECTRONIC CONSULTATION SYSTEM TO IMPROVE ACCESS TO CARE IN PAEDIATRIC HEMATOLOGY/ONCOLOGY

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Background: Electronic consultations (eConsult) allow for communication between primary care providers (PCPs) and specialists in an asynchronous manner. EConsults allow for easier access to specialists with the many associated benefits. The eConsult service has been shown to improve access of primary care providers (PCPs) to specialty expertise without the need for face-to-face consultation, which in turn should decrease wait times for patients. They have also been

shown to decrease anxiety in patients.
Objectives: This study examined provider satisfaction, topics of interest and efficiency of eConsult in pediatric hematology/oncology service delivery in Ottawa, Canada.
Design/Method: We conducted a cross sectional assessment of all the eConsult cases directed to pediatric hematology/oncology specialists using the Champlain BASE™ (Building Access to Specialists through eConsultation) eConsult service from June 1, 2014 to May 31, 2016. The eConsults were all reviewed by one pediatric hematologist/oncologist and categorized into pediatric hematology/oncology topic by the same clinician. Data on use of the eConsult service was collected.
Results: Pediatric hematology/oncology consults accounted for 8% of all pediatric eConsults during the study time period. Only general pediatrics (37%), orthopedics (15%) and psychiatry (12%) had more consultations for pediatric patients. The time spent on the electronic consult was less than 10 minutes in 84 of 85 cases, and 10-15 minutes in only one case. The majority of eConsults were pediatric hematology (77/85 or 90.5%) as opposed to pediatric oncology (8/85 or 9.5%). The most common consult was for anemia (23.5%) followed by hemoglobinopathy (12.9%), bleeding disorder (11.8%) and thrombotic state (8.2%). PCPs rated the eConsult service as very good or excellent in 95% of cases. The comments were very positive (for example "really helpful to get information so quickly. It's easier than a phone consult as you don't have to play phone tag and they can review when they are free and same for referring MD."). Fifty-five percent of PCPs reported to have received good advice for a new course of action and 41% confirmed their original care plan. Forty percent of referrals were avoided as a result of the eConsult, and in 8% a referral was not originally contemplated but now initiated.
Conclusion: This study showed successful implementation and use of the eConsult service for pediatric hematology/oncology. It resulted in avoidance of a large number of face-to-face consultations, and was very well rated by PCPs. The consultation topics identified areas for continuing medical education.

Poster # 216

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: A 5-YEAR INSTITUTIONAL REVIEW

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematopoietic stem cell disorder characterized by intravascular hemolysis and bone marrow failure with potential to evolve into myelodysplasia or acute non-lymphoblastic leukemia. It is a rare disorder with only an estimated 400-500 cases diagnosed in the United States each year. Approximately 10% of these cases occur in the pediatric population.
Objectives: During the 5-year study period, an increased number of patients presented to our institution with pancytopenia and biopsy proven bone marrow hypoplasia fulfilling diagnostic criteria for aplastic anemia (AA) and were found to have an underlying PNH clone.
Design/Method: After obtaining approval from our Institutional Review Board, we conducted a

retrospective chart review of children presenting with pancytopenia/AA from 2010-2015 who were subsequently diagnosed with PNH. Data collected included demographic information along with presenting symptoms, laboratory findings, diagnosis, and treatment. PNH clones were detected by flow cytometry using CD55 and CD59 surface molecules and fluorescently labeled aerolysin, a marker for glycosyl phosphatidylinositol-anchored proteins, which are absent in PNH.
Results: Six children with AA and PNH clonality were identified: 2 females/4 males, 3 African American/3 Caucasian; ages 10 to 17 years (median age of 11.5 years). Ethnicity, sex, and geographic location were not correlative. Four of the patients met criteria for severe AA per published standards with mean hemoglobin, white blood cell and platelet counts of 5.95 g/dL, 2.48x10^3/UL and 9x10^3/UL, respectively. Three patients underwent hematopoietic stem cell transplant (HSCT): two developed an increased PNH clone size despite immunosuppressive therapy (IST, anti-thymocyte globulin and cyclosporine) while the third patient had no evidence of bone marrow recovery and was taken for HSCT at the treating physician's discretion. Two of the 3 remaining patients continue on IST. All patients are alive and transfusion independent. None of the patients developed thrombotic events, myelodysplasia or hematologic malignancy.
Conclusion: Our study highlights an increase in pediatric patients presenting to our institution with AA and subsequent detection of PNH clonality. Although rare, PNH is an important cause of bone marrow failure/AA in children and is often overlooked. We present this small series of 6 patients to underscore the importance of considering PNH early on in the differential diagnosis and evaluation of children presenting with AA. A high index of suspicion along with close collaboration between pediatric hematology and pathology has allowed us to expedite the diagnosis and initiate appropriate therapy, which are critical in successful management of patients with PNH.

Poster # 218

PREVALENCE OF CLINICALLY SIGNIFICANT PRENATAL RED BLOOD CELL ALLOANTIBODIES

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Background: Clinically significant red blood cell (RBC) alloantibodies may develop as a result of previous pregnancies and/or transfusions. If the fetus inherits the cognate antigen from the father, Hemolytic Disease of the Fetus and Newborn (HDFN) may result in neonatal anemia and severe hyperbilirubinemia. The use of Rh immunoglobulin (RhIG) during pregnancy has decreased the incidence of HDFN due to anti-D, yet HDFN due to the other clinically significant antibodies continues to be of great concern.
Objectives: To determine the frequency of: a) clinically significant RBC alloantibodies in prenatal specimens at a single tertiary centre over a 10 year period; b) at risk pregnancies and their fetal and neonatal outcomes.
Design/Method: Data were collected from the Transfusion Medicine Laboratory Information System, antibody investigation charts, and electronic patient charts at St. Michael's Hospital (SMH), Toronto, Ontario, Canada. We reviewed all ABO/Rh and antibody screen tests

performed between January 1, 2006 and April 1, 2016, retrospectively. To avoid confounding, neonates with ABO incompatibility between mother and fetus/newborn were excluded from the outcome analysis.Average monthly statistics for ABO/Rh and antibody screen were used to calculate percentage of positive screens in prenatal versus all specimens. The frequencies of clinically significant RBC alloantibodies and at risk pregnancies (defined by presence of antigen against maternal antibody on cord testing) were recorded. This study was approved by the SMH Research Ethics Board.
Results: Pregnant patients accounted for 27% of all specimens tested for ABO/Rh and antibody screen. The prevalence of a positive antibody screen was 3.6% for all patients tested, and 1.4% among pregnant patients. Over 10 years, 300 pregnant patients had a positive antibody screen and 50% had clinically significant RBC alloantibodies. A total of 173 RBC alloantibodies were identified, with Rh antibodies being the most common (84%). Anti-D was identified in seven pregnancies, where anti-D alloimmunization may be due to failure to administer prophylactic RhIG or for reasons not described on the patient charts. There were 47 pregnant patients, and 53 deliveries with clinically significant antibodies; 31 neonates were positive for the corresponding antigen and deemed to be at risk for HDFN.
Conclusion: Rh alloantibodies, including anti-D, continue to be the most prevalent clinically significant antibodies detected in prenatal specimens. Data collection and analysis is ongoing. Fetal and neonatal outcome data is being collected.

Poster # 220

DNAJC21 FOUNDER MUTATION IN FOUR PATIENTS: CONFIRMATION OF THE LINK WITH BONE MARROW FAILURE AND EXPANSION OF THE PHENOTYPE

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Background: We studied 2 siblings and 2 double cousins from a First Nation community, who presented postnatal growth retardation, global developmental delay, skin, teeth and hair abnormalities, hyperlaxity, and bone marrow failure. In addition, all patients had short telomeres, and 2 of them eventually developed skeletal abnormalities consistent with spondyloepimetaphyseal dysplasia. These features strongly suggested an inherited bone marrow failure syndrome, such as Dyskeratosis congenita (DC), Shwachman-Diamond syndrome (SDS), Rothmund-Thomson syndrome, or Poikiloderma with neutropenia. However, they all lacked many classical features found in these conditions and single gene sequencing failed to identify a mutation in any of the associated genes.
Objectives: Recognize the link between homozygous mutations in DNJAC21 and Bone marrow failure syndrome. Assess a novel homozygous variant in DNAJC21 and infer its clinical significance. Describe the extended phenotype presented by individuals carrying homozygous mutations in DNAJC21. Acknowledge the presence of a founder mutation in a First Nation population.
Design/Method: Considering the common ethnic origin and similar clinical features, we hypothesized that the same homozygous mutation was likely responsible for this condition in all

patients, and performed exome sequencing on the proband's blood.
Results: We identified a homozygous variant (NM_001012339:exon2:c.A100G:p.K34E) in DNAJC21, a gene recently linked with Bone marrow failure syndrome 3 (BMFS3) [Tummala H. et al.]. This variant was predicted damaging by all in silico prediction algorithms. All affected individuals were confirmed to be homozygous for this variant by Sanger sequencing and available parents were all found to be heterozygous.
Conclusion: This is the first report of this specific variant in DNAJC21, which supports the association reported by Tummala et al. with bone marrow failure. Its ihneritance pattern is consistent with a founder mutaiton in this First Nation population. We describe in detail the characteristics of our patients, and expand the phenotype associated with this new syndrome. Our findings also suggest that DNAJC21, in addition to its role in ribosome biogenesis, may be involved in telomere maintenance, making it the latest gene associated with telomeropathies. (Tummala H. et al., Am J Hum Genet. 2016)

Poster # 222

PERSISTENT HEMOLYTIC DISEASE OF THE NEWBORN DUE TO BREAST MILK TRANSMISSION OF ANTI-D OR ANTI-JKA ALLOANTIBODIES

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Background: Alloantibodies against more than 50 non-ABO blood group antigens have been implicated in hemolytic disease of the newborn (HDN) and are expected to wane 6-8 weeks after delivery. Persistent anemia beyond this time leads to the hypothesis of continued exposure to red blood cell (RBC) alloantibodies via breast milk, which has not been previously reported.
Objectives: To investigate the presence of RBC alloantibodies in maternal breast milk as a factor contributing to persistent HDN.
Design/Method: Direct coombs testing and serum antibody titers were followed in three neonates with either anti-D or anti-Jka HDN. Maternal serum and breast milk was tested for the presence of anti-D or anti-Jka antibodies and titers were performed. Maternal serologic testing used standard blood bank methods, with antibody titers performed at room temperature by tube method using LISS as enhancement. Fresh breast milk samples were tested at room temperature for the presence of antibodies using indirect anti-globulin methods with standard agglutination scoring. Breast milk titers were performed using tube method without enhancement media. Fresh breast milk from an O positive, antibody negative donor was used as control for any reactivity that may have been due to milk solids or proteins alone.
Results: Three full term breastfed infants were admitted to neonatal intensive care units in the first weeks of life for severe hemolytic anemia due to Coombs positive, IgG mediated hemolysis. Two infants had 4+ anti-D Rh HDN while the third infant had HDN due to anti-JKa. The anemia persisted beyond 2 months in patient 1, and beyond 4-6 weeks in patients 2 and 3 despite RBC transfusions. Given continued need for RBC transfusion at 2 months in patient 1 with persistence of 4+ anti-D serologic testing, antibody testing was done on maternal breast milk which confirmed anti-D positivity. Similar breast milk and maternal serologic testing was confirmed in patients 2 and 3. Peak breast milk titer was 1:512 (patients 1 and 2) and 1:2 (patient 3), with peak maternal plasma titers of 1:4069, 1:8, and 1:256 respectively. Patient 1 had resolution of anemia

by 4 months after cessation of breastfeeding at 2 months, whereas patient 2 was able to continue breastfeeding with gradual improvement of anemia and resolution of alloantibodies. The evaluation of patient 3 is ongoing.
Conclusion: Utilizing a unique application of a blood bank methodology we demonstrate that maternal RBC alloantibodies present in breast milk may be clinically significant in patients with prolonged recovery from HDN.

Poster # 224

NEUTROPENIA AS A PRESENTING FEATURE OF HYPERZINCEMIA DUE TO MUTATION IN PROLINE-SERINE-THREONINE PHOSPHATASE-INTERACTING PROTEIN 1 (PSTPIP1)

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Background: The differential diagnosis of a child presenting with neutropenia is broad. Children with neutropenia and associated constitutional symptoms such as fever, fatigue and pain undergo evaluation to rule out a variety of conditions including malignancy, bone marrow failure disorders, autoimmune disease and nutritional deficiencies. Here we describe two patients seen at a large referral center for evaluation of severe neutropenia, who were ultimately diagnosed with proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1)-associated myeloid-related proteinemia inflammatory (PAMI) syndrome (also called hyperzincemia/hypercalprotectinemia) after extensive testing failed to identify the cause of their neutropenia. PAMI syndrome is a rare autoinflammatory disease characterized by periodic fever, skin and/or joint inflammation, arthralgia, failure to thrive, lymphadenopathy, hepatosplenomegaly, hematologic abnormalities and elevated inflammatory makers and zinc levels.
Objectives: To describe a rare cause of neutropenia.
Design/Method: Retrospective review of the electronic medical record and review of the literature.
Results: Case 1. A 12-year-old girl was referred for neutropenia and concern of bone marrow failure (BMF) disorder due to a family history of myelodysplastic syndrome and pulmonary fibrosis. The patient had significant long-standing history of polyarticular joint pains and difficulty walking. Testing for anti-neutrophil antibody, HIV, vitamin B12, folate, copper, hemoglobin profile and Fanconi anemia were normal. Detailed telomere length testing was significant for very short telomeres which, coupled with her family history, was suggestive of dyskeratosis congenita (DC). Bone marrow biopsy showed normal cellularity with no dysplasia or cytogenetic abnormalities, suggesting that her DC was preclinical and likely not the cause of her neutropenia. Subsequently, a customized next-generation sequencing (NGS) panel identified a heterozygous pathogenic variant in the PSTPIP1 gene (p.E250K), in addition to a novel TERT variant (p.F693C) of unknown significance which was likely related to her subclinical DC. Case 2. A 7-year-old girl, former 28-week premature infant, presented with osteomyelitis and was incidentally found to have severe neutropenia. The patient had pancytopenia since birth and hepatosplenomegaly since 3 years of age. Work up of neutropenia in the past had been negative.

Bone marrow biopsy showed features consistent with autoimmune myelofibrosis. This patient also had intermittent bilateral hip and knee pain since 2 years of age. Whole exome sequencing revealed a likely pathogenic PSTPIP1 variant (p.E257K). Zinc levels and serum inflammatory markers were significantly elevated in both patients.
Conclusion: PAMI syndrome is a rare cause of neutropenia. Measuring inflammatory markers and zinc levels should be considered in children with unexplained neutropenia and inflammatory symptoms.

Poster # 226

IMMUNE THROMBOCYTOPAENIA AS A PRESENTING FEATURE OF ACQUIRED CYTOMEGALOVIRUS INFECTION IN YOUNG INFANTS- A SINGLE CENTRE STUDY FROM SINGAPORE

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Background: Immune thrombocytopaenia (ITP) secondary to cytomegalovirus (CMV) infection is a well-recognized phenomenon in Asia where prevalence of early CMV infection is high but very little is known about this association in very young infants.
Objectives: To study the clinical characteristics of young infants (1-3 month age group) presenting with ITP secondary to acquired cytomegalovirus infection.
Design/Method: This is a retrospective study from January 2012- August 2016 of all young infants of 1-3 month age group who were diagnosed with immune thrombocytopaenia and a confirmed cytomegalovirus infection in our institution. Clinical features, blood parameters, treatment offered with response and outcome were analyzed.
Results: Total of 8 babies of age 6 weeks to 15 weeks were admitted with ITP secondary to acquired CMV infection in this period. All were born after uneventful pregnancy, none had any stigmata of congenital CMV infection or any other clinical concerns. Sites of bleeding were skin bruises only in 6/8 and two had additional mucosal haemorrhage in the form of gastrointestinal haemorrhage and epistaxis. Platelet count at presentation was 0-17 X 109/L, 6/8 had platelet of <10 X 109/L. Blood transfusion and platelet transfusion were necessary in 1 baby each for significant mucosal haemorrhage. Mild transaminitis were noted in 3/8 babies. Diagnosis of acquired CMV infection was confirmed by positive urine CMV PCR in all babies combined with CMV IgM positivity in 3/8 and blood PCR positivity of 3-4.7 logs in 4/8 where blood PCR was done. Specific immunotherapy with IVIG was done in 5/8 babies and 3/8 recovered without any treatment. IVIG dose used was 1g-3g/kg. CMV specific treatment was necessary in only 1 baby who was refractory to IVIG initially and had mucosal haemorrhage needing platelet transfusion and responded to 3rd does of IVIG (1g/kg) only after treatment with IV ganciclovir was initiated. All babies achieved complete remission with normalization of platelet count ranging 1-4 weeks after initial presentation and remains well with no long term clinical concerns
Conclusion: Acquired CMV infection at a very early age is not uncommon in Singapore and immune thrombocytopaenia appears to be a classical presenting feature. However specific anti CMV treatment is rarely necessary and treatment with IVIG is also not necessary in all cases. Long term outcome is excellent and complete remission is the norm. Treatment with IVIG

should be reserved for those with mucosal haemorrhage and anti CMV therapy for those with refractory thrombocytopaenia.

Poster # 228

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA: A CASE SERIES INDICATING TWO FOUNDER MUTATIONS IN THE MISSISSIPPI BAND OF CHOCTAW INDIANS

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Background: Congenital amegakaryocytic thrombocytopenia (CAMT) is an autosomal recessive disorder causing thrombocytopenia that progresses to pancytopenia and bone marrow failure if untreated [1]. Mutations in the MPL gene were identified as causative. The MPL gene encodes the thrombopoeitin (THPO) receptor, which is the primary ligand of the glycoprotein thrombopoeitin and results in stimulation and differentiation of megakaryocytes [3,4]. There have been more than 30 mutations identified, including missense, nonsense, frame shift, and splice-site mutations [4]. Through analysis of 5 CAMT cases at UMMC, we were able to identify two common MPL mutations within a Native American population, the Mississippi Band of Choctaw Indians (MBCI). These appear to be founder mutations in this population, dramatically increasing the prevalence of CAMT compared to the general population. The MBCI has experienced two major population bottlenecks as the result of a forced migration to Oklahoma and ensuing economic hardship in the 19th and 20th centuries. The history of the Choctaw experience is significant as it explains the high frequency of rare disorders such as CAMT.
Objectives: The objective of this research is to identify common mutations in a specific population that cause CAMT.
Design/Method: This research was conducted through a retrospective chart review. Genetic testing for mutations in the MPL gene had been done on each patient with their consent.
Results: Despite being rare, five cases have been identified within the MBCI, four of which were diagnosed within the last 8 years. All five cases involve the R537W mutation in the MPL gene. This mutation has been described once in a single patient reported by Pemberton, et al. [2]. The pathogenicity of the mutation was unclear at the time of the report since another novel mutation (S179P) was found in cis with the R537W mutation. Four of our patients were compound heterozygotes for R90X and R537W mutations. One patient was homozygous for the R537W mutation. None had other mutations observed in the MPL gene.
Conclusion: Based upon genetic analysis of these five patients, it may be concluded that the carrier frequency and prevalence of disease are markedly increased within the Choctaw population. It is important to note that Mississippi is not the only state where Choctaw Native Americans reside and to spread awareness that CAMT is not such a rare disorder within this tribe. Ongoing research projects will focus on implementing screening at birth for all Choctaw newborns in the state of Mississippi.

Poster # 230

THROMBOTIC MICROANGIOPATHY AS THE PRESENTING MANIFESTATION OF COBALAMIN G DISORDER CAUSED BY NOVEL MUTATIONS OF THE MTR GENE

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Background: Thrombotic microangiopathy (TMA) is a constellation of microvascular thrombosis, microangiopathic hemolytic anemia, and thrombocytopenia. Untreated, TMA will lead to end organ damage and morbidity/mortality, necessitating rapid recognition and treatment of the underlying etiology. The most common causes of TMA in children include thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), drug-induced TMA, and complement-mediated TMA (also called atypical HUS). However, less common etiologies including disorders of cobalamin metabolism should be considered early, as targeted therapy for these disorders may be life-saving.
Objectives: To report a rare case of Cobalamin G disorder with previously unreported mutations in the Methionine Synthase (MTR) gene, compounded by a heterozygous mutation in the Methylmalonic Aciduria and Homocystinuria type C (MMACHC) gene, presenting as TMA with end organ damage; and to discuss the associated diagnostic and management challenges.
Design/Method: Retrospective chart review with clinical and laboratory data collection.
Results: An 8-month-old Hispanic male presented with severe TMA, hypertension, altered mental status, respiratory distress, and acute kidney injury. The patient progressed to respiratory and renal failure requiring ventilator support and continuous renal replacement therapy. He was initially managed with FFP infusions for possible congenital TTP, later ruled out by normal ADAMTS13 level. Further evaluation showed elevated homocysteine and low methionine levels, despite a previously normal cobalamin level, leading to strong consideration of inborn errors of cobalamin metabolism. Whole Exome Sequencing showed two novel compound heterozygous pathogenic MTR gene variants, c.2405+1G>A and c.2473+3A>G. A heterozygous pathogenic variant in the MMACHC gene (c.271dupA [p.V90fs]) was also found. The patient was subsequently managed with betaine and hydroxocobalamin, with gradual improvement.
Conclusion: Defects in MTR affect the cobalamin-dependent pathway of DNA synthesis which converts homocysteine to methionine, causing cobalamin G disorder, resulting in delayed psychomotor development, megaloblastic anemia, homocystinuria, and hypomethioninemia; which are not detected on routine newborn screens. We report TMA as the presenting manifestation of Cobalamin G disorder caused by novel compound heterozygous pathogenic variants of MTR gene. Our patient’s phenotype was more severe than previously described, possibly due to the additional heterozygous MMACHC gene variant. This case shows severe TMA as the presenting manifestation of cobalamin G disorder caused by novel compound heterozygous mutations of MTR gene with potential exacerbation due to the additional heterozygous MMACHC variant. Our case also illustrates the importance of entertaining a broad differential diagnosis and speedy evaluation of patients with TMA, as earlier identification and appropriate treatment can be life-saving in these rare disorders.

Poster # 232

TRANSITION OF ADOLESCENTS WITH CHRONIC BLOOD DISORDERS FROM PEDIATRIC TO ADULT CARE: ASSESSMENT OF PATIENT READINESS

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Background: There is significant awareness of the need for anticipatory guidance aimed at preparing adolescents for the transition from pediatric to adult-oriented health care, however, successful completion of this milestone remains challenging for adolescents with chronic blood disorders.
Objectives: The primary aim of this study was to assess adolescent perceived transition readiness and knowledge in 4 areas that should be mastered to ensure successful transition.
Design/Method: Patients with chronic blood disorders ages 14 years and older treated at a large tertiary center completed a transition readiness survey during their clinic appointments. Patients rated confidence in their ability to manage their own health and perceived readiness for transition on a scale of 0 to 10 (lowest to highest). Four essential areas for successful transition to adult health care, including (1) disease knowledge, (2) medication management, (3) tracking of medical information and appointments, and (4) insurance and privacy information, were assessed by the patients on a scale of 1 to 4 (1, No, I do not know; 2, No, but I am learning to do this; 3, Yes, I have started doing this; 4, Yes, I always do this when I need to). Descriptive statistics were used to summarize the data.
Results: Seven patients ages 15 to 19 were assessed in our pilot study and additional survey data is being collected at this time. Scores were high for confidence in the ability to manage their own health (median 7.5, range 5-10) and perceived transition readiness (median 9, range 5 to 10). However, overall scores in 4 essential areas for successful transition were low, with greatest deficiencies in tracking of medical information and appointments (median 2, range 1-4), and knowledge about insurance and privacy information (median 1, range 1-3).
Conclusion: Adolescents with chronic blood disorders feel relatively confident about their ability to manage their own health and perceive themselves as ‘ready’ for transition to adult care, however, a closer assessment of their transition readiness in 4 important areas showed great deficiencies. This study highlights the need for targeted improvements in the guidance of adolescents for successful transition to adult care.

Poster # 234

A PATIENT WITH ALPS-LIKE PHENOTYPE FOUND TO HAVE A HOMOZYGOUS LRBA DEFICIENCY ELEVEN YEARS AFTER INITIAL PRESENTATION

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Background: Defective expression of the LRBA (Lipopolysaccharide Responsive Beige like Anchor Protein) gene produces a deficiency of LRBA protein that leads to lack of CTLA4 expression. Lack of CTLA4 expression has been identified in a group of patients who have

presented with one or a combination of autoimmune cytopenia, inflammatory bowel disease, hypogammaglobulinemia, functional T and B -cell defects and aberrant autophagy
Objectives: To describe a patient with ALPS-like syndrome treated with immunosuppression for chronic thrombocytopenia, bowel inflammation and lymphoproplipheration for eleven years before he was found to harbor a mutation of the CVID type 8 (CIVD8) gene.
Design/Method: Case Report
Results: In 2004 a four-year old boy presented with chronic diarrhea and was diagnosed with Cohn's disease and was treated with mercaptopurine. At age 7, he developed ITP and autoimmune hemolytic anemia (AIHA). He was treated with IVIG and Prednisone. AIHA resolved but ITP and diarrhea (without detectable bacterial, viral or parasitic infection) persisted. Over the next several years he received MMF, Cyclosporine, tacrolimus and steroids. At the age 9 a course of Rituximab normalized platelet count for 8 months, after which thrombocytopenia recurred. Treatment with tacrolimus/prednisone/IVIG was started without benefit. In 2009, testing for ALPS ruled out elevated DNT (while immunosuppressed) and genetic markers associated with ALPS. Thrombocytopenia became symptomatic again and a second round of Rituximab was administered in June 2010. Patient developed gastric outlet obstruction resulting in severe refractory vomiting and malnutrition requiring parenteral nutrition. A gastric biopsy did not show CMV infection nevertheless our patient improved with Ganciclovir therapy and discontinuation of immunosuppressive drugs. He was started on Sirolimus and prednisone therapy after GI complications have resolved (October 2010). Sirolimus normalized platelet count (100,000 - 200,000/μL) for 28 months (February 2013). In May 2015 recurrent lymphadenopathy occurred and a second opinion was sought at Cincinnati Children's Hospital. At Cincinnati, patient was diagnosed with homozygous LRBA deficiency (PCR analysis C.1931dupC(pR645fs) confirming CVID8 with autoimmunity. All immunosuppressive medications were discontinued and treatment with a CTLA4-mimetic (Abatacept) was initiated. After therapy with Abatacept was started lymphadenopathy resolved immediately, platelet count increased to > 200,000/μL, and his diarrhea subsided. He has now been asymptomatic without infection or lymphoproliferation for almost 18 months.
Conclusion: LRBA deficiency should be considered in the diagnosis of ALPS-like presentations in whom a mutation in the FAS pathway is not identified. This report supports the phenotypic overlap of ALPS-like disorders and CIVD8 and beneficial effect of Abatacept therapy.

Poster # 236

EVALUATION OF SIGNIFICANCE OF PEDIATRIC HEMATOLOGY REFERRALS FOR ELEVATED PTT

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Background: Many surgeons will often screen with coagulation studies pre-operatively to assess the patient's risk of both intra and post-operative bleeding. Partial thromboplastin time (PTT) and prothrombin time (PT) screening will allude to the function of the coagulation proteins of the intrinsic and extrinsic clotting pathway. Deficiency of the clotting proteins in the intrinsic

pathway can result in prolongation of PTT. The use of routine pre-operative screening for bleeding disorders in pediatric patients is controversial and there is no set guidelines in how to work up patients pre-operatively. Prolonged PTT is a common indication for referral to the Pediatric Hematologist.
Objectives: Patients with prolonged PTT are theoretically at increased risk of bleeding, however not all deficiencies in the coagulation proteins will lead to clinical bleeding. This study aims to review the referrals to our hematology clinic for prolonged PTT and to assess the clinical correlation to the laboratory finding.
Design/Method: The study is a retrospective nonrandomized chart review to assess the severity of PTT prolongation and whether any bleeding disorder is diagnosed on further work up. Variables such as personal or family history of bleeding or easy bruising will be assessed to aid in the correlation between the clinical presentation and laboratory findings.
Results: Subjects are divided into those with negative or positive personal and/or family history of prolonged bleeding or easy bruising. Thus far in the research screening PTT in the absence of family and personal history of prolonged bleeding and easy bruising has not identified any patient with a bleeding disorder.
Conclusion: In conclusion the data is suggestive that laboratory screening in asymptomatic patients results in unnecessary referrals to the pediatric hematology clinic. This laboratory evaluation also delays necessary surgery for the patient, and an increased cost in working up patients.

Poster # 238

RESOLUTION OF ESSENTIAL THROMBOCYTOSIS IN TWO CHILDREN - ALTERNATIVE FORM OF MPN?

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Background: Essential thrombocytosis (ET) is uncommon in children. Many children with prolonged periods of thrombocytosis without a persistent secondary cause are diagnosed with ET. Their bone marrow features are consistent with ET, but often they are “triple-negative” for gene mutations frequently found in adults with ET (in JAK2, MPL, and CALR). The question as to whether these diseases in children are different than those in adults has been raised, and resolution of myeloproliferative neoplasms (beyond Down’s syndrome) has been reported only in children. This implies there may be a separate class of pediatric transient myeloproliferative conditions.
Objectives: To report two cases of children diagnosed with ET who later had spontaneous resolution of their thrombocytosis.
Design/Method: We evaluated two children diagnosed with ET who showed resolution of thrombocytosis over a period of years.
Results: Patient A presented at age 5 with a platelet count of 1,888 x 109/L. Bone marrow findings led to a diagnosis of ET. Platelet counts on hydroxyurea trended down initially and were maintained in the range of 500-700 x 109/L for a few years. She was weaned off hydroxyurea after 1 year. Five years after diagnosis, her bone marrow was unremarkable, and platelet count

was 378 x 109/L. Patient B presented at age 7 with a platelet count of 600 x 109/L; subsequent counts showed platelets from 1300-2500 x 109/L. Bone marrow findings led to a diagnosis of ET. His platelet count on only aspirin declined over time and ultimately normalized at 7 years after diagnosis, with his most recent count being 290 x 109/L. Repeat bone marrow examination was unremarkable.
Conclusion: These cases demonstrate two children with prolonged periods of thrombocytosis, originally identified during periods of mild illness that persisted long after resolution of initial illness. Bone marrow findings were consistent with ET but later showed normal megakaryocytes. While reactive thrombocytosis in children can last for months, it does not persist for years. The late resolutions of thrombocytosis raise the question of whether these two cases represent a form of transient myeloproliferative disease in children, or if the natural course of ET in certain children is different than in adults. It is possible that triple-negative disease in children represents a unique subset of ET in which the natural course may be spontaneous resolution. Close monitoring of children with prolonged thrombocytosis and further molecular research are needed to determine if ET in children is truly the same as ET in adults.

Poster # 240

COMPARISON OF COMPLETE BLOOD COUNTS IN BONE MARROW AND PERIPHERAL BLOOD SAMPLES FROM HEALTHY BONE MARROW DONORS

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Background: The bone marrow aspiration test is only performed in healthy people if they are bone marrow donors. Bone marrow cell populations has traditionally been assessed visually by light microscopy because most automatic blood cell analyzers cannot adequately capture erythroblasts and immature granulocytes; however, advances in modern hematology analyzer technology have improved detection of immature cells. These advances and the rapid availability of complete blood count (CBC) results can be advantageous for both patients and clinicians; however, CBC data for the healthy population are lacking.
Objectives: The objective of this study was to compare CBC results for bone marrow and peripheral blood samples from healthy bone marrow donors.
Design/Method: Bone marrow and peripheral blood from 40 healthy non-mobilized bone marrow donors were simultaneously analyzed in a DxH 800 (Beckman Coulter, Inc) automated analyzer. CBC results were compared statistically.
Results: Mean leukocyte, lymphocyte and neutrophil counts were all significantly higher in the bone marrow samples than in the peripheral blood samples (leukocytes 32,914±3,477 vs. 11,980±2,155, respectively, p=0.03; lymphocytes 9,941±3,658 vs. 3,161±390, p=0.02; neutrophils 27,284±5,240 vs. 7,597±1,784, p=0.001). Mean hemoglobin (Hb), hematocrit (Hct), and platelet count (Plt) were significantly higher in peripheral blood than in bone marrow (Hb 11.8±1.8 vs. 10.7±2.2 g/dL) respectively, p=0.04; Hct 35.3±5.1 vs. 30.1±5.1, p=0.03; Plt 303,650±18,264 vs. 176,430±11,762, p=0.02). Several parameters in the two sample types were correlated: Hb 0.53, p=0.02; Hct r=0.50, p=0.03; lymphocyte count r=0.70, p=0.001; monocyte count r=39, p=0.04; Plt count r=45, p=0.03.
Conclusion: To our knowledge, no previous study has investigated CBC values in healthy bone

marrow donors. In these donors, we found the three times higher differential leukocyte counts and slightly lower Hb and Plt count in bone marrow sample feature a higher proportion of immature nucleated cells than peripheral blood. These preliminary findings warrant further investigations to determine clinically useful metrics for healthy bone marrow cells, such as age-specific reference ranges. Our results need to be confirmed in a prospective study with a large number of healthy bone marrow donors.

Poster # 242

LONG-TERM THERAPY WITH DEFERASIROX IN YOUNG PEDIATRIC PATIENTS WITH TRANSFUSIONAL HEMOSIDEROSIS COMPLETING UP TO 5 YEARS OF TREATMENT IN THE OBSERVATIONAL ENTRUST STUDY

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Background: Regular supportive transfusion therapy from an early age is common practice in children with β-thalassemia major (βTM), sickle cell disease (SCD), and Diamond-Blackfan anemia (DBA). Patients accumulate iron, which may affect organ function and delay growth/development. Iron chelation therapy is often necessary from an early age, with lifelong requirements for patients who cannot be cured with hematopoietic stem cell transplantation. Deferasirox, a once-daily oral iron chelator, has demonstrated efficacy and safety in adult and pediatric patients with chronic iron overload.
Objectives: To report safety and efficacy outcomes in pediatric patients with transfusional hemosiderosis receiving up to 5 years of continuous deferasirox treatment in clinical practice.
Design/Method: Patients aged 2 to <6 years at enrollment were prescribed deferasirox according to local labels, with recommendations to adjust dose based on serum ferritin (SF) levels, therapeutic goals, tolerability, and weight gain. Patients were followed prospectively for 5 years in this observational study. Safety was evaluated by regular monitoring and recording of adverse events (AEs) in all patients who received ≥1 dose of deferasirox and had ≥1 postbaseline safety assessment. SF levels were also analyzed in all patients who received ≥1 dose of deferasirox.
Results: 267 patients (mean age 3.2 years) with βTM (n=176, 65.9%), SCD (n=52, 19.5%), DBA (n=12, 4.5%), and other anemias (n=27, 10.1%) were enrolled and received ≥1 deferasirox dose. Overall mean±SD deferasirox exposure was 44.1±21.2 months and mean±SD dose was 25.8±6.5 mg/kg/d. Dose was generally aligned with weight, although initial doses were suboptimal to manage iron intake and adjustments based on weight gain were delayed. 130 patients (49.8%) received deferasirox for ≥60 months; 122 patients (45.7%) discontinued treatment prematurely, most commonly because of loss to follow-up (n=19, 7.1%) and AEs (n=18, 6.7%). In the 130 patients exposed to deferasirox for 5 years, median SF levels decreased from 1777 ng/mL at baseline to 1414 ng/mL. 145 patients completed 5 years of follow-up and had AE data collected during this entire period. Most frequently occurring AEs with suspected relation to study drug were increased ALT (n=29, 20.0%), increased AST (n=12, 8.3%), vomiting (n=9, 6.2%), rash (n=6, 4.1%), and increased blood creatinine (n=6, 4.1%). Overall, there was a gradual decrease in number of patients experiencing drug-related AEs with each year of deferasirox exposure.

Conclusion: This long-term, observational study of deferasirox in pediatric patients supports previous findings indicating favorable safety and efficacy. Patients remaining on deferasirox benefited from sustained improvements in iron load.

Poster # 244

IMPROVED PATIENT-REPORTED OUTCOMES WITH A FILM-COATED VERSUS DISPERSIBLE TABLET FORMULATION OF DEFERASIROX: RESULTS FROM THE RANDOMIZED, PHASE II ECLIPSE STUDY

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Background: Patients with hematologic disorders such as transfusion-dependent thalassemia (TDT) and myelodysplastic syndromes (MDS) require long-term supportive therapy with iron chelation therapy (ICT) to remove excess iron and prevent organ failure. The once-daily dispersible tablet (DT) formulation of the iron chelator deferasirox has been available since 2005, offering an alternative to parenteral deferoxamine. However, barriers remain to patient adherence, including the need to take the drug in a fasting state, palatability, and gastrointestinal tolerability. A deferasirox film-coated tablet (FCT) was developed that can be taken orally, once daily, with or after a light meal.
Objectives: To report patient-reported outcomes during the ECLIPSE study.
Design/Method: ICT-naïve or pretreated patients aged ≥10 years, requiring ICT with deferasirox DT ≥30 mg/kg/d (TDT) or ≥20 mg/kg/d (MDS), with serum ferritin (SF) >1000 ng/mL, were enrolled. ICT-naïve patients were to receive deferasirox DT 20 mg/kg/d or FCT 14 mg/kg/d. ICT pretreated patients were to receive a deferasirox dose equivalent to their prewashout dose. Dose was adjusted based on SF and investigator's judgment after week 4 for ICT-naïve patients and after 3 months for ICT pretreated patients; dose adjustments for safety reasons were permitted at any time. Modified satisfaction with ICT (SICT) response scales to assess adherence, satisfaction/preference, and concern, and palatability questionnaires were completed at weeks 2, 3, 13, and end of treatment. Gastrointestinal symptoms diary was completed daily.
Results: 173 patients were enrolled; 87 were treated with FCT and 86 with DT. Twenty-one patients were aged 10 to 17 years. Completion rates for SICT and palatability questionnaires as well as gastrointestinal symptoms daily diary were similar for both formulations. FCT patients consistently reported greater adherence, greater satisfaction/preference, fewer concerns, and higher satisfaction on palatability scores compared with DT patients. The difference in score between DT and FCT was >1 point for all domains and palatability at most visits, indicating a clinically meaningful difference between formulations. Overall gastrointestinal summary scores were low for both formulations, indicating patients experienced little trouble/concern associated with gastrointestinal symptoms.
Conclusion: A clear preference in favor of deferasirox FCT was shown in all domains of the modified SICT. More patients were satisfied with deferasirox FCT compared with DT at all visits. Deferasirox FCT could offer patients an improved formulation that did not require administration in a fasting state, and had better palatability. Enhanced patient satisfaction with

the new deferasirox FCT formulation may improve adherence, thereby reducing iron overload–related complications.

Poster # 246

NEW FILM-COATED TABLET FORMULATION OF DEFERASIROX IS WELL TOLERATED IN PATIENTS WITH THALASSEMIA OR MDS: RESULTS OF THE RANDOMIZED, PHASE II ECLIPSE STUDY

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Background: Patients compliant with iron chelation therapy (ICT) experience improved organ function and survival. Once-daily deferasirox dispersible tablets (DT) have a well-defined safety/efficacy profile and, compared with parenteral deferoxamine, provide greater adherence, patient satisfaction, and quality of life. However, barriers to patient adherence still exist for deferasirox DT, including gastrointestinal tolerability and palatability, leading to development of a film-coated tablet (FCT).
Objectives: To evaluate safety of deferasirox FCT and DT formulations in patients with transfusion-dependent thalassemia (TDT) or low- to intermediate-risk myelodysplastic syndromes (MDS).
Design/Method: ICT-naïve or pretreated patients aged ≥10 years, requiring ICT with deferasirox DT ≥30 mg/kg/d (TDT) or ≥20 mg/kg/d (MDS), with serum ferritin (SF) >1000 ng/mL, were enrolled. ICT-naïve patients were to receive deferasirox DT 20 mg/kg/d or FCT 14 mg/kg/d. ICT pretreated patients were to receive DT or FCT dose equivalent to prewashout dose. Dose was adjusted based on SF and investigator's judgment after week 4 for ICT-naïve patients and after 3 months for ICT pretreated patients; dose adjustments for safety reasons were permitted at any time. Primary endpoint was overall safety, measured by frequency and severity of adverse events (AEs), and changes in laboratory values from baseline over 24 weeks.
Results: 173 patients were randomized 1:1 to DT or FCT. Twenty-one patients were aged 10-17 years. Mean daily deferasirox dose±SD over 24 weeks was 27.5±7.7 mg/kg/d (DT) and 20.8±5.4 mg/kg/d (FCT). Median duration of exposure was 168 and 169 days, respectively, for DT and FCT. Seventy-three (84.9%) DT and 77 (88.5%) FCT patients completed the study. Relative consumed tablet count was slightly lower for DT (85.3%) than FCT (92.9%). Absolute median change in SF at end of treatment was -85.5 ng/mL (2485 ng/mL at baseline) for DT and -350 ng/mL (2983 ng/mL at baseline) for FCT, corresponding to median relative change of -4.1% (DT) and -14.0% (FCT). AEs regardless of causality were reported in similar proportions of patients for each formulation. Fewer severe AEs were observed in FCT patients. Most common AEs for both formulations were consistent with known deferasirox safety profile. Notable laboratory evaluation frequencies were similar for both formulations.
Conclusion: Comparable FCT and DT safety profiles were observed in patients with TDT or low- to intermediate-risk MDS, consistent with known deferasirox profile. In patients with prior DT exposure, fewer gastrointestinal AEs were seen with FCT than DT. Patients receiving FCT had better compliance, continued longer on treatment, and experienced greater SF reduction.

Poster # 301

SYMPTOMS IN HOSPITALIZED ADOLESCENT AND YOUNG ADULT ONCOLOGY PATIENTS AT THE END OF LIFE

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Background: Adolescent and young adult (AYA) patients with cancer often experience a significant number of physical and psychological symptoms at the end of life (EOL) and many of these symptoms are poorly recognized, addressed, and treated. Symptoms can be the result of refractory or progressive disease and/or due to side effects from cancer-directed treatment. Control of symptoms at the EOL is important as parental perceptions of suffering are associated with distress and can complicate grief and bereavement.
Objectives: To further investigate the characteristics of patients with cancer aged 15 to 25 who died while inpatient at a pediatric oncology institution with a focus on identifying symptoms present during the last month of life (LMOL) and to compare symptoms in different patient populations.
Design/Method: A standardized data extraction tool was used to collect information about demographics, treatment, end-of-life characteristics, and symptoms during the LMOL for AYA patients who died while hospitalized between 2008 and 2014. Data on 24 symptoms were collected, 17 physical symptoms and 7 psychological symptoms.
Results: There were 69 AYA patients included in the analysis with a median age of 17.3 years. Fifty-nine percent of patients had a diagnosis of leukemia or lymphoma and 49% had received an allogeneic hematopoietic cell transplant. Forty-five (65%) of the hospitalized AYA patients died of progressive disease, 30 (67%) of which received chemotherapy in the LMOL. Patients had median of 11 symptoms documented during the LMOL. The three most common symptoms present were pain (99%), fatigue (86%) and edema (78%) and all three symptoms were persistent for >7 days. A median of 2 refractory symptoms were documented in this cohort with 86% of patients having at least one refractory symptom at the EOL. When compared to AYA patients that did not receive a transplant, those that had undergone an allogeneic transplant were more likely to have diarrhea (74% vs. 26%, $P<0.0001$) and less likely to have constipation (15% vs. 66%, $P<0.0001$) documented during the LMOL.
Conclusion: AYA patients with cancer that die in the hospital experience a large number of persistent symptoms, including those refractory to treatment at the end of life. Symptoms at the EOL may vary among patients based differences in disease and cancer-directed treatments. Prospective symptom and distress assessment using validated tools should be performed in all AYA patients with progressive disease with a goal to comprehensively address and treat distressing symptoms to improve patient and family quality of life.

Poster # 302

SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY (ROSAI DORFMAN DISEASE): DIAGNOSTIC AND TREATMENT MODALITIES FOR THIS RARE ENTITY REVISITED

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Background: Rosai-Dorfman Disease (RDD), also known as Sinus Histiocytosis with Massive Lymphadenopathy (SHML) is a non-Langerhans cell histiocytic disease resulting from the proliferation and accumulation of sinus histiocytes within lymph nodes. Extra-nodal involvement frequently occurs increasing morbidity and mortality. The most effective diagnostic and treatment modalities remain largely unknown.
Objectives: This report will focus on the diagnostic imaging, treatment, and outcomes for 3 cases of RDD. Imaging has typically utilized CT/MRI to detect extra-nodal involvement. However, the addition of FDG PET/CT scans has shown value in identifying lesions unidentified or ambiguous on other modalities. Additionally, chemotherapy used to target RDD has not consistently displayed regression of the disease lending credence to the pursuit of more successful treatment. Notably, Clofarabine has shown promise in the treatment of histiocytic disorders. This report will further describe the use of Clofarabine therapy and the potential for treatment refinement.
Design/Method: This case series review employed the use of medical records, radiology and pathology archives for 3 cases of RDD diagnosed at Cook Children's Medical Center occurring between the years 2010 and 2016. Methods of diagnosis, radiology, treatment, and follow up for each case were evaluated in the Electronic Medical Record (EMR) and combined with literature review in the analysis.
Results: This study included 3 female patients aged 4, 2 and 9 years with varying sites of extra-nodal involvement including the lung pleura, liver, bone, and paranasal sinus. FDG PET/CT detected disease involvement in 2 instances either not reported, or not felt to be significant on correlative CT imaging. Areas of involvement included the stomach/liver in Case 1, and the paranasal sinus in Case 3. Treatment with Clofarabine resulted in lesion resolution in Case 1 after completion of therapy; she remains in remission in her 4th year post therapy. Case 2 achieved resolution of lesions as well and is currently asymptomatic at 21 months off therapy. Case 3 has displayed decreased lesion avidity on PET/CT imaging suggestive of treatment response following three therapy courses. None of the patients developed complications from therapy requiring hospitalization, dose reduction, or therapy delay.
Conclusion: RDD is a rare entity with diagnostic and treatment modalities in evolution. The advent of FDG PET/CT scans have added utility which may serve more beneficial than CT in identifying extra-nodal involvement of RDD. Further, Clofarabine therapy has shown promising results as a successful chemotherapeutic treatment for extra-nodal RDD.

Poster # 303

LONG-TERM PULMONARY MORBIDITY OF RESPIRATORY VIRAL INFECTIONS DURING CHEMOTHERAPY IN CHILDREN WITH LEUKEMIA

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Background: Respiratory viruses are a common cause of infection in immunosuppressed children undergoing cancer therapy. Pulmonary sequelae have been documented following respiratory viral infections in both young infants and bone marrow transplant (BMT) recipients; however potential late effects in children undergoing chemotherapy have not been investigated. To date, the pulmonary function of cancer survivors treated without known pulmonary-toxic exposures have also been rarely assessed.
Objective: To evaluate the long-term pulmonary morbidity of respiratory viral infections during chemotherapy in children with acute lymphoblastic leukemia (ALL), treated without known pulmonary-toxic therapy.
Design/Method: Dual-site, historical prospective study of childhood ALL survivors, aged 7-18 years, > 6 months post-treatment. Exclusion criteria: pulmonary-toxic therapy as defined by the Children's Oncology Group, including craniospinal radiation; relapse; BMT; and proven bacterial/fungal respiratory infection during treatment. Subjects were classified into 'viral' or 'control' groups according to the presence of laboratory proven respiratory viruses during chemotherapy. Symptom questionnaires (Liverpool and ISAAC), and pulmonary function testing (spirometry, body plethysmography, diffusing capacity, forced oscillation technique) were performed to American Thoracic Society standards.
Result: Fifty-four patients (31 viral; 23 control) were recruited: median (range) age 11.2 (7.2-18.1) years, and at 4.9 (0.5-13) years post-therapy. Children with respiratory viral infections had more respiratory symptoms, particularly wheeze (OR 3.0, 95%CI: 0.9-10.0) and cough (OR 2.7, 95%CI: 0.8-9.5). No differences in physiological lung function were observed, and all mean pulmonary function results were within normal limits. Overall, abnormalities were detected in 17 (31%) individuals, with the most common being DLCO impairment (60-80% predicted) and reduced respiratory reactance at 5Hz (z score <-1.64).
Conclusion: In this study, children with respiratory viruses during chemotherapy had more long-term respiratory symptoms but no increase in static lung function defects. Overall, pulmonary abnormalities were detected in nearly a third of ALL survivors, treated without known pulmonary-toxic therapy, up to 13 years post-treatment. Prospective, longitudinal studies with viral surveillance and more comprehensive physiological measures of dynamic and peripheral lung function are warranted to further investigate the aetiology and clinical significance of pulmonary abnormalities in cancer survivors.

Poster # 304

THROMBOTIC MICROANGIOPATHY CAN OCCUR BEFORE TRANSPLANT IN CHILDREN WITH HLH

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare clinical syndrome of excessive immune activation, characterized by signs and symptoms of extreme inflammation, largely driven by interferon γ and other pro-inflammatory cytokines. Diagnostic criteria for HLH include either a molecular HLH diagnosis or five of the following eight criteria: fever, splenomegaly, cytopenias, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low or absent NK cell activity, elevated ferritin, and elevated sIL-2 receptor (sIL2R). These criteria are not specific and there is considerable overlap with other conditions. We present here a cohort of six patients referred to our center for evaluation of HLH, found also to have evidence of thrombotic microangiopathy (TMA).
Objectives: To report an association of TMA in patients who present as HLH.
Design/Method: Retrospective chart review of patients with HLH and evidence of TMA.
Results: All six patients met clinical HLH criteria, four with 6/7 criteria and two having all 7 criteria. Fever, splenomegaly, cytopenias, hyperferritinemia, and hypertriglyceridemia were present in all six patients. Hemophagocytosis was identified in the bone marrow in 3/6 and in the cerebral spinal fluid of one patient. Four patients received HLH-directed therapy prior to arrival, and one patient was not treated following evaluation. HLH genetic studies were done on 3/6 patients with no pathologic mutations identified. All six patients also met clinical criteria for TMA including presence of schistocytes, elevated LDH for age, thrombocytopenia, Coombs negative hemolytic anemia, proteinuria, and hypertension. Additionally, 4/5 patients tested had terminal complement activation (elevated C5b-9). All six patients required ventilator support, 5/6 needed renal replacement therapy, and one needed ECMO. Four patients were treated with eculizumab for TMA and one with therapeutic plasma exchange. Three patients are alive: two recovered after eculizumab and one received HSCT. Three of the five tested patients were found to have complement gene variants previously reported in aHUS.
Conclusion: TMA is likely initiated by endothelial damage, and the high levels of pro-inflammatory cytokines seen in HLH are a potent cause of endothelial injury in susceptible individuals. HLH can cause liver failure but rarely causes direct renal or pulmonary failure, and TMA in addition to HLH should be considered in children with multi-organ failure. Early institution of complement blocking therapy may improve clinical outcomes in these patients.

Poster # 305

CLINICAL CHARACTERISTICS AND OUTCOME OF RHINO-CEREBRAL FUNGAL INFECTION IN CHILDREN WITH HEMATOLOGIC MALIGNANCIES

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Background: Children with hematologic malignancies are especially vulnerable to fungal infection; by virtue of their disease process and the intensive chemotherapy they receive. Rhino-cerebral fungal infection is rare but requires careful attention and prompt management due to its almost deadly outcome.
Objectives: To evaluate the clinical characteristics and outcome of rhino-cerebral fungal infection in children with hematologic malignancies.
Design/Method: Retrospective data analysis of patients with hematologic malignancies who had pathologically proven rhino-cerebral fungal infection through the period from July 2007 to

December 2015.
Results: 34 patients were diagnosed with fungal sinusitis. Of them, 5 patients (15%) had intracranial extension and were diagnosed during induction/consolidation chemotherapy for treatment of Acute Lymphoblastic Leukemia (ALL). Clinically; all patients had fever and neutropenia, three had facial edema and necrotic patches and one had focal neurologic deficits. Three patients had histo-pathologically proven mucormycosis and two had aspergillosis with positive β – D glucan test. All patients had incomplete surgical debridement due to intracranial extension and all except one died. The remaining 29 patients (85%) had ALL n= 16 (55%) , acute myelogenous leukemia (AML) n= 11 (38%), 2 patients had non Hodgkin's lymphoma and mixed phenotype acute leukemia. 24 patients were undergoing induction/consolidation chemotherapy (82.8%) and 5 (17.2%) were receiving salvage for refractory/relapsing disease. All patients were febrile, 17 (58.6%) were neutropenic, 7 (24%) had iron overload, 6 (20.6%) were ICU admitted and 3 (10.3%) had uncontrolled hyperglycemia. Eight patients (27.5%) had facial edema, 18 (62%) had necrotic tissue, 3 (10.3%) had perforated hard palate and another 3 (10.3%) had bone erosion. Eleven patients (37.9%) had lung lesions on chest scans and one patient (3.4%) had retinal involvement in addition. Mucormycosis was documented in 15 patients (51.7%), coupled with Aspergillus infection in 4 cases and with Candida in one case. Isolated Aspergillus infection was documented in 9 patients (31%), while mixed Aspergillus and Candida infection in 2 patients (6.9%). Of the 29 patients who didn't have intracranial extension, 15 (51.7%) had surgical debridement, one of them died due to disseminated fungal infection. Fourteen patients (48.3%) were not eligible for surgical debridement, of them 6 patients died despite maximal supportive care. All patients received liposomal amphotericin -B empirically till pathology result and those who were diagnosed with aspergillosis were shifted to therapeutic voriconazole.
Conclusion: Early surgical debridement, proper antifungal therapy and reversal of the underlying risk factors are of paramount importance to improve outcome of rhino-cerebral fungal infection.

Poster # 306

PRF1-RELATED FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYCTOSIS IN A PAKISTANI FAMILY: IMPORTANCE OF MOLECULAR TESTING

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Background: Mutations in PRF1 (Perforin gene) are the commonest cause of familial hemophagocytic lymphohistiocytosis type-2 (FHL-2). Patients with severe perforin deficiency usually present within the first year of life with severe clinical manifestations. However, delayed presentations have been reported with hypomorphic mutations.
Objectives: This report reviews the importance of molecular testing in familial hemophagocytic lymphohistiocytosis type-2 (FHL-2) especially with late onset atypical presentations.
Design/Method: Case report.
Results: We report a family with perforin deficiency due to 2 missense mutations presenting with delayed onset and atypical clinical presentation. The proband presented at 23 years of age with fever, lymphadenopathy, splenomegaly and mild pancytopenia. His lab workup revealed

hypofibrinoginemia, hyperferritinemia, hypertriglyceridemia and deranged liver function studies. Thus he met clinical criteria for HLH. His family history revealed 3 siblings who died in their late teens with similar symptoms, which raised a strong suspicion for FHL. Molecular testing was performed at Prevention Genetics, using their FHL-NGS panel, which includes PRF1, UNC13D, STX11, STXBP2, XIAP, SH2D1A, RAB27A, LYST and AP3B1. This revealed 2 variants of unclear significance (VUS) in PRF1, which were both suspicious for being pathogenic. The p.Trp129Ser variant had been reported previously, whereas the p.Ser326Pro variant was novel. Testing of other family members revealed both heterozygous carriers, as well as a sibling who carried both variants but was asymptomatic. Our patient tolerated HLH therapy followed by conditioning regimen and underwent allogeneic HSCT (Hematopoietic stem cell transplantation) from his (Human leukocyte antigen) HLA-matched sibling who carried neither mutation. Unfortunately, he had lack of engraftment, followed by a massive GI bleed, and died of hemorrhagic shock.
Conclusion: Molecular testing not only enabled us to appropriately diagnose and manage our patient, but also ensured that the non-affected, non-carrier sibling could be the donor for HSCT. It also enabled us to counsel and do appropriate surveillance for the sibling who was at risk for developing symptoms as well as the heterozygous carriers who were at risk of having future children with the disorder.

Poster # 307

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) IN PEDIATRIC CANCER PATIENTS

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Background: Posterior reversible encephalopathy syndrome (PRES) is associated with a range of medical conditions and medications.
Objectives: In this retrospective analysis we attempted to identify predisposing factors for PRES in children with cancer on chemotherapy.
Design/Method: We identified 19 patients, 4 females and 15 males. These patients were diagnosed with PRES on clinical and radiological features. Patient charts were reviewed from January 2013 to June 2016 after authorization from the Institutional review board (IRB).
Results: The average age of patients with PRES was 7-years. Primary diagnosis of these patients included non-hodgkin lymphoma (n=9), acute pre-B-leukemia (n=5), relapsed pre-B-leukemia (n=2), hodgkin-lymphoma (n=2) and Ewing sarcoma (n=1). PRES occurred during induction chemotherapy in 12 patients. Sixteen patients had hypertension when they developed PRES. Most of these patients (n=14) were on steroids when they were diagnosed with PRES. Common clinical features included hypertension, seizures and altered mental status. Excluding 3 patients all others required anti-epileptic therapy. 10 of these patients got re-imaged with an MRI. Ten of our patients are still alive.
Conclusion: PRES is becoming a commonly recognized complication in pediatric patients with cancer. Patients presenting to our center with signs and symptoms of hypertension, seizures, visual loss or altered mental status get an MRI. PRES was mostly seen in patients undergoing

systemic induction chemotherapy, intra-thecal chemotherapy and on steroids. Despite reversal of clinical and radiological findings most patients could not be weaned off anti-epileptics.

Poster # 308

THE USE OF ANAKINRA (INTERLEUKIN-1 RECEPTOR ANTAGONIST) IN THE TREATMENT OF SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Background: Hemophagocytic Lymphohistiocytosis (HLH) can be familial or secondary, often triggered by infection or malignancy. HLH is characterized by a cytokine storm, which can result in multiorgan failure and death. HLH-04 therapy includes corticosteroids, cyclosporine, and etoposide. However, HLH-04 is associated with significant morbidity and mortality. Successful treatment of HLH in the setting of rheumatic disease, called Macrophage Activating Syndrome (MAS), has been reported using anakinra, a recombinant interleukin-1 receptor antagonist. Given the short half-life, wide therapeutic index, and superior side effect profile of anakinra compared to standard HLH therapy, we explored the use of anakinra in our patients with secondary HLH (sHLH).
Objectives: To report our experience treating six sHLH patients with anakinra.
Design/Method: Between December 2014 and August 2016, six consecutive pediatric patients diagnosed by criteria for HLH were treated with anakinra. Anakinra dosing started at 5-10 mg/kg/day prior to, concurrently, or after dexamethasone (10 mg/m2/day). Therapy escalation was planned for no improvement, clinically or by laboratories within 2 days. Both medications were eventually weaned based on clinical and laboratory response.
Results: Five of six patients were treated with anakinra and dexamethasone, and one with anakinra alone due to active CMV pneumonitis. The median age of diagnosis was 1.8 years (range, 0.8–14.9). None had CNS disease. No pathogenic mutations associated with HLH were identified, but 2 of 6 possessed genetic variants (PRF1 and LYST) of unknown significance. Infectious workup identified a potential viral trigger for 4 patients. Average treatment duration was 8 weeks with 6-24 months of follow-up. All patients showed complete resolution of clinical symptoms without HLH recurrence. One patient had erythroid leukemia and expired 7 months after diagnosis. Laboratory parameters normalized for all patients, except the erythroid leukemia patient (persistently elevated ferritin) and another had mildly elevated soluble CD25 without other signs of recurrence/inflammation. Anakinra was well tolerated, and no significant adverse effects were seen. None needed escalation of therapy to include cyclosporine or etoposide.
Conclusion: Initial treatment with anakinra (with or without dexamethasone) is a feasible treatment approach for patients with secondary HLH and may allow for avoidance of etoposide/cyclosporine. Formal guidelines to escalate therapy in patients without response need to be established. A clinical trial to test the use of anakinra as a first line agent for sHLH is underway.

Poster # 309

ABERRANT PRECURSOR B LYMPHOID BLAST POPULATION IN A PATIENT WITH JUVENILE MYELOMONOCYTIC LEUKEMIA

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Background: Juvenile myelomonocytic leukemia (JMML) is a rare mixed myelodysplastic/myeloproliferative neoplasm seen in early childhood. JMML, in general, is a poor prognosis disease, including risk of transformation to acute leukemic blast crisis in approximately 15% of patients. Like adult chronic myeloid leukemia (CML) the blast phase of JMML is typically myeloid, however B and T cell transformations have been reported. Interestingly, in CML, a minority of patients will have a small aberrant B-lymphoblast population that does not inevitably herald progression to B-lymphoblastic blast crisis, however this has never been reported in JMML.
Objectives: To describe a novel case of immunophenotypic detection of an aberrant population of precursor B lymphoid blasts in a child with JMML
Design/Method: Review of literature and medical records at Texas Children's Hospital, Houston, TX.
Results: An 11-month-old boy presented with splenomegaly, thrombocytopenia, neutropenia and monocytosis. Bone marrow findings were consistent with JMML. Flourescent in-situ hybridization (FISH) showed monosomy 7 in 74% of cells. Next generation sequencing revealed a KRAS p.G12A mutation (allele frequency- 35%). Due to persistent monosomy 7, mutant KRAS and lack of an appropriate marrow donor, we pursued hypomethylating agent, 5-azacitidine. Surprisingly, we were halted by detecting a B lymphoid blast population (6%) with characteristic flow findings, including positive CD45 (dim), CD19, CD10, CD20, CD22, CD34, HLA-DR, CD52, CD99, CD58 and CD38. Additionally, a new partial CDKN2A deletion was detected by FISH in 10% of cells. These findings were concerning for an emerging precursor B-acute lymphoblastic leukemia, possibly driven by the new CDKN2A deletion. However, after flow sorting the aberrant B lymphoblast population, the partial CDKN2A deletion was present in only 1.25% of these cells, whereas 100% were positive for monosomy 7 suggesting this population had emerged from his original JMML clone. A reanalysis of flow from a 4-month prior marrow revealed the presence of this same aberrant B lymphoblast population with similar frequency. The stability of this population over the course of months was inconsistent with an evolving lymphoid blast crisis. Thus, we initiated treatment with azacitidine. After one cycle, CDKN2A deletion resolved. The patient achieved molecular and cytogenetic remission after 6 cycles of therapy. The aberrant B cell population steadily declined to 0.02% over 12-months.
Conclusion: While longer follow up and additional patients will be necessary to reach definitive conclusions, our case suggests that the immunophenotypic detection of a small, stable abnormal B-lymphoblast population in patients with JMML does not inevitably herald progression to B-lymphoblastic phase.

Poster # 310

IBRUTINIB SIGNIFICANTLY ENHANCES PROGRAMMED CELL DEATH AND

OVERALL SURVIVAL IN BURKITT LYMPHOMA (BL) NSG XENOGRAFTS: A PRE-CLINICAL STUDY

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Background: Burkitt Lymphoma (BL) represents the most common Non-Hodgkin Lymphoma (NHL) in children aged 5-14 years. (1) Children and adolescents with recurrent/refractory BL continue to have poor outcomes,(2) emphasizing the need for novel therapeutic agents. Bruton's Tyrosine Kinase (BTK), a component of the B-cell receptor (BCR), regulates growth and survival of normal and malignant B-cells. Ibrutinib, a selective and irreversible BTK inhibitor, is effective in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL). (3, 4)
Objectives: To investigate the efficacy of ibrutinib alone and in selective adjuvant combinations against BL cells in-vitro and in a human BL xenografted immune-deficient NSG mouse model.
Design/Method: Raji and Ramos (BL) cells were treated with and without ibrutinib (0-10uM, generously provided by Janssen R&D LLC) alone and in combination with dexamethasone, rituximab, obinutuzumab, carfilzomib, idelalisib, ABT-199 and doxorubicin. Cell proliferation was assessed using MTS assay. The IC50 values were determined with CompuSynTM software (5) based on data from MTS assay. Raji-Luc xenografted NSG mice were generated as we have previously described. (6) Mice were treated with ibrutinib alone (12.5 mg/kg) or in combination with the drugs listed above and compared to IgG or PBS (control) treatment. Drugs were given by oral gavage or intraperitoneal (i.p.) injection based on the route of drugs. Survival rates were determined by Kaplan-Meier method and differences evaluated by log-rank test using the Prism Version 6.0 software.
Results: We observed a significant reduction in p-BTK in both cell lines treated with 0.1 uM ibrutinib ($p < 0.001$). A significant decrease in proliferation was observed in both cell lines with ibrutinib treatment compared to DMSO, with IC50 values of 5.20 uM for inhibition of Raji and 0.868uM for inhibition of Ramos cell proliferation ($p < 0.05$). Moreover, we observed a significant decrease in cell proliferation as well as significant decrease in IC50 of ibrutinib in combination with dexamethasone, rituximab, obinutuzumab, carfilzomib, doxorubicin ($p<0.001$), and ABT-199 ($p<0.05$). In-vivo studies demonstrated that ibrutinib treated mice had a significantly prolonged survival compared to PBS controls, with median survival of mice following ibrutinib treatment 32 days compared to 24 days in PBS controls ($p<0.02$).
Conclusion: Ibrutinib warrants further investigation in BL as an adjuvant therapeutic agent.

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Poster # 311

TRANSIENT MONOSOMY 7 ABNORMALITY IN CHILDREN AND ADOLESCENTS: A REVIEW OF THE LITERATURE

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Background: Childhood transient monosomy 7 is uncommon. Only case reports/series have been reported.
Objectives: Improved characterization may allow identification of clinically predictive features.
Design/Method: PubMed was searched with terms: children, transient, monosomy 7. Cases in children/adolescents up to 21 years were included. Transient was defined as presence with resolution.
Results: 17 cases were identified. Two populations emerged: de novo (n=9) and secondary (n=8). In de novo, male:female ratio was 1.25:1. At diagnosis, all patients were less than 3 years with average age 16.7 months. Presentations included fever/viral symptoms (7/9), and cytopenia signs/symptoms (2/9). Hepatosplenomegaly was noted in 3/9. All complete blood counts showed cytopenia: pancytopenia (4/9), thrombocytopenia with or without anemia (5/9). All bone marrow evaluations revealed hyperplasia and/or dysplasia. Average monosomy 7 marrow burden was 60%. Interventions included transfusions (3), IVIG (1), splenectomy (1), chemotherapy (1). Three patients had no intervention. Time to resolution averaged 19 months with range 2 months to 4 years. No recurrences. Seven cases had greater than 1 year follow-up, two cases apparently well at last follow-up at less than 1 year. Secondary monosomy 7 developed in patients with aplastic anemia (2/8), solid tumors (2/8), leukemia (1/8), lymphoma (1/8), solid organ transplant on immunosuppression (1/8), and EBV infection (1/8). Male:female ratio was 1.67:1. Average age at diagnosis was 10.5 years. Presentations included cytopenia on routine surveillance (5/8), evidence of infection (3/8; zoster, varicella, EBV). 1 of 5 patients with reported physical examinations showed hepatosplenomegaly and lymphadenopathy. All 6 patients with reported blood counts had cytopenias: pancytopenia (3), thrombocytopenia with or without anemia (2), and anemia alone (1). Bone marrow evaluations appeared morphologically normal in 2 whereas 4 had evidence of dysplasia/dyspoiesis and/or hypo/hypercellularity. Average monosomy 7 marrow burden was 55%. Interventions included medication changes (3), IVIG (1), bone marrow transplantation (1), chemotherapy (1). Two patients had no intervention. Time to monosomy 7 resolution averaged 7 months with range 2 months to 1 year. Monosomy 7 recurred in 2 patients; both subsequently succumbed to infectious complications related to underlying diagnosis and treatment. Follow-up greater than 1 year without recurrence was documented in 3/8. There was no information regarding follow-up of 3 patients.
Conclusion: Transient monosomy 7 can occur de novo or secondary. While presentations were similar, de novo cases were younger with longer duration to resolution. Careful watchful waiting may be appropriate for children presenting with monosomy 7 to identify those who will not progress to MDS and leukemia.

Poster # 312

LENGTH OF STAY DIFFERENT, WHILE TREATMENT-RELATED COMPLICATIONS SIMILAR IN PEDIATRIC AND AYA LYMPHOMA PATIENTS IN U.S. CHILDREN'S HOSPITALS

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Background: Adolescent and young adult (AYA) cancer patients have been shown to have unique clinical characteristics and inferior outcomes compared to younger patients. More than 81,000 new cases of lymphoma, Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL), are diagnosed every year, many of whom are AYA patients treated at pediatric hospitals. It is important for pediatric providers to understand the impact of increasing age on complications, costs, and outcomes.
Objectives: To determine if AYA patients with lymphoma have increased health care utilization and treatment-related complications as compared to younger patients.
Design/Method: Data were obtained from the Pediatric Health Information System for lymphoma admissions at 49 free-standing US children's hospitals from 2009-2015. Patients were followed for 1 year from their first encountered admission for lymphoma and had to have at least three unique admissions with a lymphoma diagnostic billing code during the study period to be included. Patient demographics, morbidities, and hospital utilization were compared in patients 0-14 and 15-30 years using non-parametric methods.
Results: We identified 1608 unique pediatric patients and 1169 AYA patients with lymphoma. Mean 1-year length of stay (LOS) days was statistically greater in the pediatric age group versus the AYA group (32 and 26 days, $p < 0.0001$). Cost was statistically higher in pediatric patients for all categories. Most of the more common cancer treatment-related complications, such as mucositis, diarrhea, nausea and vomiting, and bacterial infections had similar frequencies between the two groups, with the exception that fever and neutropenia admissions were more likely encountered in younger patients. Thrombosis, septic shock, and pain were more common in AYA patients.
Conclusion: In U.S. children's hospitals, AYA lymphoma patients had a shorter LOS, and did not have an increased risk of the most common treatment-related complications as compared to younger patients. Longer LOS and increased cost in the pediatric group may be related to more inpatient therapy in younger patients, while AYA patients may pursue more outpatient therapy. Finally, the incidence of febrile neutropenia may be skewed due to the possibility that older patients do not always report their fevers in order to avoid admission.

Poster # 313

NOVEL INTERVENTIONS FOR TREATMENT OF CANCER AND BLOOD DISORDERS IN PATIENTS WITH AUTISM

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Background: Autism spectrum disorder is a severe, lifelong, neurodevelopmental disorder characterized by impairments in social interactions and communication, with restrictive and repetitive behaviors1. Autism results in varying levels of disability in functioning1. We have treated 5 patients with autism and cancer or blood diseases at the Medical university of South Carolina (MUSC). There is no literature on successful interventions for these challenging patients. The highly variable manifestations of Autism make standardizing care difficult.

Treating patients with Autism poses unique challenges that require innovative thinking.
Objectives: We sought to describe the social, medical, surgical, environmental and medication interventions that our series of patients required to complete their treatment at our institution. We hope this description will help our colleagues.
Design/Method: We reviewed the medical records of five patients with Autism who received cancer treatment and/or bone marrow transplantation at MUSC from January 2011- December 2016.
Results: Our 5 patients were treated for: Burkitt lymphoma (n=1), Diffuse large B cell lymphoma (n=1), Acute lymphoid leukemia (N=2), relapsed Acute lymphoid leukemia (n=2) and Immune thrombocytopenic purpura treated with BMT (n=1). We grouped our interventions into 5 categories. All of our patients had at least 1 intervention from all of the groups listed. 1) Social: parental involvement to minimize changes to established routine. 2) Surgical: we preferentially placed ports, but 3/5 patients required broviacs due to treatment plans. 3) Medical: we used a multidisciplinary approach for patients including Psych, PICU staff, Developmental pediatrics, and our Pharm D. 4) Environmental: Modifications included padding to beds, bedside commodes, and restraints. And 5) Medication: our patients required a variety of medications including: Haldol, abilify, risperidone, and melatonin. With these interventions our patients were able to receive the chemotherapy needed to treat their cancer and blood diseases. Three of 5 patients are alive and in remission. One patient succumbed to relapsed leukemia, and one patient is still undergoing treatment.
Conclusion: Autism is vastly heterogeneous and presents unique obstacles to providing cancer treatment. We recommend G-Tube placement to be beneficial for all patients. We recommend pediatric Oncologists creatively address the aggressive behaviors and social anxieties that are part of this disease. Co management with psychiatry, behavioral pediatrics and child life is integral to providing safe and curative treatment. The interventions described were used at our institution to meet the unique challenges of providing treatment for our patients with Autism and Cancer or blood disorders. (Poustka Curr Top Beh Neuroscience, 2015)

Poster # 314

CLINICAL FEATURES AND TREATMENT OUTCOMES OF CHILDREN WITH ANAPLASTIC LARGE CELL LYMPHOMA IN PAKISTAN: A MUTLICENTER STUDY

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Background: Anaplastic large cell lymphoma (ALCL) is a rare disease in children accounting for 10% to 15% of all childhood non-Hodgkin Lymphomas. The most common clinical features include a generalized adenopathy with the frequent association of B symptoms and involvement of extra nodal sites such as the skin, liver, lung, soft tissues, and bone. Treatment options differ among various study groups and there is still no consensus regarding the standard treatment for ALCL.
Objectives: Due to lack of data on ALCL outcomes in low and middle income countries, we proposed to study the clinical features and treatment outcomes of children with ALCL at two major pediatric oncology centers in Pakistan.

Design/Method: We included patients treated from January 2005 to December 2015 at Aga Khan University Hospital and Indus Children Cancer Hospital with a histologically confirmed diagnosis of anaplastic large cell lymphoma. Case records of all patients were analyzed for demographic profile, clinical features, pathology, imaging studies, toxicity and management plans. Kaplan-Meier curves were created to assess overall survival (OS) and event free survival (EFS) with relapse and death as outcomes.
Results: Thirty-three patients met inclusion criteria. Twenty-Five (75.25%) were male and 8 (24.2%) were female. Cervical node 12 (36.3%) was the most common site of presentation. Advanced disease was seen in 22 (66.6%) (Stages III and IV) whereas 10 (30.3%) were standard risk (Stage I and stage II) while status of one patient was unknown. Fourteen (42.4%) were treated on ALCL-99 protocol, 10 (30.3%) on MCP-842 Regimen (a multi-agent alkylator based therapy), 3 (9%) on APO (doxorubicin, prednisone, vincristine) regimen and 6 (18%) were abandonments. CNS and bone marrow involvement was present in 2 patients each (6%). Five-year overall event-free survival and overall survival were 82.5% (95%CI: 44.4%-95.3%) & 68.6% (95%CI: 47.7%-82.5%) respectively. A total of 18 events occurred; 2 patients experienced relapse (6%), 9 (27.7%) treatment related mortality (TRM), 1 (3%) mortality at the time of diagnosis and 6 (18%) abandonments.
Conclusion: Significant therapy related mortality was observed with the regimens used in our analysis. Majority of our patients received therapy per ALCL 99 and MCP-842 regimen. Treatment abandonment and therapy related toxicity is the major barrier in improving the outcomes in lower middle income countries. Less intensive outpatient regimens with reduced toxicity, such as the APO regimen may be more suited for our set up. This may decrease the number of hospitalizations, hence reducing treatment abandonment as well.

Poster # 315

NILOTINIB IN PEDIATRIC PATIENTS WITH PHILADELPHIA CHROMOSOME-POSITIVE (PH+) CHRONIC MYELOID LEUKEMIA (CML) OR PH+ ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): A PHARMACOKINETIC STUDY

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Background: Nilotinib is a treatment option for adults with Ph+ CML and has demonstrated activity in adults with Ph+ ALL.
Objectives: This phase 1 study evaluated nilotinib in pediatric patients with Ph+ CML/ALL.
Design/Method: Eligible patients were 1-<18y and had newly diagnosed Ph+ CML in chronic phase (CML-CP), Ph+ CML-CP/-accelerated phase (AP) and resistance/intolerance to imatinib/dasatinib, or relapsed/refractory Ph+ ALL. Patients were assigned to 2 cohorts by age (Group 1 [G1], 1-<10y; G2, ≥10-<18y) and received nilotinib 230mg/m2 BID (rounded to nearest 50mg, based on 400mg BID adult dose scaled to body surface area [BSA]) for ≤24 28-day cycles (1 dose given on Cycle 1 Day 1 [C1D1]). Primary objective was to characterize

nilotinib pharmacokinetics. Single-dose parameters were calculated from C1D1 pharmacokinetic profiles. Steady-state parameters were derived from trough concentrations on C1D8, D15, D22, and D28 and compared with reference data from adult patients given nilotinib 400mg BID. Efficacy (best response per response category) and safety (adverse events [AEs]) were assessed.
Results: Fifteen patients enrolled (median [range] age, 9 [5-17]y): G1, 8 (5 CML, 3 ALL); G2, 7 (6 CML, 1 ALL). All patients with CML were in CP; 2 patients with ALL had active leukemia and 2 were in remission. Single-dose pharmacokinetics were generally comparable between G1 and G2. Steady-state area under the concentration-time curve was slightly lower, and BSA-adjusted systemic clearance was slightly higher, in pediatric vs adult patients; geometric mean ratios (90% CI) were: all patients, 0.86 (0.70-1.06) and 1.30 (1.04-1.62); G1, 0.89 (0.68-1.15) and 1.28 (0.97-1.68); G2, 0.84 (0.65-1.09) and 1.32 (1.01-1.74). Among 11 patients with CML, responses were: complete hematologic response (confirmed) or better, 10; complete/partial/minor cytogenetic response (CyR) or better, 4/1/1 (another 4 had complete CyR at baseline); major molecular response (MMR), 3. No patient progressed to AP/blast crisis. Responses among 4 patients with ALL were: complete remission (CR) with platelet recovery, 3; stable disease, 1. Eight patients discontinued early: new cancer therapy, 6 (CML: 5 had inadequate responses [no MMR or substantial BCR-ABL1 reduction]; ALL: 1 had CR); AEs, 1; disease progression, 1. All patients experienced ≥1 AE; 6 had grade 3/4 AEs (hematologic, 2 [neutropenia]). Five patients had serious AEs (all resolved); 1 discontinued due to multiple AEs. No deaths were reported.
Conclusion: In pediatric patients with Ph+ CML/ALL, nilotinib 230mg/m2 BID provided steady-state exposure generally comparable to that in adults given 400mg BID and demonstrated efficacy, with no new safety concerns.

Study Sponsor: Novartis

Poster # 316

A RARE PRESENTATION OF PLASMABLASTIC LYMPHOMA IN A 12YO FEMALE WITH ACQUIRED IMMUNODEFICIENCY SYNDROME

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Background: Human Immunodeficiency Virus (HIV) is a deadly virus that currently affects 38.6 million people worldwide, having killed more than 25 million people since the epidemic began. This virus leads to devastating immunosuppression targeting CD4+ T-cell function, making the host increasingly susceptible to opportunistic infections and malignancy. HIV-infected children have a 40x increased risk of developing malignancy compared to non-infected children. Roughly 80% of these cancers are Non-Hodgkin's Lymphoma, primarily Burkitt's lymphoma. Plasmablastic Lymphoma (PBL) is a very aggressive disease seen in only 2% of pediatric HIV-related malignancies; it is most commonly seen in adults with a median age of diagnosis of 42 years. While there have been advances in highly active antiretroviral therapy (HAART) and chemotherapy, the prognosis remains dismal with a 25% 3-year overall survival. We present the rare case of a young 12 year old Uzbekastani female with HIV/AIDs and multiple prior HIV-related complications who presented with a rapidly progressive left maxillary mass

who was diagnosed with stage IV PBL.
Objectives: Our case report serves to highlight the rarity of a pediatric case of PBL, as this disease is primarily seen in adults. We further aim to determine if she can achieve and maintain complete remission, as PBL is often refractory to treatment.
Design/Method: ENT performed a biopsy whose pathology showed PBL. Tumor staging included MRI of the face, CT of the neck/chest/abdomen/pelvis, PET scan, bone marrow biopsy and lumbar puncture. She was found to have a focal 4.5cm x 6cm left maxillary mass with both marrow and CNS involvement leading to stage IV disease. She was started on treatment per protocol ANHL 01P1. She has undergone one reduction cycle, two induction cycles, and two consolidation cycles of chemotherapy composed of cyclophosphamide, vincristine, prednisolone, high dose methotrexate, doxorubicin, cytarabine, and triple intrathecal chemotherapy. She is set to begin 4 cycles of maintenance therapy to complete her treatment. She has received repeat tumor evaluations with imaging, lumbar punctures, and bone marrow biopsies after each phase of therapy. She has continued HAART therapy with an undetectable HIV viral load.
Results: She quickly responded to therapy, achieving complete remission per PET, CT, lumbar puncture, and bone marrow biopsy by the end of induction. Aside from fever and cytopenias, she has experienced minimal side effects from therapy.
Conclusion: While PBL is rare and aggressive, complete remission can successfully be achieved using protocol ANHL01P1, without any dose reductions, while simultaneously administering HAART therapy.

Poster # 317

VARIATIONS IN CLINICAL PRACTICE DURING THERAPY FOR PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer. Patients treated on Children's Oncology Group (COG) protocols typically receive standardized care. However a number of important patient care practices vary among providers.
Objectives: To document current practices employed during pediatric ALL therapy by surveying COG institutional principal investigators.
Design/Method: Two hundred and nineteen COG institutional principal investigators were sent a 10-question survey regarding their current practices during pediatric ALL therapy.
Results: After the initial email and two reminders 59 principal investigators (26.9%) completed the survey. The first question inquired about the preference of placing a port (81.4%) versus other forms of central venous access at the start of Induction. The remaining questions addressed practices during Maintenance. Majority of responders reported monitoring a complete blood count (CBC) every 4-weeks (83%) over every 2-weeks (17%). High absolute neutrophil count (ANC) was the prevailing reason to assess 6-Mercaptopurine (6-MP) metabolites (42.4%) followed by prolonged neutropenia (30.5%). Most practitioners increased 6-MP beyond 100% only when the ANC was greater than 1500 on two consecutive monthly CBC checks (81.4%) with the remainder increasing beyond 100% when ANC was greater than 1500 three times within a 6-week period. A narrow majority (52.5%) prescribed Trimethoprim-sulfamethoxazole

(Bactrim) twice weekly for Pneumocystis jiroveci (PJP) prophylaxis with the remainder prescribing three times weekly. Intravenous pentamadine was the favored second line agent (37.3%) used for PJP prophylaxis followed by inhaled pentamadine (33.9%) and oral Dapsone (25.4%). Bactrim was held for neutropenia predominantly after the second hold of chemotherapy for neutropenia (50%) as opposed to the first hold of chemotherapy for neutropenia (12%) or patients' inability to tolerate 100% dosing (20.7%). Medi-ports are most commonly removed within the first 6-months after finishing therapy with the majority (67.2%) removing it immediately after completion of therapy. Most practitioners resume all vaccinations 6-months after the completion of chemotherapy (64.4%) versus separating dead and live vaccinations to 6- and 12-months respectively (27.1%). Lastly, responders overwhelmingly preferred following serial physical exams and CBCs after the completion of chemotherapy and only perform a bone marrow evaluation if there is concern for relapse (98.3%).
Conclusion: A number of practices were consistent across practitioners including: placing a medi-port at diagnosis, checking CBCs every 4-weeks during maintenance therapy and following serial physical exams and CBCs after the completion of ALL maintenance therapy. Other practices varied widely amongst responders. Further studies are necessary in order to define the best standard of care.

Poster # 318

IMPACT OF INITIAL PRESENTATION AND RISK FACTORS ON THE OUTCOME OF REFRACTORY/RELAPSED PEDIATRIC HODGKIN LYMPHOMA IN A DEVELOPING COUNTRY

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Background: pediatric Hodgkin Lymphoma (HL) usually characterized by a high cure rate meanwhile refractory/relapsed cases still remain a challenge to achieve a good outcome. Salvage chemotherapy remains the backbone for treatment of these cases in addition to auto bone marrow transplantation.
Objectives: to analyze the initial characteristic parameters of refractory/relapsed patients with HL in children and to assess their outcome using salvage treatment.
Design/Method: retrospective study for patients with HL who were refractory or relapsed to first line chemotherapy (Doxorubicin, Bleomycin, Vinblastin, Dacarbazine) (ABVD) and were salvaged by chemotherapy (Ifosfamide, Carboplation, Etopside) (ICE) with or without auto BMT and were treated at pediatric oncology department, National Cancer Institute, Cairo University, Egypt from 2006 till June 2013.
Results: thirty patients were refractory/relapsed. Age ranged from one to 18 years. Seventeen patients were females and 13 were males. The majority of cases were advanced stages (III, IV) (19 cases; 63.3%) while early stages (I, II) were 11 cases (36.7%). The nodular sclerosis subtype were 43.3% followed by mixed cellularity (36.7%). High risk group was the highest percent (50%; 15 cases) followed by intermediate risk (30%; 9 cases) then the low risk category (20%; 6 cases). Only 8 cases (26.7%) were in complete remission after the second cycle of the first line while 22 cases (73.3%) were not. Median time to progression was 12.9 months. Sixteen cases

were refractory to first line while 14 cases were in CR then developed relapse after a varying period of follow up. Eighteen cases (60%) achieved CR post salvage while 10 cases (33.3%) were still refractory and only two cases (6.7%) died post chemotherapy. Only 11 cases underwent auto BMT. Early responders to first line did not develop early relapse (within the first year) while 59.1% of cases who were late responders developed early relapse (P=0.004). The 5-year overall survival of the whole group was 40.6% while 18 months event free survival was 17.2%. The OS for high risk group was 23.7% while for low/intermediate group was 58.7% (P=0.036). Also, OS for patients who received radiotherapy was 100% versus 26.7% for those who did not (P=0.011). Event free survival was low among those with initially bad prognostic parameters but without statistical significance.
Conclusion: Initial risk stratification and early response to first line significantly affect the outcome of refractory/relapsed patients with HL. Treatment Intensification for high risk group and late responders is needed to achieve better outcome.

Poster # 319

VITAMIN D REPLACEMENT ALGORITHM IN CHILDREN AND YOUNG ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Pediatric cancer patients are known to have a high prevalence of vitamin D deficiency. Children and young adults with acute lymphoblastic leukemia (ALL) are at increased risk of vitamin D deficiency due to contributing effects of multiple medications including corticosteroids, methotrexate and azole antifungals. Evidence-based vitamin D supplementation guidelines lack in this population.
Objectives: Evaluate the impact of implementing a vitamin D supplementation algorithm on 25-hydroxy vitamin D (25-OH-D) levels in pediatric and young adult ALL patients in a single institution.
Design/Method: We performed a retrospective study following the adoption of a vitamin D replacement algorithm proposed by a multidisciplinary team. The study included all newly-diagnosed ALL patients initiated on vitamin D therapy with at least 2 25-OH-D levels. In addition to systematically checking levels on all newly-diagnosed patients, the algorithm provided standardized dosing based on 25-OH-D level and patient age. Goal 25-OH-D level was set as ≥30ng/mL (sufficiency) with a safe upper limit of 150ng/mL. Recommended repletion dosing for levels <30ng/mL was cholecalciferol 50,000 units weekly for patients >1 year and 1,000 units daily for younger patients. Once 25-OH-D levels were ≥30ng/mL, maintenance dosing was used ranging between 400-1,000 units daily or 5,000-10,000 units weekly based on patient age. Levels were checked every 3 months and doses were adjusted accordingly.
Results: Over a period of 22 months, 69 patients (median age 8 years, range: 1-32 years) met inclusion criteria. At diagnosis, 42 patients (60.8%) were deficient (25-OH-D level <30ng/mL), including 20 who were severely deficient (25-OH-D level <20ng/mL). Among deficient patients

at diagnosis, 83.3% had sufficient levels at first follow-up at a median time of 80 days (range: 39-117 days) following dosing per the algorithm. Most recent 25-OH-D levels in all patients showed 95.6% were sufficient at a median follow-up of 10 months (range: 2-22 months). At diagnosis, vitamin D deficiency was significantly affected by seasonality; patients were more deficient during winter (74.3%) than summer (47.1%, p=0.03). The impact of seasonality was overcome after supplementation following the algorithm; across all follow-up levels only 17% of winter levels and 10% of summer levels were deficient. Throughout the study, 4 patients had supra-therapeutic but non-toxic levels.
Conclusion: Vitamin D replacement guidelines implemented in the pediatric and young adult ALL population markedly increased the percentage of vitamin D sufficient patients in a short period of time. The impact of these guidelines in other oncology diagnoses, on bone health and growth outcomes remain to be evaluated.

Poster # 320

HODGKIN LYMPHOMA: CHARACTERISTIC AND OVERALL SURVIVAL AT A SINGLE INSTITUTION IN MEXICO

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Background: Hodgkin lymphoma represents an important pediatric neoplasia and overall survival rates for all stages combined have exceeded 90% in high income countries. There is limited information regarding the incidence, overall survival and prognostic factors for pediatric Hodgkin lymphoma patients in Mexico.
Objectives: To describe patient characteristics and estimate the overall survival rate of patients with Hodgkin's lymphoma at Hospital Infantil de México Federico Gómez.
Design/Method: This is a retrospective study single institution chart review. We reviewed 50 subject charts that had undergone treatment of Hodgkin´s Lymphoma from January 1st, 2009 to December 31th, 2015. We applied descriptive statistics, chi-square analysis and Kaplan-Meier survival curves.
Results: Mean age of patients was 8.5 years (68% under 9 years of age) and males (74%) represented the majority of patients. Staging was as follows: I 0%, II 20%, III 52%, and IV 28%. Fifty-eight percent of patients presented with B-symptoms. The most common histopathological diagnoses were nodular sclerosis (48%) and mixed cellularity (40%). Ninety-two percent of patients were treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), 8% with VAMP (vinblastine, doxorubicin, methotrexate and prednisone) and all patients received radiation therapy. Overall survival was 92% from 2009 to 2015.
Conclusion: There was predominance of male patients and those younger than 9 years. B-symptoms and advanced stage disease were higher than those reported in the US. The implementation of educational programs for first contact medical providers aimed at the early detection of pediatric cancer could be instrumental in identifying early stage disease and improving disease outcomes. The overall survival of Hodgkin lymphoma (92%) at our institution is comparable to large international health care centers.

Poster # 321

HYPERTENSION DURING CHEMOTHERAPY FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA: INCIDENCE, PERSISTENCE, AND RISK FACTORS

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Background: Although the treatment of acute lymphoblastic leukemia (ALL) has improved dramatically, with cure rates exceeding 80% in developed countries, the therapy is toxic and has potential to damage many organs, including the cardiovascular system.
Objectives: We sought to determine the incidence of hypertension throughout the first year of treatment in children undergoing therapy for ALL. The incidence of hypertension during induction with high-dose corticosteroids is known to be increased but blood pressure (BP) trends throughout the remainder of treatment are unknown. In this study, we evaluated the presence of hypertensive BPs recorded throughout the first year of treatment.
Design/Method: Data were obtained from the medical records of 36 newly diagnosed children with ALL receiving therapy at the Hershey Medical Center in 2004 and 2005. Data collected include: dates of birth, diagnosis, & remission, gender, height, weight, prescribed steroid, available inpatient and outpatient BP measurements, and anti-hypertensives given. Daily averages of available BP readings were calculated for each participant, then categorized as normal, pre-hypertensive, Stage 1 or 2 according to the most recent National High Blood Pressure Education Program Working Group guidelines. The number of days the average BP fell into each category was organized into four time periods: Induction, Quarter 2: months 4-6, Quarter 3: months 7-9, and Quarter 4: months 10-12. Overall, 2,645 total BP measurements were analyzed; the average number of BP measurements included per participant was 73 (range 34-126).
Results: The incidence of hypertension was higher than the under 5% expected for a healthy pediatric population. Over the course of the year, the percent of normo- or pre-hypertensive readings increased (56% to 65%) and the percent of Stage 1 and 2 readings slightly decreased (44% to 35%) but remained well above normal. Only three patients received treatment for recognized hypertension. Children receiving dexamethasone were 3.1 times more likely during induction ($p=0.014$) and 2.56 times more likely during Q4 ($p=0.0205$) to have a higher degree of hypertension than those children receiving prednisone, although their hypertension fell more rapidly.
Conclusion: These results suggest that steroid-induced hypertension is common during induction therapy and throughout maintenance and consolidation; it is frequently persistent, unrecognized, and untreated in children undergoing treatment for ALL. Furthermore, those children receiving dexamethasone may be more likely to experience elevated BPs than those taking prednisone, although that group may expect to see normalization of BP more rapidly.

Poster # 322

A CASE SERIES OF HODGKIN'S LYMPHOMA EPIDEMIOLOGY AND OUTCOMES IN YOUNG PEDIATRIC PATIENTS

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Background: Hodgkin lymphoma (HL) is a highly curable disease with a disease free survival approaching 90% in pediatrics. However, many patients suffer from significant co-morbidities, including risk for secondary malignancies and cardiovascular disease due to treatment-related late effects. With recent advances in the understanding of the biology of HL and risk stratification, current treatment protocols are looking to decrease exposure to chemotherapy while maintaining the high survival rates.
Objectives: Having a better understanding of risk groups is important to determine who may benefit most from a decrease in chemotherapy. Given the low incidence of Hodgkin's Lymphoma in the younger age group (10 years of age or less) outcomes data in this group is lacking. We aim to better understand this age group by presenting our experience in these patients.
Design/Method: Retrospective chart review of 15 patients diagnosed with Hodgkin's Lymphoma at 10 years or less at Children's National Medical Center from 2005 to 2015.
Results: The median age of diagnosis was 7(range 3-10 years). The majority of patients had low stage disease (IA 2 patients, IB 1 patient, and IIA 8 patients) with 3 patients having stage IIIA and 1 patient with stage IIIB. The majority of patients had lymphocyte predominant histology (9 patients); the others had nodular sclerosis (3 patients) and mixed cellularity (3 patients). The two patients with Lymphocyte Predominant stage IA disease had excision of the node and no chemotherapy. Only 1 patient with Stage IIA required radiation therapy after chemotherapy due to positron emission tomography (PET) positive disease. One patient with Stage IIIB and one patient with IIIA also received radiation therapy. Median follow-up was 4 years (range 1-10 years), and all 15 children were alive and disease free on the most recent follow up. On follow up, 2 patients had obesity, 1 patient had radiation induced hypothyroidism, 1 patient had sleep apnea, and 1 patient had type II diabetes. All patients were followed with echocardiogram except for the two patients who did not receive chemotherapy. Other than one patient with a history of bicuspid aortic valve, all patients had normal echocardiograms. No recurrence or secondary malignancies were detected at follow up.
Conclusion: In line with previous reports, most of the patients in this case series had low stage HL. Lymphocyte predominant Hodgkin's lymphoma was the most common subtype. In this small sample, there is currently 100% overall survival to date with no cardiac disease or secondary malignancy detected.

Poster # 323

HYPERHYDRATION ALONE IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AT VERY LOW RISK FOR DEVELOPING TUMOR LYSIS SYNDROME (TLS)

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Background: TLS is considered a potential oncologic emergency. Guidelines for the prevention and management of TLS typically involve some combination of hydration, alkalinization, and hypouricemic agents.
Objectives: There is however a lack of published data addressing the best management for patients with low risk of developing TLS and this would be the first publication since the most recent 2010 guidelines to propose management without hypouricemic agents for certain populations.
Design/Method: We reviewed the records of all patients diagnosed with ALL at our institution between January 2010 and December 2016 to identify those who did not receive either allopurinol or Rasburicase. Data required to establish either laboratory or clinical TLS (serum levels of potassium, phosphorus, uric acid, creatinine, and evidence of cardiac arrhythmia, seizure, or death) per the 2010 Cairo-Bishop definition [Br J Haematol, 149 (2010)] were collected. We reviewed lab values from three days prior to seven days following the start of systemic therapy.
Results: Of the two hundred and ten children diagnosed with ALL during this time period, eighteen met our inclusion criteria. The group consisted of six females and twelve males. The median age was 4.5 years (range 2.2 to 17 years). The median white blood cell (WBC) count at presentation was 2.9 (range 0.6 to 39.4). Nine were hyperhydrated and alkalinized while the other nine received hyperhydration alone. All eighteen were diagnosed with B-Lymphoblastic Leukemia. All but two were considered standard risk; the other two were assigned high risk because of age. None developed either lab or clinical TLS. In fact only two of the 668 labs for the key components of the TLS (potassium, phosphorus, uric acid, and creatinine) were even abnormal, for the patients' age.
Conclusion: These results suggest there is a proportion of children with ALL for whom hyperhydration alone is sufficient and appropriate for the prevention of TLS. Given the incidence of ALL, this potential change in management could have significant financial implications for practitioners worldwide who care for this population of patients. When we project characteristics common to our eighteen patients (WBC count less than 50, age between 1 and 18, and without hyperuricemia at presentation) onto our most recent population of patients diagnosed with ALL, we estimate that over half (43 of 77) of them who received a hypouricemic agent might have been successfully managed without one. We encourage other centers to review their similar data to confirm our findings.

Poster # 324

THE NEED FOR EARLY PHASE TRIAL OPTIONS IN DOWN SYNDROME ACUTE MYELOID LEUKEMIA (DS-AML) - A CASE REPORT USING EPIGENETIC THERAPY

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Background: Acute myeloid leukemia in Down syndrome (DS-AML) is a unique entity reporting overall greater treatment response and survival compared to non-DS AML. Despite very good outcomes those experiencing relapse or refractory (R/R) disease have dismal survival. Successful treatment of these patients is challenged by toxicities and death when receiving

intensive chemotherapy and early phase trials are not an option as DS is a common exclusion. Epigenetic modifications are well recognized as drivers of oncogenesis in AML and recently reported in DS-AML. Here we report the first use of epigenetic therapy combined with intensive chemotherapy in a patient with refractory DS-AML.
Objectives: Report the feasibility of delivering intensive epigenetic chemotherapy to a child with DS-AML and call out the need for inclusion of DS patients to early phase studies.
Design/Method: Decitabine (7.5mg/m2) and vorinostat (180mg/m2) were given days 1-5 followed by Filgrastim (5 μ/kg/dose) days 5-12, and fludarabine (30 mg/m2), cytarabine (2000 mg/m2/day) days 6-10.
Results: 17 month old boy diagnosed with DS-AML, megakaryoblastic phenotype (M7) harboring der(20)t(11;20)(q13;q13.3),+21,+11 was enrolled on COG AAML1531 for DS-AML. Post-Induction I (TAD therapy) bone marrow reported 14% leukemia allocating him to High Risk. Post-Induction II (Mito/AraC) marrow had 11% leukemia with an additional clone [der(8)t(8;11)(q24;q13)]. He was removed from study for an M2 marrow (>5% blasts). The patient developed peripheral blasts and a large left mandibular chloroma. Given no early phase trial options for DS-AML and recent evidence suggesting sensitivity in DS-AML to histone deacetylase inhibition, the patient was treated per our phase I epigenetic study for relapse AML. The 5 days of epigenetic therapy were well tolerated without toxicity with rapid clearance of peripheral blasts by day 2 and complete resolution of the chloroma by day 15. No Grade 4/5 toxicity occurred with only 3 Grade 3 adverse events: anemia; nausea; and febrile neutropenia. By day 31 he had recurrence of peripheral blasts and left facial swelling by day 36. His end of therapy marrow confirmed progressive disease (51% blasts).
Conclusion: We report feasibility of treating refractory DS-AML with intensive chemotherapy that included epigenetic agents. Despite an early clinical response the disease remained refractory. This case highlights the deficiency that exists across pediatric oncology with an absence of clinical trial options for R/R DS-AML. Future trial development must consider inclusions for DS patients who continue to be left out for fear of intolerability to novel regimens; for which data is lacking.

Poster # 325

IMPACT OF THE NUTRITIONAL STATUS ON THE OUTCOME OF INDUCTION IN PATIENTS OF ACUTE LYMPHOBLASTIC LEUKEMIA IN PAKISTAN”

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Background: Acute Lymphoblastic Leukemia (ALL) is the most frequently occurring cancer among the children and adolescents. Cure rate is improved up to 90% with early diagnosis, multi-agent treatment protocols, good infection control and better supportive care. Under nutrition among pediatric acute leukemia patients is more in developing countries than developed countries i.e. 60% as compared to 10% in developed countries. The poor nutritional status is found to be associated with an increased risk of fungal infections, hematologic complications and drug toxicities and overall increased mortality rate in developing countries. Therefore, optimum nutritional support can play a vital role in the outcome of induction in patients of ALL.
Objectives: The study was conducted to see the impact of nutritional status on the outcome of

induction remission in patients of acute lymphoblastic leukemia in a developing country.
Design/Method: The population of the research was newly diagnosed patients of ALL, who were reported from June 2016 to November 2016, in the Pediatric Hematology& Oncology Department of Children's Hospital & Institute of Child Health, Lahore. A total of 112 patients of ALL were analyzed prospectively. The study subjects were stratified into undernourished & well-nourished based on the Z-score for weight for height. Then, the protocol based induction chemotherapy started. . The data was collected irrespective of any discrimination based on demographic factors. Following characters were recorded in both the groups: Mid treatment & end of treatment bone marrow response, culture proved infection, duration of hospital stay & outcome.
Results: Among the 112 patients of ALL 84.8 %(n=95) were Pre-B and 15.2%(n=17) were Pre-T .Male to female ratio was 1.6:1. Malnutrition was established in 44 (39.3%) patients on the bases of Z-score. The undernourished patients of ALL had significantly increased rate of culture proven sepsis (12% vs. 2%) respectively and required longer duration of hospital stay ($p<0.001$).Rapid early response was observed in 31.8% malnourished and 20.6% well-nourished patients. End of treatment complete response was recorded in 65% vs. 69.1% respectively with significant p value. Expiry was observed in 9.1% malnourished patients.
Conclusion: On the basis of this study it is concluded that the nutritional status at the initial presentation had a significant impact on the induction outcome. The undernourished patients of ALL are more prone to infections, requiring longer duration of hospital stay. Therefore, optimum nutritional support to such patients can help to decrease the chances of infections & ultimately improve the outcome

Poster # 326

APPLICATION OF DRUG SENSITIVITY AND RESISTANCE TESTING TO IDENTIFY NOVEL THERAPEUTIC AGENTS FOR DOWN'S SYNDROME PATIENTS WITH AML

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Background: Patients with Down's syndrome who develop acute myeloid leukemia (AML) are at increased risk of toxicity secondary to chemotherapy regimens. These patients are harder to treat with conventional therapies at relapse. Overall, the use of targeted drug therapy is rising in the pediatric oncology field, and the development of a drug sensitivity and resistance test will allow identification of specific targeted therapies for patients' with difficult to treat leukemia.
Objectives: The identification of specific chemotherapeutic targets for treatment of patients' with Down's syndrome and AML to improve cure and reduce therapeutic toxicities.
Design/Method: Studies have been conducted at The Institute of Molecular Medicine at Phoenix Children's Hospital and The University of Arizona College of Medicine in Phoenix, Az. Our laboratory is working on the development of a drug sensitivity and resistance screening assay that would provide functionally relevant drug response data of the patient's leukemia cells. The drug sensitivity and resistant assay is composed of 56 different drugs at 5 different concentrations. Two Down's syndrome AML cell lines CMY and CMK were used and seeded onto the pre-dosed assay plates. These plates are placed in a normoxic and hypoxic incubator at

37 ˚C for 72 hours, thereafter cell viability was determined. Drug dose response data including IC50 values and Area under the Curve (AUC) were calculated for each cell line. Normalized AUC values were used to assess changes in sensitivity and resistance and hierarchical clustering was performed to determine similar responses between cell lines.
Results: Down's syndrome cell lines, CMK and CMY were found to be resistant to most conventional chemotherapeutic agents, but susceptible to targeted therapies such as Navitoclax and 17-AAG. Improved sensitivity of the CMK and CMY cells to Navitoclax and 17-AAG were demonstrated under normoxic and hypoxic conditions.
Conclusion: The results from these studies could lead to the establishment of improved therapeutic regimens for Down's syndrome patients with AML. Further testing will be done to look at combination therapies with 17-AAG and other chemotherapeutic agents. Moreover, validation studies will be done to evaluate the sensitivity of CMY and CMK cells to the targeted agent 17-AAG.

Poster # 327

HONGKONG-SINGAPORE (HK-SG) ALL 97 (MODIFIED BFM ALL) PROTOCOL IN A CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN A SINGLE CENTER: A LONG TERM SURVIVAL FOLLOW UP REPORT

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Background: Childhood Acute Lymphoblastic Leukemia (ALL) is highly curable today but second malignancy and late relapse are still a concern.
Objectives: To study the long term overall survival (OS) and disease free survival (DFS) in our children treated with HongKong-Singapore (HK-SG) ALL 97 protocol.
Design/Method: The HK-SG ALL 97 study protocol was based on modified ALL BFM95 protocol with participating hospitals in HongKong and Singapore for children with ALL. Data on the long term outcome, relapse and occurrence of second malignancy were reviewed in a single center in Singapore, KK Women's and Children's Hospital (KKH).
Results: A total of 144 patients with childhood ALL were treated with this protocol between June 2000 to July 2007. Median age 4.66 years (range from 1.14 to 16.73 years). There were 80 males (55.6%). Only 12 (8.3%) were T-lineage ALL. The median duration of follow up was 10.93 years (range from 0.56 to 15.71 years). There were 39.6%, 52.1%, 8.3% in standard risk(SR), intermediate risk (IR) and high risk (HR) group respectively. Thirty patients relapsed - 12 cases <18 months, 9 cases 18 to 30 months, 8 cases 30 to 60 months and only 1 at >5 years from diagnosis. Sites of relapse were bone marrow (BM) 17, bone marrow and extra-medullary sites 7 and extra-medullary sites 6. Isolated CNS occurred in 5 patients and 3 had combined BM and CNS. Eighteen patients (12%) died; 1 patient died from infection while in remission during induction (treatment related death) and the rest were associated with relapse. 6 out of 12 cases in HR group relapsed. The global 10 year overall survival (OS) and event free survival (EFS) were 87.2% and 78.4% respectively. 10 years OS for SR, IR and HR groups were 94.7%, 85.9%,58.3% respectively and 10 year EFS were 86%, 77.2%, 50% respectively. One patient developed second malignancy (PNET in brain) at 8 years after initial diagnosis and died. He had T cell ALL with CNS relapse while on treatment and received cranial RT with allogeneic BMT.

Conclusion: Our data showed good outcomes for SR and IR group of patients. Outcome of HR group is comparable to other groups using the modified BFM protocol. Majority of relapse occurred within 5 years from diagnosis. There was only 1 case (3%) relapse after 5 years. Fatal second malignancy occurred in one patient in CNS likely secondary to cranial irradiation he received for CNS relapse.

Poster # 328

EFFECTIVENESS OF ANTI-INFECTIVE PROPHYLAXIS IN CHILDREN WITH DOWN SYNDROME WHO ARE RECEIVING CHEMOTHERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Children with Down Syndrome (DS) have an increased risk of acute lymphoblastic leukemia (ALL) and higher rates of treatment-related mortality (TRM). Increased TRM has been attributed to infection occurring during periods of chemotherapy-induced neutropenia.
Objectives: To assess the effectiveness of antifungal and antibacterial prophylaxis at reducing ICU care and in-hospital mortality during the period of neutropenia after induction chemotherapy for ALL in children with DS.
Design/Method: A retrospective cohort of children with DS who received ALL induction chemotherapy between 1999 and 2014 was assembled from the Pediatric Health Information System (PHIS). PHIS is an inpatient administrative database representing over 40 free-standing United States children's hospitals. Receipt of prophylaxis was determined by reviewing daily pharmaceutical billing data contained in PHIS. A propensity score adjusted Cox regression was performed to compare the effectiveness of prophylaxis versus no prophylaxis on reducing the need for ICU care and inpatient all-cause mortality within 30 days of starting induction chemotherapy. A spline regression analysis explored whether there was a non-linear association between age and need for ICU care or mortality.
Results: A cohort of 437 patients with DS receiving induction ALL therapy was identified. Need for ICU care was 8.9% and induction mortality was 1.4%. Adjusted Hazard Ratio (HR) estimates suggested that antifungal (HR: 0.79, 95% CI: 0.31 - 2.01) and antibacterial (HR: 0.53, 95% CI:0.20 - 1.41) prophylaxis were associated with a reduced need for ICU care or death; however, these associations were not statistically significant. The spline regression suggested a stable risk for ICU care and death in children less than 6 years, but an increasing linear risk for those 6 years and older. After restricting the analysis to patients 6 years and older, the HRs for antifungal (HR: 0.62, 95% CI: 0.19 - 2.04) and antibacterial (HR: 0.54, 95% CI: 0.17 - 1.80) prophylaxis again suggested prophylaxis was protective against ICU care or mortality, but were not statistically significant.
Conclusion: The HR estimates suggest a possible protective effect of anti-infective prophylaxis against ICU care or death; however, the study had limited power to detect statistical significance. The spline regression analysis revealed a clear increase in ICU care and death after six years of age. While the rarity of DS ALL inherently limits the available statistical power, the direction of

the point estimates and the spline regression suggest anti-infective prophylaxis may be justifiable in patients with DS six years of age and older.

Poster # 329

HEPATIC TOXICITY MANIFESTATIONS IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA DURING INDUCTION CHEMOTHERAPY

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Background: Hepatic toxicity is a rare complication of induction chemotherapy for acute lymphoblastic leukemia (ALL), and the risk factors for and incidence of this relatively rare toxicity are at present unclear. Early identification of risk may permit implementation of strategies for early recognition and management. Current treatment protocols require assessment of hepatic function at only the first and final days of induction therapy, so that in the absence of relevant clinical symptoms, more frequent assessment of hepatic function is not part of routine practice. However, several medications routinely administered during leukemia induction have well-recognized potential for inducing hepatotoxicity, including peg-asparaginase, vincristine, and daunorubicin (National Cancer Institute (NCI) high risk patients only).
Objectives: To determine potential risk factors associated with hepatotoxicity during leukemia induction.
Design/Method: Retrospective medical record review of five cases with severe hepatotoxicity observed during ALL therapy at Texas Children's Cancer Center between July 2013 and September 2016.
Results: The median age of the five cases reviewed was 14 years (range 10-14 years), and all were male. Four patients were diagnosed with leukemia that was classified as very high risk post-induction, and one as high risk. All five subjects developed hepatic dysfunction during leukemia induction, four on day 22 and one on day 29. Four of the five patients were Hispanic, three were obese (defined as BMI $\geq$30), and one had been diagnosed with steroid-induced diabetes. All five had laboratory evaluations that were prompted by clinical symptoms, including scleral icterus, abdominal pain, dark urine, and drowsiness. All patients presented with significant transaminitis (10-23 times upper limit of normal) and conjugated hyperbilirubinemia (range 4.3-10.3 mg/dL). Four of the five patients underwent a liver biopsy and were found to have varying degrees of non-alcoholic steatohepatitis (NASH). One patient was also diagnosed with veno-occlusive disease. All patients were given ursodiol and chemotherapy was dose-reduced or held per protocol recommendations. All experienced complete resolution of hepatic dysfunction.
Conclusion: Hepatotoxicity is a rare complication of leukemia induction, but our findings suggest that specific populations may be at higher risk, such as adolescents or those with obesity or of Hispanic ethnicity, potentially corresponding with a higher risk of NASH. These subgroups may merit more frequent monitoring of liver function, especially during induction therapy. The results of this case series provide evidence to substantiate a more formal analysis, currently in progress, to investigate the incidence of and contributing risk factors to development of hepatotoxicity in our pediatric leukemia patient population.

Poster # 330

OUTCOME OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN WITH DOWN SYNDROME: REPORT FROM A SINGLE INSTITUTION

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Background: Down syndrome (DS) is the most common chromosomal abnormality in children, and carries a 10-20 times increased risk of acute lymphoblastic leukemia (ALL).Children with DS-ALL have less favorable outcome due to both a high relapse rate and increased treatment-related mortality.
Objectives: To analyze the demographic features, toxicity and outcome of ALL patients with DS treated at King Faisal Specialist Hospital and Research Center, Jeddah (KFSH&RC-J) from Jan-2002 to Dec-2015.
Design/Method: We retrospectively reviewed the charts of 12 patients with newly diagnosed DS-ALL. Data abstracted from medical records included: Age, sex, WBC on presentation, CNS status and risk stratification. Chemotherapy protocol received and drug modifications. Treatment related toxicity was graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
Results: Between 2002 and 2012, a total of 12 patients with DS-ALL were include in the analysis (Total ALL =218 cases), comprising 5% of all pediatric ALL. Six patients were males (50%) and 6 were females (50%). The mean age at time of diagnosis was 6.4 (+/- 3.82) years (range 2-15 year). Three patients were stratified as Low risk ALL (25%) and 9 patients with High risk ALL (75%) according to NCI risk stratification. CNS status at diagnosis: 9 patient with CNS1 (75%), one patient with CNS2 (8%) and 2 with CNS3 (17%). Four patients had congenital heart disease (CHD) (34%). All patients had pre B immunophenotype (100%). All patients were treated by CCG protocols (1882, 1991 and1961). During maintenance phases, most of patients received less than 50% of oral chemotherapy (6-MP & MTX). Moderate to severe toxicity (grade III-V) occurred in nine patients (14 events). Most of toxicity was during induction (6 events) and re-intensification phases (4 events). Most of toxicities were infections and mucositis.
Cytogenetic and FISH studies: Eight patients had cytogenetic data available: ETV6-RUNX1 (t (12; 21) (p12, q22)) was detected in one patient (12%). MLL rearrangement and Trisomies (4,10&17) were detected in none (0%). BCR-ABL1 (t(9;22)(q34;q11)) was negative for all six patients tested for the translocation. Three patients relapsed (25%), all of them with HR disease and all had bone marrow relapse. Three patients died (25%): Two of them died with relapsed and refractory disease (Disease-related mortality) and one died during induction with presumed sepsis. The 5-year Overall Survival (OS) and Relapsed Free Survival (RFS) were 83% and 78% respectively.
Conclusion: The data derived from this study shows that the clinical characteristics, outcome of DS-ALL are similar to results published internationally.

Poster # 331

DECREASE OF IMMUNOGLOBULINS IN CHILDREN ON MAINTENANCE TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children. Chemotherapy can induce secondary immunodeficiency due to decreased immunoglobulins. Limited information is available regarding the severity of hypogammaglobulinemia during treatment with chemotherapy and its implications. We report a group of children who developed low immunoglobulin G (IgG) during maintenance treatment in ALL.
Objectives: To describe our experience with children treated for ALL who developed hypogammaglobinemia during maintenance therapy, documented infections during that time and the use of replacement immunoglobulin therapy.
Design/Method: Descriptive retrospective review of children diagnosed with ALL in a single institution from 2010 to 2016 (Stollery Children's Hospital, Edmonton, Alberta, Canada) who had documented low IgG levels during maintenance treatment. Data also included concomitant lymphocyte count, treatment with Intravenous immunoglobulin (IVIG) and documented infections.
Results: Eleven out eighty-nine patients treated for ALL between 2010 and 2016 had documented hypogammaglobinemia during maintenance therapy for ALL. Eight patients had B and three patients had T cell ALL. Based on the Children's Oncology Group ALL protocol classifications, for the B-cell group, 4/8 were very high risk , 2/8 were high risk ALL (treated as per COG AALL 1131) and 2/8 were standard risk (treated as per COG AALL 0932). Patients with T cell ALL were treated as per COG AALL 0434.In the B-Cell group, 24 measurements of IgG were available with a median of 3.84 g/L (range 2.08 – 6.8), and median lymphocyte count of 0.56 *109 (range 0 – 1.7). In the T cell group, 13 IgG level were measured with a median of 3.14 g/L (range less than 2 – 6.25), and median lymphocyte of 0.41 *109 (range 0.1 – 1). IVIG was provided on twenty four occasions for IgG levels less than 4 g/L and recurrent infections. Episodes of infections during this period included nine episodes of fever and neutropenia, eight upper respiratory tract infection, three episodes of gastroenteritis, two urinary tract infections, one line infection and one herpes simplex infection.
Conclusion: During maintenance therapy, children with ALL can present with hypogammaglobulinemia that may require IVIG replacement to prevent recurrent infections. The hypogammaglobulinemia is likely secondary to the persistent lymphopenia due to ongoing chemotherapy. Prospective data is required to determine the severity of hypogammaglobulinemia over the maintenance phase of ALL therapy, the associated risk of infections and the need and benefit of IVIG replacement.

Poster # 332

THERAPEUTIC LEUKAPHERESIS IN INFANTS & CHILDREN WITH LEUKEMIA AND HYPERLEUKOCYTOSIS: A SINGLE INSTITUTION EXPERIENCE

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Background: Hyperleukocytosis, described as white blood cell (WBC) count above 100 x 10^9/L, is associated with high early morbidity and mortality from leukostasis-related complications, namely intracranial hemorrhage and pulmonary distress. Initiating chemotherapy without prior leukoreduction can lead to a dreaded complication called "Tumor Lysis Syndrome." Currently, leukapheresis (LK) is commonly used as an adjunctive therapy in some patients with hyperleukocytosis and/or leukostasis-related symptoms, but specific guidelines for its use and its safety and efficacy have not been established in pediatric population.
Objectives: To evaluate safety of LK in infants and children with leukemia, and its efficacy as an early management procedure in patients with hyperleukocytosis and/or leukostasis-related complications; to analyze and discuss the patient population that underwent LK at Cook Children's Medical Center (CCMC).
Design/Method: Medical records of 14 children with acute lymphoblastic leukemia and five with acute myeloid leukemia who underwent LK at CCMC between 2000 and 2014 were reviewed for WBC count, metabolic panel at presentation and following apheresis, complete remission (CR), short-term and overall survival.
Results: Three patients presented with central nervous system (CNS) symptoms, two with respiratory symptoms, and two with both. Patients who underwent LK had median WBC count of 460.9 x10^9/L (516.3 in patients with ALL and 291 in patients with AML). Round 1 LK reduced WBC count by 63.8% to 167 x10^9/L. Round 2 LK in six patients showed additional 28.8% reduction with a final median WBC count of 139.3 x10^9/L. Short-term survival immediately after LK was 100%. Thirteen patients achieved long-term survival of 2 years and 11 achieved an overall survival of 4 years or longer; median survival in patients with AML and ALL were 11 months and 5.5 years, respectively. Eighteen patients obtained complete remission status. Cause of death were: disease relapse, CNS hemorrhage, hypoxic ischemic CNS change, and septic shock.
Conclusion: LK significantly reduced WBC count without any major procedural complication even in patients as young as 22 days. LK may be considered a safe adjunctive procedure in pediatric leukemia to prevent early morbidity and mortality associated with hyperleukocytosis &/or leukostasis prior to initiation of chemotherapy.

Poster # 333

ASPARAGINASE-INDUCED HEPATIC INJURY AND ROLE OF LEVOCARNITINE IN MANAGEMENT: A MULTI-INSTITUTIONAL CASE SERIES

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Background: Asparaginase is an important component of combination chemotherapy used for the treatment of childhood acute lymphoblastic leukemia (ALL). Grade 3-4 hepatotoxicity in children treated with pegylated-asparaginase (PEG) occurs in about one in six children (1). Mechanisms contributing towards hepatotoxicity include impaired protein synthesis and mitochondrial dysfunction. Levocarnitine is a mitochondrial cofactor and can potentially ameliorate the mitochondrial toxicity of asparaginase. Increased awareness in the pediatric oncology community about this drug toxicity and role of levocarnitine in management is warranted. There are published reports about this clinical scenario in adults (2), however data pertaining to pediatric patients is lacking.
Objectives: To assess clinical characteristics and the effect of levocarnitine in children with asparaginase-associated hepatotoxicity.
Design/Method: Retrospective case series.
Results: Our case series included 5 patients who were 9 to 11 years of age: 2 patients with high-risk ALL, 1 patient with standard-risk ALL and 1 patient with relapsed-ALL. Three of 5 patients were obese (BMI >95%). All patients received 2500 IU/m2 of PEG on Day 3-4 of Induction. All patients developed direct hyperbilirubinemia, with mean/median (range) peak total bilirubin of 17.9/10.2 (5.9-42.4) mg/dL noted 19-27 (median 22) days after PEG administration. A diagnosis of asparaginase-induced hepatotoxicity was based on the temporal relationship of cholestatic abnormalities with PEG administration. Patients 1-4 received levocarnitine 1-18 (median 10) days after hyperbilirubinemia was noted. A downward trend in bilirubin was noted 0-12 (median 3.5) days after levocarnitine was started and a median of 26.5 days after PEG administration. Patient 5 did not receive levocarnitine and showed a downward trend in bilirubin 29 days after PEG administration. Complete normalization of biochemical parameters of hepatotoxicity was seen in 4 of 5 patients (Patients 2-5). Patient 1 died of bleeding complications. No recurrence of hepatotoxicity was noted in patients 2, 3 and 4 with subsequent PEG rechallenge accompanied by levocarnitine prophylaxis. Adverse events related to levocarnitine therapy were not observed.
Conclusion: Asparaginase-induced hepatotoxicity can cause significant morbidity, chemotherapy treatment delays and can result in potentially fatal outcomes. It needs prompt recognition in children to allow appropriate treatment initiation and to prevent any escalating liver damage. Treatment with levocarnitine can help reverse this toxicity, and prophylaxis with levocarnitine may allow for continued use of PEG as a component of ALL therapy.

References: 1. Silverman LB et al. Blood, 2016 (ASH meeting abstract) 2. Alshiekh-Nasany R et al. Acta Haematol 2016

Poster # 334

INSIGHTS INTO THE MOLECULAR BASIS OF CRM1-AF10 LEUKEMOGENESIS

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Background: CALM-AF10 translocations are seen in 5-10% of childhood T-cell acute lymphoblastic leukemia (T-ALL), and are associated with poor outcomes. Our lab previously found that the CRM1 nuclear export chaperone plays an essential role in CALM-AF10

leukemogenesis by interacting with a Nuclear Export Sequence (NES) in CALM. To demonstrate the critical importance of CRM1 in leukemia development, we created a CRM1-AF10 fusion, and showed that, like CALM-AF10, CRM1-AF10 causes increased HOXA gene expression and induces leukemias in mice. The presence of a 41 aa C-terminal CRM1 domain has been reported to inhibit binding of NES-containing proteins to CRM1. We hypothesized that removal of this inhibitory domain would enhance binding to NES-containing proteins, and potentially increase CRM1-AF10 leukemogenicity.
Objectives: Determine the importance of binding to NES-containing proteins on the leukemogenic properties of CRM1-AF10.
Design/Method: We prepared a CRM1Δ-AF10 fusion construct, which lacks the C-terminal 41 aa of CRM1. This construct was tested for its ability to activate the transcription of a HOXA7-luciferase reporter and to bind to HOXA genes via chromatin immunoprecipitation (ChIP). We also examined the impact of leptomycin B (LMB, a CRM1 inhibitor) on CRM1Δ-AF10-dependent HOXA7 transcriptional activation. Finally, we examined the ability of CRM1Δ-AF10 to induce leukemias in vivo.
Results: Similar to CALM-AF10 and CRM1-AF10, CRM1Δ-AF10 increased transcription of the HOXA7 luciferase reporter: the transcriptional effect of all three fusion proteins was repressed by exposure to LMB. In addition, each of the fusion proteins was shown to bind to HOXA gene loci through ChIP analysis. The fusion constructs all induced leukemia in vivo: CRM1Δ-AF10 yielded leukemias with similar latency (100-130 days) and penetrance (100%) to CALM-AF10, while CRM1-AF10 leukemias had a longer latency (250-350 days) and decreased penetrance (50%). Increased HOXA gene expression was confirmed by RT-qPCR of murine leukemia samples.
Conclusion: Our results demonstrate that similar to CALM-AF10 and CRM1-AF10, the truncated CRM1Δ-AF10 construct binds to HOXA gene loci, causes increased HOXA gene expression and induces leukemia. The absence of the inhibitory CRM1 C-terminal tail likely enables stronger binding to an as yet unidentified NES-containing partner protein that plays an important role in leukemogenesis. Of note, the CRM1 C-terminal domain is missing in a recently described CRM1-AF10 translocation in a T-ALL patient (Bond, BLOOD, 2014). These studies shed further light on the importance of CRM1 in pediatric leukemogenesis, and suggest that inhibition of the CRM1-NES interaction by newly available selective inhibitors of nuclear export (SINEs) may represent an effective therapeutic approach.

Poster # 335

DOES INFECTION WITH CLOSTRIDIUM DIFFICILE GASTROENTERITIS INCREASE THE LIKELIHOOD OF DEVELOPING RENAL TOXICITY/DELAYED METHOTREXATE CLEARANCE IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA RECEIVING HIGH DOSE METHOTREXATE? – A CASE SERIES

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Background: High dose methotrexate (HDM) is an effective agent to maintain remission in children with high risk Acute Lymphoblastic Leukemia (HRALL). Known side effects of HDM include renal toxicity, mucositis, hepatotoxicity and myelosuppression. Risk factors associated with increased risk of delayed methotrexate clearance (DMC) and methotrexate toxicity (MT) include underlying renal impairment, volume depletion, acidic urine and drug interactions. Clostridium difficile (CD) gastroenteritis has not been reported as a risk factor for DMC and MT. We report a cohort of children with HRALL being treated with HDM who developed MT and concomitant CD.
Objectives: To describe our experience in managing children with HRALL and CD who develop DMC and MT when treated with HDM.
Design/Method: Case series of children diagnosed with HRALL treated with HDM between the ages of 1 and 17 years who presented with CD gastroenteritis concomitant with MT and DMC.
Results: All children received HDM [dose 5 grams/meter square body surface area (m2 BSA)] over 24 hours treated in Stollery Children's Hospital, Edmonton, Alberta, Canada. Three patients who were receiving HDM were found to be toxin assay positive in stools for CD after becoming symptomatic (diarrhea, nausea and vomiting) within 24 hours from start of the infusion. No risk factors for renal toxicity were present. First and second patient received their first dose and both developed acute kidney injury. Hour 24 MTX level were 114.88 umol/L and creatinine of 92 mg/dl (baseline 35) on the first and 201.60 umol/L with creatinine of 200mg/dl (baseline 32) on the second patient. Both patients received increased hydration from 125 ml/m2 BSA/hour to 200 ml/m2 BSA/hour initially and increase of leucovorin rescue. The first patient also required one dose of glucarpidase (given hour 36). Both patients developed severe complications including mucositis, myelosuppression and hypertension. The first patient also had encephalopathy and respiratory failure secondary to fluid overload, hypertension, and pneumonia. Both patients required aggressive and prolonged supportive care. The third patient presented with DMC after the third HDM dose requiring 9 days for the methotrexate to clear to less than 0.1 umol/L, no increase of creatinine however she complicated with hypertension. All patients fully recovered within four weeks of the methotrexate infusion. CD was treated with oral Vancomycin.
Conclusion: We report a case series of children with HRALL who developed MT and DMC while having a concomitant CD gastroenteritis. We suggest close monitoring of this population. Prospective data collection is required to further explore possible association.

Poster # 336

THE ROLE OF NUCLEOPORINS IN CALM-AF10 AND CRM1-AF10 LEUKEMOGENESIS

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Background: The t(10;11) CALM-AF10 translocation occurs in pediatric patients with T-ALL and AML and is associated with a poor prognosis. CALM-AF10 leukemias are characterized by upregulation of HOXA gene expression, which is a known driver of leukemogenesis. Interaction of the CALM-AF10 oncoprotein with the nuclear export factor CRM1/XPO1 is essential for upregulation of HOXA expression. We have previously shown that CRM1 interacts with Hoxa chromatin, suggesting that CRM1 recruits CALM-AF10 to its target genes. CRM1 can also

substitute for CALM, such that CRM1-AF10 also induces HOXA gene transcription and induces leukemias in mice. However, CRM1 does not contain any recognized DNA-binding domains, implying that other proteins must be involved. Nucleoporins (NUPs) such as NUP98 and NUP214 are components of the nuclear pore complex and interact with CRM1 during nucleocytoplasmic transport of macromolecules. Both NUP98 and NUP214 are also involved in leukemogenic translocations that result in HOXA transactivation.
Objectives: To determine whether the NUP214 nucleoporin cooperates with CRM1-AF10 to transactivate HOXA genes and induce leukemias.
Design/Method: A recent report identified several binding residues within CRM1 that are important in mediating interaction with NUP214 (Port, Cell Reports, 2015). We created a mutated CRM1mutNUP-AF10 expression vector in which binding to NUP214 is impaired, but interaction with nuclear export signal-containing molecules is retained. Using Hoxa7- and Hoxa9-luciferase reporter assays, we measured Hoxa gene transcription in HEK293 cells transiently transfected with either CRM1-AF10 or CRM1mutNUP-AF10 constructs. Murine hematopoietic progenitor cells transduced with these fusion vectors were transplanted into sublethally irradiated mice that continue to be evaluated for leukemia development.
Results: The ability of CRM1mutNUP-AF10 to activate Hoxa7- and Hoxa9-luciferase reporters was reproducibly decreased (by 10-20%) compared with CRM1-AF10. Mice were transplanted with CRM1-AF10- and CRM1mutNUP-AF10- transduced hematopoietic progenitors four months ago (September 2016) and continue to be monitored for development of leukemia. The average leukemia latency for CRM1-AF10 transduced cells is 100 days; thus far (120 days), none of the CRM1mutNUP-AF10-transplanted mice (n=5) has developed leukemia.
Conclusion: Interfering with the ability of CRM1 to interact with NUP214 moderately diminishes Hoxa7 and Hoxa9 transcriptional activation. Ongoing in vivo experiments suggest that the interaction of CRM1 with NUP214 may contribute to CRM1-AF10 leukemogenesis. We are currently performing ChIP studies to directly assess the binding of CRM1mutNUP-AF10 to Hoxa genes. Targeting the CRM1-NUP interaction may be a novel therapeutic approach for CRM1-dependent leukemias.

Poster # 337

A RETROSPECTIVE COMAPARISON OF RATES OF VENOUS THROMBOEMBOLISM BETWEEN PERIPHERALLY INSERTED CATHETERS AND INDWELLING CATHETERS DURING INDUCTION AND CONSOLIDATION FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: At the Christchurch Children's Haematology and Oncology Centre (CHOC) we have used peripherally inserted central catheters (PICC) lines as our initial CVC in the last few years due to easier availability and removal.We retrospectively studied our Acute lymphoblastic leukemia (ALL) patients for the incidence of venous thromboembolism (VTE) during Induction and Consolidation and the rates of VTE in patients with PICC lines compared to the earlier cohort where central lines were inserted at the start of induction.
Objectives: To determine the risk of VTE for ALL patients with PICC lines used in induction

compared with upfront insertion of central catheters
Design/Method: Retrospective cohort study from 2010 - 2016Data collection from electronic medical record and supplemented with paper medical record for all patients with a positive finding of venous thromboembolism.
Results: 108 with ALL were identified between January 2010 and July 2016. 60 patients had PICCs inserted initially, 48 had a Port-a-Cath or Hickman line inserted initially. 8 VTEs were diagnosed in 7 patients. Ages ranged from 4- 19 years, 4 boys and 3 girls.These events consisted of 7 DVTs and 1 Pulmonary Embolus (PE) in a patient with a previous PICC associated DVT. 7 VTEs Occurred in association with PICC lines, 1 DVT occurred secondary to an infected peripheral cannula in a patient who had a Portacath removed due to line dysfunction. None were diagnosed in patients with CVCs as initial lines inserted.6 VTEs were diagnosed clinically. 1 was diagnosed incidentally when a PICC was replaced with a Port-a-Cath. All of these were upper limb and on the side of the CVC. Ages ranged from 4- 19 years, 4 boys and 3 girls.
Conclusion: Our findings suggest that PICC lines increase the risk of clinical VTEs in children with ALL compared to Port-a-Caths and other CVCs.

Poster # 338

THE SIX1 HOMEOBOX GENE IS A NOVEL TRANSCRIPTIONAL TARGET OF THE LEUKEMOGENIC CALM-AF10 PROTEIN

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Background: CALM-AF10 leukemias account for approximately 10% of childhood T-ALL (T-cell acute lymphoid leukemia) as well as a small proportion of AML (acute myeloid leukemia), and are associated with poor prognosis. CALM-AF10 leukemias share many characteristics with leukemias associated with Mixed-Lineage Leukemia gene (MLL) fusions. CALM-AF10 and MLL fusion leukemias share similar gene expression profiles, characterized by excessive levels of proleukemic HOXA gene expression. While HOXA genes are known drivers of leukemogenesis, they are also important in normal hematopoiesis, making making them suboptimal drug targets. We have previously shown through RNA-sequencing and Affymetrix microarray studies that expression of SIX1 is increased in CALM-AF10 leukemias, and that SIX1 expression decreases in response to the CRM1 inhibitor, Leptomycin B (LMB), similar to HOXA genes. Six1 (Sine Oculis Homolog 1) is a homeobox protein involved in cell proliferation, apoptosis, and embryonic development, and is overexpressed in numerous cancers.
Objectives: To evaluate the role of SIX1 in CALM-AF10 leukemias.
Design/Method: To validate the RNA-sequencing and microarray, quantitative RT-PCR was performed to confirm overexpression of SIX1 in CALM-AF10 leukemia. Chromatin Immunoprecipitation (ChIP) analysis was used to test for binding of CALM-AF10 to the SIX1 locus. To evaluate the potential of SIX1 to transform bone marrow cells, murine bone marrow hematopoietic progenitors were infected with a retroviral SIX1 expression vector and observed for colony growth in methylcellulose assays. Fetal liver cells were used in the same procedure.
Results: Similar to HOXA genes, qRT-PCR confirmed overexpression of SIX1 in CALM-AF10 leukemia cells. In addition, we showed that CALM-AF10 binds to the SIX1 gene locus by ChIP analysis. Overexpression of SIX1 by itself was not able to transform hematopoietic progenitors

from murine bone marrow. We have recently transduced fetal liver hematopoietic progenitors with SIX1; the results of these studies will be presented.
Conclusion: Using gene expression profiling, we identified SIX1 as a candidate target gene in CALM-AF10 leukemias. qRT-PCR and ChIP analysis further confirmed that CALM-AF10 binds to the SIX1 gene locus. SIX1 overexpression in hematopoietic bone marrow progenitors did not result in transformation, suggesting that SIX1 expression by itself is not sufficient for leukemogenesis. We are currently developing a retroviral SIX1 knockdown vector to determine the contribution of SIX1 in the pathogenesis of CALM-AF10 leukemia. Identification of SIX1 as a candidate target gene in CALM-AF10 leukemias could lead to the development of novel therapeutic approaches.

Poster # 339

INFECTION AND RISK FOR DISEASE RELAPSE IN CHILDREN ADOLSCENTS AND YOUNG ADULTS WITH AND ACUTE MYELOGENOUS LEUKEMIA

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Background: Recent studies suggest that infectious pathogens, like cytomegalovirus, may play a role in affecting relapse rates in patients with acute myelogenous leukemia (AML) after allogeneic hematopoietic cell transplantation. Whether infection similarly influences relapse risk in children with AML receiving conventional chemotherapy remains largely unknown.
Objectives: Primary objective was to describe the amount and type of infections in patients with AML receiving conventional chemotherapy who experience disease relapse and to compare results to those patients whom do not experience relapse. Secondary objective was to compare incidence of specific infectious pathogens between patient groups.
Design/Method: Single-center, retrospective study involving patients (ages 0-17 years) diagnosed and treated for AML from January 1, 2008 to December 31, 2014 at Nationwide Children's Hospital. Control patients included those whom did not experience relapse within 3 years after being diagnosed. Relapsed patients experienced relapse within 3 years after diagnosis. In addition to clinical and disease-related information, laboratory data including clinical-, microbiologic-, and radiographic-proven infections ("proven" infection) were recorded. "Possible" infections were defined as fever in setting of central venous catheter and without symptoms. "Probable" infections were defined as fever and symptoms. Any comparisons between groups was performed using non-parametric methods.
Results: 27 patients with AML (n=13 control group, n=14 relapsed group) with a median age of 8 years (range 0-17 years) were evaluated. 96 total infections were identified in the control group (41% definite, 20% probable, 38% possible). Bacterial bloodstream infection (BSI) (n=22, 35%) occurring in intensification (n=16, 73%) was the most common infection type, and Streptococcus viridans (n=9, 39%) was the most common isolate. 80 total infections occurred in the relapse group (53% definite, 13% probable, and 35% possible). BSI (n=23, 29%) due to S. viridans (n=10, 43%) occurring in intensification (n=18, 78%) was the most common infection. For both patient groups, initial BSIs occurred mostly during profound neutropenia (ANC<200) within the first 200 days from start of induction therapy [Control median day first BSI, 103.5 days (range, 1-1000 days) vs. Relapse median day first BSI, 97 days (range, 1-1000 days), p=0.96]. No

statistical differences in clinical demographics and laboratory data were noted between patient groups.
Conclusion: In conclusion, post-therapy infectious epidemiology and timing was similar between control and relapse pediatric AML patients receiving conventional chemotherapy. Study limitations include small sample size and predilection for most patients to be tested for BSI via blood culture and not other diagnostic modalities, which may influence incidence of true infection.

Poster # 340

NOVEL COMPUTABLE PHENOTYPE FOR PEDIATRIC LEUKEMIA AND LYMPHOMA

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Background: The ability to reliably identify patients with specific medical conditions is essential for constructing study cohorts. Traditional cohort construction relies upon chart abstraction or administrative datasets comprising coded diagnoses, procedures, and similar charges. Electronic health record (EHR) data provides a large number of clinical variables to allow for complex cohort construction. Computable phenotypes (CP) utilize EHR data elements such as laboratory results, medications, vital signs and clinical notes to define cohorts. We describe our experience developing a CP for pediatric leukemia and lymphoma from EHR-derived data standardized in the PEDSnet Common Data Model to support translation of results across datasets.
Objectives: We report a novel CP to identify pediatric oncology patients with leukemia or lymphoma in EHR data.
Design/Method: To evaluate the leukemia/lymphoma CP, we used a test population of PEDSnet patients at the Children's Hospital of Philadelphia from 2011-2015. EHR diagnostic and procedure codes, lab tests, and medications were extracted and standardized to a PEDSnet common data model (CDM, based on the widely-used OMOP CDM version 5). Our CP algorithm included any patient receiving a leukemia or lymphoma diagnosis twice, plus one of the following medications: cyclophosphamide, cytarabine, daunorubicin, doxorubicin, etoposide, mitaxantrone, or vincristine. Results were compared to the known oncology patients from the hospital tumor registry. To test construct validity of our CP, models were developed with clinical experts choosing the exposures and outcomes of interest that would likely be associated with oncology cases.
Results: When the presence of two diagnosis codes for leukemia or lymphoma is used in isolation, 1951 patients are identified; addition of chemotherapy reduced the CP cohort to 793 patients. By comparison, the tumor registry contains 773 patients with leukemia or lymphoma. Our CP cohort has a diagnosis distribution similar to the expected population prevalence: Acute Lymphoid Leukemia (ALL) 57%, Acute Myeloid Leukemia 13%, Hodgkin Lymphoma 12%, Non-Hodgkin Lymphoma 13%, and Other 5%. For construct validity, we expect patients undergoing chemotherapy to have neutropenia; 779/793 patients had an absolute neutrophil count <200 at least once. For ALL, 90% of patients had at least 3 lumbar punctures consistent with standard treatment. Our ALL cohort had appropriate age distribution with incidence

peaking at 4 years.
Conclusion: Diagnosis codes alone do not yield sufficient specificity as a CP algorithm. Integrating chemotherapy improves patient identification significantly. Developing a CP results in improved cohorts of pediatric oncology patients within EHR datasets and enhances the ability of “big data” to perform meaningful research.

Poster # 341

ACUTE KIDNEY INJURY DURING CHEMOTHERAPY FOR ACUTE MYELOID LEUKEMIA

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Background: In the United States there is an estimated 600 new cases of acute myeloid leukemia (AML) per year in children and young adults. Even though front line chemotherapy, directed to treat pediatric AML is not considered nephrotoxic there has been a concern in recent years among our local physicians regarding a high incidence of acute kidney injury (AKI) in these patients. Data however is limited in defining the epidemiology of AKI in this population. AKI in hospitalized children is associated with increased morbidity and mortality along with an increased risk of developing chronic kidney disease in survivors.
Objectives: To determine the incidence of AKI in children and adolescents receiving multi-agent chemotherapy for de-novo AML and to identify risk factors associated with these episodes.
Design/Method: This is a single institution, retrospective cohort study assessing all serum creatinine (SCr) values in patients with AML during the first three chemotherapy cycles. The Kidney Disease: Improving Global Outcomes (KDIGO) SCr criteria was used to define AKI. Stage 1: SCr rise of ≥50%, Stage 2: SCr rise of ≥100%, Stage 3: SCr rise of ≥200% or the initiation of renal replacement therapy. AKI stages 2 and 3 are classified as severe AKI. Urine output was not assessed as an AKI indicator. Patients treated from May 2005 to April 2016 were considered for inclusion.
Results: A total of 53 patients were eligible for review, with a median age of 9.1 years. AKI was identified in 34 patients (64%) while 22 patients (42%) suffered severe AKI. Ten patients (19%) were identified with more than one episode of AKI during their first three cycles. More than half (52%) of severe AKI episodes occurred during the first chemotherapy cycle, with 26% of these requiring an admission to the intensive care unit. On univariate analysis patients with severe AKI were more likely to have sepsis than those without AKI (41% vs 27%, P=0.005). In severe AKI episodes vancomycin was used in 91% of cases, caspofungin in 50% and aminoglycosides in 39%.
Conclusion: AKI is common in children and adolescents with AML receiving chemotherapy, with almost half of patients suffering from severe AKI in this cohort. These episodes occurred more often during induction chemotherapy and are associated with sepsis and exposure to other potential nephrotoxic agents. Survivors of childhood AML should be monitored for long term kidney health. Further prospective, multi-center AKI studies are needed in this susceptible population.

Poster # 342

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) THERAPY GUIDED BY MULTIPARAMETER FLOW CYTOMETRY MINIMAL RESIDUAL DISEASE (MRD): LONG TERM EXPERIENCE IN A SINGLE INSTITUTION

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Background: MRD evaluation during ALL therapy has helped identify risk groups for relapse and may be used to make early modifications in treatment protocols to improve survival and reduce long term toxicity. Since 1999 we have used flow cytometry to evaluate MRD and guide therapy.
Objectives: To present our long term results and compare them with patients treated without MRD analysis.
Design/Method: Consecutive ALL patients diagnosed in our center were treated in this protocol from July 1989 through April 2016. Patients with PHI+, down syndrome and T(4;11) were excluded from this analysis. Patients received a standard BFM 4 drug induction plus early intensification, interim maintenance with high dose methotrexate, reinduction plus delayed intensification and 18 or 24 months of continuation.T ALL and CNS+ patients received 12 GY cranial radiation since 1999 MRD was evaluated at day 15 and 35 of induction with multi parameter flow cytometry (CD34, TDT, CD45, CD79A, CD10, CD19, CD20, CD3, CD7, CD13, CD33, AND HLA). Based on residual marrow blasts at 15 and 35 days of the first dose of Vincristine/Daunorrubicin, patients were divided in 4 groups: • GR (<15% blasts at day 15 and <0.1% at day 35), who received standard therapy. • GR0 (0% blasts at day 15 and 35), who received shortened reinduction • PR15 (>15% blasts at day 15 and/or 0.1-1% blasts at day 35), who received 6 cycles of BFM based intensive chemotherapy (blocks HR 1, HR 2 and HR 3)• PR35 (>1% blasts at day 35), who received 3 HR blocks and were referred for ALLO BMT. EFS and OS were analyzed with Kaplan Meier and differences by log rank (MANTEL COX) test.
Results: 135 patients were included in this analysis (111 CALL, 23 TALL, 4 NULL ALL); percentages correspond to 10 years EFS and OS respectively. 56 PTS were GR0 (48 CALL and 8 TALL) with 91.8% and 94.2%; 27 were GR (26 CALL and 1 TALL) with 91.3% and 94.2%; 6 PR15 and 8 PR35 with 92.8% and 92.8%; historical cohort had 72.7% and 80.9%. Median time to follow up was 20 years in the historical cohort and 4.3 years in the MRD group.
Conclusion: ALL Therapy guided by multiparameter flow cytometry and MRD analysis provides excellent results in this protocol. High risk patients can be identified by response on day 15 and 35 and salvaged successfully with therapy intensification including ALLO BMT. Good responders are candidates for therapy reduction.

Poster # 343

T-CELL FUNCTION IS HETEROGENEOUS AND IMPAIRED IN A SUBSET OF PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Background: Despite intensification of chemotherapeutic regimens, survival rates in acute myeloid leukemia (AML) have plateaued which has created an impetus to explore novel therapeutics. Immune checkpoint inhibitors (ICIs) are an immune based therapy that have shown efficacy in solid malignancies and Hodgkin disease. We are performing functional studies on the bone marrow from patients with newly diagnosed AML to assess for T-cell dysfunction. Dysfunction, if present, may be reversed by ICIs and represent a therapeutic target.
Objectives: Assess for T-cell dysfunction within patients with newly diagnosed AML.
Design/Method: Total bone marrow mononuclear cells, including tumor cells and T-cells are labeled with cell trace violet, which is a proliferation tracking dye. The labeled cells are then incubated in 1 ug/ml anti-CD3-coated plates. Cells are harvested after 5 days and the effect of tumor cells on T-cell proliferative capacity is assessed by violet dilution of CD3+ cells by flow cytometry. At the time of harvest, the supernatant from the culture is removed and a multiplex bead-based assay is performed to measure the effect of tumor cells on T-cell cytokine production.
Results: Twenty-three bone marrow samples from patients with newly diagnosed AML were compared to 7 bone marrow samples from healthy donors. The average proliferation, reported as change in % of T-cells undergoing at least one division from the parent population, was lower in the patients with AML compared to the healthy donors (31.4% vs. 73.0%, $p<0.05$). AML samples were categorized as proliferators (n=11) or non-proliferators (n=12) if their proliferation was above or below the mean proliferation (31.4%), respectively. Proliferators had higher fold production of IL-2 (106.8 vs. 1.1, $p<0.05$), IL-10 (26.3 vs. 2.3, $p<0.05$), and IFNγ (962 vs. 7, $p<0.05$) when compared to the non-proliferators.
Conclusion: T-cell dysfunction is heterogeneous but present in a subset of patients with AML. Studies are concurrently being performed to define the mechanism behind this immune dysfunction which include functional assays in the presence of various ICIs. Additionally, immunophenotyping with time-of-flight mass cytometry is being performed to identify cell subsets present, evaluate their differentiation and activation status, and quantify the density of immune modifiers with a goal of predicting which patients have T cell dysfunction and may respond to ICIs.

Poster # 344

Ki-67 PROLIFERATIVE INDEX AS A PROGNOSTIC MARKER FOR THERAPEUTIC RESPONSE AMONG PEDIATRIC PATIENTS WITH DE-NOVO ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Early response to induction therapy is prognostic. Ki-67 is proliferation marker that has been used to predict treatment response and outcome in some adult cancers like breast and cervical cancer.
Objectives: To correlate Ki-67 activity in leukemic blasts at diagnosis with day 8 peripheral blood and day 29 bone marrow minimal residual disease (MRD) for therapeutic response at the end of induction chemotherapy.
Design/Method: Single institution prospective cohort study that evaluated the Ki-67 activity in 30 de-novo Pre-B ALL patients from September 2015 to December 2016. Ki-67 activity was measured using flow cytometry on the initial bone marrow samples. We used t-tests to look for relationship between Ki 67 levels at diagnosis and various continuous variables. For our study purpose, MRD is defined as "zero'' percent blasts on day 8 peripheral blood and day 29 bone marrow.
Results: We analyzed Ki-67 activity on initial diagnostic bone marrow samples in 30 patients (17 standard-risk and 13 high- risk patients based on National Cancer Institute criteria). MRD was positive in 18 and 7 patients on day 8 and day 29 respectively. There was a significant difference in the initial Ki-67 activity when analyzing the day 8 peripheral blood MRD ($p=0.0001$). The initial mean Ki-67 activity at diagnosis for MRD positive subjects on day 8 peripheral blood was 29.8 (SD 14) compared to MRD negative with a mean of 50.7 (SD 10). There was also a significant difference in the Ki-67 level when analyzing day 29 bone marrow MRD ($p=0.009$). The initial mean Ki-67 activity at diagnosis for subjects with positive MRD on day 29 bone marrow was 24.6. (SD 14) compared to MRD negative with the mean of 42.3 (SD 14). The mean ki-67 activity on high-risk patients was 46 (SD 13) compared to 33 (SD 15) on standard-risk ($P= 0.027$). The mean Ki-67 activity in females was 44.7 (SD 14) compared to 32.4 (SD 16) in males ($P =0.037$). There is no statistical difference in Ki-67 activity in relation with age, race, white blood cell count, percentage of bone marrow blasts and cytogenetics.
Conclusion: Our study concludes that patients with higher Ki-67 activity at diagnosis are more likely to achieve remission at day 8 and day 29 of induction chemotherapy. Ki-67 could be considered as a prognostic bio-marker for the therapeutic response.

Poster # 345

ADENOVIRUS INFECTION IN CHILDREN WITH AML: A REPORT FROM THE CANADIAN INFECTION IN AML RESEARCH GROUP

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Background: Children with acute myeloid leukemia (AML) are at high risk of life-threatening bacterial and fungal infection. However, little is known about the prevalence or severity of adenovirus infection in this population.
Objectives: To describe the characteristics, treatments and outcomes of adenovirus infection in a cohort of children with newly diagnosed AML.
Design/Method: We performed a retrospective chart review based upon two multi-center cohort studies which focused on identifying risk factors for infection in children with AML. Inclusion

criteria were patients with de novo AML who were ≤ 18 years of age at diagnosis with a clinical specimen positive for adenovirus.
Results: Among the 235 patients with AML, 12 (5.1%) had positive adenovirus testing. The most common site of isolation was stool (n=11, 91.6 %) and the most frequent symptom was diarrhea (n=11, 91.6 %). Two patients received specific treatment for adenovirus, namely intravenous immunoglobulin (IVIG) only in one patient and both IVIG and inhaled ribavirin in a second patient. In 11 patients, adenovirus resolved uneventfully without recurrence including 10 that received no adenovirus-specific therapy. However, one patient developed sepsis syndrome in the setting of disseminated adenoviral infection and died from multi-organ failure.
Conclusion: Conclusion: In children with AML, adenovirus infection was rare and typically not associated with severe disease, even without specific treatment. However, disseminated and fatal disease can occur in this population. Further investigations are needed to identify pediatric AML patients at particular risk for severe adenovirus infection and to determine optimal treatment approaches in these patients.

Poster # 346

LEUKEMIA-DERIVED EXOSOMES INDUCE PARACRINE AND AUTOCRINE CELL PROLIFERATION IN PEDIATRIC ALL

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Background: Exosomes are microvesicles (30-100 nm) produced by normal and malignant cells in most biological fluids. Exosomes represent the fingerprint of the parental tumor and are loaded with bioactive markers such as proteins, RNA and DNA, which may regulate tumor growth. Exosomal cargo can be transferred into target cells changing their biological properties. Our data present the first study to investigate a biological role of exosomes in pediatric acute lymphoid leukemia (P-ALL).
Objectives: 1/ Demonstrate transfer of ALL-exosomes into target cells with induction of cell proliferation2/ Confirm that leukemic exosome-induced paracrine and autocrine cell proliferation of leukemic cell lines is regulated by expression of proliferative and pro-survival genes with suppression of pro-apoptotic genes.3/ Analyze differences in miRNA profiling of ALL cell lines after induction with leukemic exosomes
Design/Method: Exosomes were isolated by ultracentrifugation from healthy donor (HD) serum, P-ALL serum and conditioned medium (CM) of SUP-B15 (B-ALL), JM1 (B-ALL), and CL-01 (normal B cells) human cell lines. All cell lines were exposed to different sources of leukemia-derived exosomes in a paracrine or autocrine fashion for 24hrs in duplicates. Proliferation was assessed by microscopic cell counting (trypan blue) and confirmed by colorimetric assay and gene expression for proliferation (Ki-67, PCNA), pro-survival (MCL1, BCL2) and pro-apoptotic (BAD, BAX) genes. Fold change was calculated by comparing controls (naive) vs. exosome-induced cell lines both in autocrine and paracrine fashion. miRNA profiling was performed with the Human Cancer Pathway Finder microarray (Qiagen).
Results: Exosomal internalization into the incubated cells was visualized by exosome labeling with a PKH67 fluorescent dye. We elucidated that CM-derived exosomes from SUP-B15 and JM1 cell lines induce cell proliferation in SUP-B15, JM1 (autocrine and paracrine for both cell

lines) and CL-01 cells (paracrine) ($p<0.01$). Moreover, P-ALL serum-derived exosomes promote paracrine cell proliferation in SUP-B15, JM1 and CL-01 cell lines compared to HD-derived exosomes ($p<0.0001$). At a molecular level, we found that exosomes from JM1 and SUP-B15 cells enhance expression of proliferation genes (PCNA, Ki-67) and pro-survival genes (MCL-1, BCL2), and suppress pro-apoptotic genes (BAD, BAX) in JM1 cells. Heatmap analysis of miRNA profiles of ALL cell lines before and after exposure of exosomes will be discussed.
Conclusion: Our data suggest that ALL exosomes induce cell proliferation in both paracrine and autocrine fashion of leukemic and non-leukemic B cell lines. Exosomes regulate these phenomena in a highly orchestrated way, by induction of proliferative and pro-survival genes, with suppression of pro-apoptotic genes.

Poster # 347

REVIEW OF CLOFARABINE IN PEDIATRIC PATIENTS WITH RELAPSE/REFRACTORY ACUTE MYELOID LEUKEMIA (AML) IN A CHILDREN'S CANCER CENTRE IN SAUDI ARABIA

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Background: Acute Myeloid Leukemia accounts for more than 30% of deaths from Leukemia. Although the outcome of pediatric AML has improved significantly with the use of anthracycline-based chemotherapy and good nursing care, approximately 50% children still develop disease recurrence with resistant disease. The conventional chemotherapy is also very toxic causing significant morbidity amongst the survivors. There is an urgent need for therapeutic options which are both more effective and less toxic than the conventional treatment.
Objectives: To evaluate the outcome of relapsed/ refractory A.M.L. in children after Clofarabine therapy.
Design/Method: This is a retrospective chart review of 10 pediatric (age at diagnosis $\leq$ 14 years) A.M.L patients, treated at our hospital, post relapse/ induction failure between 2005 and 2015, with reference to their clinical characteristics and treatment outcome.
Results: A total of 10 pediatric patients diagnosed with A.M.L. and after their 1st Relapse or Progressive Disease were included in the study. 60% (6) were male. Median age at diagnosis was 7.8 years (Min: 1.2 Max: 12.2 years), WBC 16.3X10^9, (Min: 2.3, Max: 317), Platelets 49X10^9 (Min: 13, Max: 161), HGB 70.5 (Min: 5.2, Max: 90). MLL Gene rearrangement was positive in 50% (3 of 6 done). CBFB was done in 5 patients, all were negative. 90%(9) were CNS-1 while the remainings were CNS-2. Cytogenetics were done in five, 60%(3) turned out abnormal with t(6;11), t(11;19) and t(10;11) each. 57.1%(4) were M5, 28.6%(2) M7 and 14.3%(1) was M0; for remaining FAB Classification data was not available. 60%(6) received PAML010, 20%(2) FLAG, 10%(1) MRC12 and ADE each as first line chemotherapy.CR-1 rate was 80%(8) after 1-2 cycles with 10.1 months median time to BM relapse. All received Clofarabine as salvage therapy. 80%(8) developed febrile neutropenia, 60%(6) had sepsis, 40%(4) had episodes of fungal infections, and 30%(3) had reversible mucositis. 50%(5) had recorded PICU admissions while refrectoriness to Clofarabine was seen in half of the cohort. Eventually 50%(5) were into CR post-Clofarabine therapy. 40%(4) went ahead for SCT. At the last contact, 40%(4) were in

Complete Remission. With 80 %(8) events and median follow-up time of 38.6 months, three years overall survival of our small group of patients was observed to be 0.150±0.128 (Median 14.8±4.5 months, 95% CI: 6.0-23.7).
Conclusion: Clofarabine is already being used as a key drug for relapsed/refractory A.M.L. patients in many countries, the efficacy of Clofarabine in Saudi pediatric patients needs to be evaluated in larger national trials.

Poster # 348

EXOSOMES SERVING AS LEUKEMIA BIOMARKERS THAT CORRELATE WITH DISEASE STATUS IN PEDIATRIC ALL

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Background: Exosomes are microvesicles (30-400nm) secreted by most cells including tumor cells in biological fluids. Exosomal cargo such as proteins, RNA and DNA can be horizontally transferred into target cells, changing their biological properties. Because exosomes are easily accessible by liquid biopsy and carry the genetic fingerprint of parental cells, exosomes emerge as promising biomarkers in cancer diagnostics. Although many hurdles such as high throughput methods for exosome isolation and poor exosomal RNA recovery remain to be solved, clinical applications of exosomes as biomarkers will certainly gain momentum in this rapidly expanding field.
Objectives: To identify leukemia-specific exosomes harvested from conditioned medium (CM) of ALL cell lines as well as from serum of P-ALL patients that correlate with disease status.
Design/Method: Exosomes were isolated from healthy donor (HD) and P-ALL serum by ultracentrifugation. Exosomes were also isolated from CM of JM1 (B-ALL), SUP-B15 (Ph+ALL) and CL-01 (normal B cells) human cell lines. Exosomal identity was confirmed with NanoSight Tracking Analysis as well as by Western Blot. We used an innovative method for direct conversion of very small starting volumes of purified exosomes into cDNA followed by gene amplification by 2-step PCR. Gene amplification was confirmed on 1.5% agarose electrophoresis.
Results: CM-exosomes of JM1 and SUP-B15 tested positive for CD10/CD34 expression by 2-Step PCR in contrast to CL-01 cells (control) that were negative. In addition, we evaluated serum exosomes in duos of liquid biopsies for either CD10/CD34 or CD10/CD19 expression (according to phenotypic expression of the parental leukemic blasts). P-ALL exosomes at Day 1 (diagnosis) tested positive for CD10/CD34 or CD10/CD19 while P-ALL exosomes of the same patients at Day 29 (remission) became negative by 2-step qPCR. Similarly, serum-derived exosomes from P-ALL relapse patients (blast count in bone marrow aspirates range 60-85% by FCM) were positive in contrast to P-ALL-exosomes of the same patients at time of 1st remission (blast count in bone marrow aspirate 0%) that tested negative. Protein expression was confirmed by ELISA assay. HD exosomes (controls) tested negative for CD34 expression.
Conclusion: P-ALL exosomes secreted in serum can be detected by gene expression analysis for leukemia-specific markers CD10/CD34 or CD10/CD19 and may serve as leukemia biomarkers

that correlate with disease status in the bone marrow. These preliminary data need validation in larger cohort clinical biomarkers studies.

Poster # 349

EPIGENETIC COMBINATION THERAPY FOR CHILDREN WITH SECONDARY MYELODYSPLASTIC SYNDROME (MDS)/ACUTE MYELOID LEUKEMIA (AML) AND CONCURRENT SOLID TUMOR RELAPSE

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Background: Secondary myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) is a rare but devastating complication of solid tumor treatment involving high dose topoisomerase II inhibitor and alkylator chemotherapy. For patients ineligible for hematopoietic stem cell transplantation (HSCT), epigenetic therapies, including DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors, have been utilized as palliative therapy, offering a well-tolerated approach to disease stabilization, prolonged survival, and quality of life. There is also emerging data that combination epigenetic therapy can stabilize certain solid tumors. Therefore, this approach holds appeal for patients with concurrent solid tumor relapse and secondary MDS/AML. However, literature is scarce on the use of epigenetic therapies in children and there are no published reports for palliative use in the setting of concurrent relapsed solid tumor disease and secondary MDS/AML.
Objectives: Report two pediatric patients with solid tumor relapse concurrent with secondary AML and MDS, respectively, who were treated with decitabine and vorinostat.Review the risk of secondary MDS/AML associated with cumulative doses of topoisomerase II inhibitor and alkylator therapy. Describe their responses to therapy and ability to achieve goals of care in the palliative setting.
Design/Method: This is a case series.
Results: Both patients required intensive multi-modal chemotherapy for metastatic solid tumors, involving high dose topoisomerase II inhibitor and alkylator chemotherapy. Patient 1, presenting with relapsed rhabdomyosarcoma and concurrent secondary AML, was treated with decitabine and vorinostat and achieved normalization of white blood cell count with a significant decrease in blast percentage, lasting 4 cycles. She experienced transfusion-dependent myelosuppression, but no other toxicity, and remained outpatient. Patient 2, presenting with multiply relapsed neuroblastoma and concurrent secondary MDS, achieved stable marrow disease without conversion to AML, lasting 9 months until she died from progressive solid tumor disease. She also experienced transfusion-dependent myelosuppression but no other toxicity. She remained predominantly outpatient and the family reported excellent quality of life. Neither patient appeared to have a response in solid tumor disease to the epigenetic therapy.
Conclusion: Based on our experience, we suggest that combination epigenetic therapy, decitabine and vorinostat, be considered in the palliative setting for pediatric patients with secondary AML/MDS who are ineligible for HSCT and faced with limited options. Further research is needed to better elucidate the mechanism of action of this drug combination in targeting MDS/AML and a prospective clinical trial is needed to evaluate clinical response, measure biomarkers, and objectively assess quality-of-life measures.

Poster # 350

EPIGENETIC INACTIVATION OF MIR-9 IN EVI1 HIGH PEDIATRIC AML: A ROLE FOR HYPOMETHYLATING AGENTS IN PEDIATRIC AML

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Background: EVI-1 hyper expression seen in 25% of pediatric AML patients is associated with an inferior prognosis (Balagobind Leukemia). The role of EVI1-induced aberrant methylation in AML is elusive. Oncogenic role of miR-9 has been reported in solid tumors, however is undetermined in AML. We showed a unique epigenetic role of miR-9 in murine myelopoesis previously (Senyuk PNAS).Targeted strategies for improving survival of certain patients with unfavorable cytogenetics are needed. Clinical trials in adult AML patients have evaluated hypomethylating agents however, why certain AML patients respond to these drugs is unknown. Pediatric experience with hypomethylating drugs in upfront treatment of de-novo AML is lacking.
Objectives: To determine the role of miR-9 in EVI1-high pediatric AML and to establish if hypomethylating agents may be a therapeutic strategy in these patients.
Design/Method: AML cell lines (AML-1, Kasumi-3, U-937) and 38 primary AML pediatric samples obtained from COG were checked for EVI-1 and miR-9 expression by q-RT PCR. Methylation of the CpG enriched miR 9 promoter was evaluated by direct sequencing of bisulfite-converted DNA. Human EVI1-high/EVI1-low AML cell lines and patient cells were treated with 5-AZA, analyzed for miR-9 expression, growth, apoptosis and colony formation. miR-9 was re-expressed in EVI1-high/EVI1-low cell lines and primary bone marrow cells using lentiviral vector and growth, apoptosis and colony formation were assessed. Xenograft models were generated by injecting AML1 cells infected with miR-9-Lego or Lego empty control vector into sublethally irradiated NSG-hSCF/hGM-CSF/hIL3 mice. The bone marrow, spleen and peripheral blood of the mice were analyzed for engraftment by flow cytometry.
Results: EVI1 hyperexpression in cell lines and AML patient samples correlates with downregulation of miR-9. There was significantly increased methylation of miR-9 promoter in EVI1-high cell lines (AML-1, Kasumi-3) and EVI1 high patient bone marrow cells compared to EVI1-low cell line (U 937) and EVI1 low patient cells. miR-9 expression was significantly reactivated by 5-AZA in EVI1-high in contrast to EVI1-low cell lines. Activation of miR-9 using 5-AZA treatment and re-expression of miR-9 by lentivirus results in significant growth inhibition, increased apoptosis and decreased colony formation in EVI1-high cell lines/BM samples but not EVI1-low cell lines, BM samples and control CD-34 cells. AML1 xenograft mice with ectopic expression of miR-9 had prolonged survival and delayed disease latency compared to control vector.
Conclusion: Our studies establish the critical role of EVI1 induced hypermethylation of miR-9 promoter in leukemogenesis in EVI1-high pediatric AML and suggest that hypomethylation is a potential therapeutic strategy for EVI1-high pediatric AML patients.

Poster # 352

USING IN-VITRO AND IN-VIVO DATA TO PERSONALIZE THERAPY AND DISCOVER NOVEL AGENTS FOR AML

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Background: Acute myeloid leukemia (AML) is a clinically and molecularly heterogeneous disease. The genetic heterogeneity of AML influences the natural course of disease progression and underlies clinical variation in therapy response. Recent advances include better risk classification, improved supportive care, and improvements in allogeneic hematopoietic stem cell transplantation. However, it is unlikely that further gains can be made through these measures alone.
Objectives: There is a need for development of novel chemotherapeutic and molecularly targeted agents against AML. Our aim is twofold – First to develop robust animal model systems to conduct preclinical studies that will help discover rational treatment approaches. Secondly we are developing and validating a drug screening platform for primary AML samples. We believe that in vitro drug sensitivity of leukemia cells could be used to guide personalized treatment for high risk patients in future.
Design/Method: Recent advances in genetic engineering have led to development of the transgenic mice that express human myeloid growth factors and are ideal for expansion of patient derived leukemia cells. Our laboratory uses transgenic mice to generate patient derived xenografts (PDX) using leukemia cells obtained directly from patients diagnosed with de-novo AML. Flow cytometry using human myeloid markers is done to confirm engraftment in the animal. We also perform in-vitro cytotoxicity studies on patient derived leukemia cells to assess their sensitivity to a panel of FDA approved and experimental drugs.
Results: Our PDX models match the heterogeneity of disease and offer an excellent option for testing the efficacy and toxicity of novel agents. Focused mutation analysis done on the myeloblasts reveal that driver mutations present in the founding clone of primary AML specimens are preserved in xenografts. Histological assessment demonstrates myeloid infiltration in spleen and liver of the xenograft. We perform cell viability, apoptosis and western blot analyses on patient's leukemia cells to assess their sensitivity to various chemotherapeutic agents. In one of our patients the choice of post-transplant maintenance therapy was governed by such in-vitro data.
Conclusion: Patient derived xenograft models will prove an excellent tool to test efficacy and toxicity of novel anti-leukemia agents and compare them with established chemotherapeutic agents. The results from these xenograft studies can provide the foundation for phase 2/3 clinical trials. Our study also validates the principle and clinical relevance of in-vitro drug testing. We believe that data obtained by these in-vitro studies on primary AML cells will be helpful in guiding clinicians in making rational modifications to treatment.

Poster # 401

EXPRESSION OF IMMUNE CHECKPOINT PROTEINS IN PEDIATRIC SARCOMA

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Background: Pediatric soft-tissue sarcomas are a group of malignant tumors that are treated with surgery, conventional chemotherapy and radiation, which are all very damaging to a developing child. While these therapies have improved survival rates for children with soft-tissue sarcomas, outcomes remain extremely poor for a subset of patients with metastatic, refractory disease. Thus, to improve outcomes and lessen toxicities, novel, directed therapies and reliable preclinical models are needed. Recently, immunosuppressive checkpoint molecules that negatively regulate immune cell function and enable local tumor escape, such as PD-L1, CTLA-4, CD200 and Indolamine 2,3-dioxygenase (IDO), have been described in adult solid tumors. Agents designed to inhibit these proteins have shown significant efficacy in human adult solid tumor studies. Oncolytic herpes simplex virus therapy (oHSV) is another innovative approach at targeting pediatric sarcomas. In addition to killing cancer cells directly, the virus stimulates the immune system to attack the tumor. Checkpoint protein inhibition may be the ideal therapy to combine with oHSV; however little is known about the expression of these checkpoint molecules in pediatric sarcomas, and a reliable pre-clinical model for testing oHSV with immune checkpoint inhibition is needed.
Objectives: We sought to evaluate the expression of immunosuppressive checkpoint molecules at baseline and in response to treatment with oHSV in two murine models of soft-tissue sarcoma.
Design/Method: Using two new murine models of undifferentiated sarcoma (SARC28 and SARC45), we performed flow cytometry to measure the expression of checkpoint molecules CTLA-4, PD-L1, CD200 and IDO. BALB/c immunocompetent mice bearing SARC28 received one intratumoral injection of oHSV or saline. Checkpoint molecule expression was measured by flow cytometry at days 3 and 7 post-injection.
Results: SARC28 and SARC45 showed expression of all four checkpoint proteins. IDO expression was the highest in both cell lines (93 ± 5.7% for SARC28; 91.2 ± 2.8% for SARC45), whereas CTLA-4 expression was lowest (32.3 ± 17.1% and 1.1 ± 1.3%, respectively). PD-L1 expression ranged from 35.1-58.1%. CD200 expression was significantly higher in SARC28 (63.3 ± 10.5%) than SARC45 (15.6 ± 2.2%). SARC28 demonstrated increased expression in all checkpoint molecules in response to treatment with oHSV compared to saline.
Conclusion: Both SARC28 and SARC45 have variable expression of targetable immune checkpoint molecules at baseline. SARC28 demonstrated increased expression of these molecules in response to oHSV, suggesting that these may be excellent models for testing immunovirotherapy approaches.

Poster # 402

EVALUATION OF PARENT-CHILD CONVERSATIONS SURROUNDING LI-FRAUMENI SYNDROME GENETIC TESTING

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Background: Advances in the application of genetic technologies have revealed a growing number of heritable disorders associated with an increased risk to develop cancer during childhood. Dialogues about cancer genetic testing and the implications of genetic risk status on children rest primarily with parents. As genetic testing approaches are increasingly used in the clinic, it is vital to understand if, when and how parents and children communicate about genetic testing for heritable cancer risk and to elucidate the factors that influence the content and outcomes of these conversations.
Objectives: To determine whether and how families communicate with their children about genetic testing for Li-Fraumeni syndrome (LFS), a rare and highly penetrant cancer predisposing condition.
Design/Method: Thirty-nine families with at least one child offered LFS testing were recruited. Semi-structured interviews examined parents' experiences in making decisions regarding the pursuit of LFS testing for their children and the communications surrounding test results. Transcripts were evaluated using a grounded theory approach for the criteria parents used to decide whether to initiate a conversation with their children and their self-efficacy for holding this conversation.
Results: This study evaluated interviews from 14 parents whose children tested positive for LFS. All 14 parents emphasized the importance of involving their child(ren) in conversations about undergoing LFS genetic testing and disclosure of the test results. Many parents self-identified as being from a "cancer family". Based on negative past experiences consisting of exclusion from conversations regarding cancer, these parents stated that they would approach communications about cancer with their children in a more open and inclusive manner. Nevertheless, evaluation of the interviews showed that only 9 of 14 parents (64%) actually disclosed the LFS test result to their child(ren). The remaining 5 parents, whose children ranged in age from 6-17 years old (mean: 11years), discussed having an increased cancer risk but did not reveal their child(ren)'s specific outcomes of LFS genetic testing. When asked, parents preferred to wait until their child(ren) were older before disclosing the results and/or discussing their broader implications.
Conclusion: While parents express a desire for open conversations with their child(ren) regarding LFS genetic testing, such discussions do not always occur. Communication is essential to enable understanding of genetic risk status and compliance with treatment, prevention and surveillance measures. Development of educational materials and other interventions to facilitate age-appropriate parent-child conversations about genetic testing and genetic risk status for cancer is needed.

Poster # 403

IL6 AND IL8 INHIBITION AUGMENT EFFECTS OF CYTOTOXIC CHEMOTHERAPY IN A MURINE MODEL OF METASTATIC OSTEOSARCOMA

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Background: Osteosarcoma (OS) is the most common primary bone tumor affecting adolescents. Metastatic disease leads to a dismal prognosis and more effective treatment is desperately needed. We have shown that IL6 and IL8 play a central role in OS metastasis. Both cytokines are reported to mediate survival and proliferation in other types of cancer. Prior work in our lab has demonstrated that disruption of IL6 and IL8 signaling pathways prevents the emergence of OS lung metastasis.
Objectives: In this study, IL6 and IL8 inhibitors were combined with standard cytotoxic chemotherapy to evaluate for synergy in vitro and in a murine model of metastatic OS.
Design/Method: In vitro studies – OS-17, a human OS cell line, was treated with vehicle alone, doxorubicin alone, doxorubicin plus SC144 (an inhibitor of IL6 receptor signaling), doxorubicin plus DF2156A (an inhibitor of IL8 receptor signaling) or doxorubicin plus both inhibitors. Measurements of cell proliferation were obtained over a period of 96 hours.Murine studies - SCID mice bearing OS-17 intra-tibial tumors were treated as follows: control mice received no treatment, anti-cytokine only mice received SC144 and DF2156A, chemotherapy only mice received doxorubicin alone, and dual therapy mice received IL6 & IL8 inhibitors in addition to doxorubicin.
Results: In vitro, inhibition of IL6 and IL8 pathways did not augment the cytotoxic effects of doxorubicin. However, mice bearing orthotopic OS tumors treated with IL6 and IL8 inhibitors showed increased responses to doxorubicin relative to those treated with chemotherapy alone.
Conclusion: This study suggests that microenvironmental factors, likely mediated by paracrine tumor-host interactions can alter a tumor's sensitivity to chemotherapy, as evidenced by the synergy observed in vivo, which was absent in vitro. Further investigation regarding this phenomenon, including investigations identifying the mechanisms that mediate this effect and larger studies validating these findings may prove valuable in the design of therapies intended to restore chemosensitivity.

Poster # 404

COMBINATION MET AND MEK INHIBITION IS HIGHLY EFFECTIVE IN NF1-MET AND NF1-P53 MPNST MODELS

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Background: Malignant Peripheral Nerve Sheath Tumors (MPNSTs) are highly resistant sarcomas that occur in approximately 8-13% of individuals with Neurofibromatosis Type 1 (NF1), with up to 20% of cases occurring in the 1st two decades of life. The prognosis for patients with NF1-related MPSNT remains poor, with 5-year survival rates ranging from 20-50%. In cases of unresectable disease, chemo resistance and recurrence typically follow any early responses to medical therapy. The lack of effective therapies for MPNSTs remains a significant issue for individuals affected by NF1 with a pressing need for novel therapeutic strategies. These MPNSTs have been shown to arise from NF1 null myelinating Schwann cells where neurofibromin deficiency results in deregulation of the RAS signaling pathway comprised of RAS–RAF–MEK–ERK. Additionally, several studies have implicated oncogenic MET signal

activation in NF1-related MPNST disease progression. We hypothesize MET and RAS interactions potentially drive key aspects of NF1 associated MPNST disease progression and that targeted therapy with MET inhibition in combination with further downstream MEK inhibition will be therapeutically effective.
Objectives: Define the pre-clinical activity of MET and MEK inhibitors through in vivo and in vitro models of NF1 associated MPNSTs.
Design/Method: We developed and characterized a unique mouse model unique of MET activation in p53 wild type, NF1-null myelinating cells (NF1-MET). Comparisons were made to other clinically relevant models of NF1 associated MPNSTs (i.e. NF1 deficient, p53-deficient MPNSTs (NF1-P53) and NF1 deficient MPNSTs (NF1)). Murine tumorgrafts were established in NSG mice as well as stable cell lines. Tumorgraft mice were treated with vehicle, capmatinib (MET inhibitor), trametinib (MEK inhibitor), and doxorubicin as single agents and in combination. Signaling responses to therapeutic interventions were followed through in vitro studies in the derived cell lines.
Results: Treatment of cell lines with capmatinib and trametinib showed effective inhibition of activity within the MET and RAS signaling pathways. In vivo studies revealed NF1-MET MPNSTs were uniformly sensitive to MET inhibition whereas only a small subset of NF1 P53 and NF1 MPNSTs were inhibited. Similarly therapy with MEK inhibition led to a response in a subset of all three models. Combination therapy with MET and MEK inhibition shows uniform sensitivity in the NF1-MET and NF1 MPNSTs, with a larger subset inhibited in the NF1-P53 compared to single agent treatment.
Conclusion: These results verify the role of MET and RAS interactions in MPNST progression and the potential of combination MET/MEK-targeted therapy in MPNST.

Poster # 405

IMMUNOVIROTHERAPY WITH ONCOLYTIC HERPES SIMPLEX VIRUS M002 IN MURINE MODELS OF PEDIATRIC SARCOMA

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Background: Pediatric soft-tissue sarcomas are a rare group of malignant tumors that represent approximately 7% of pediatric cancers. The mainstay of therapy includes surgery, conventional chemotherapy and radiation. While these therapies have improved survival rates for children with soft-tissue sarcomas, outcomes are extremely poor for patients with metastatic or refractory disease. Furthermore, these therapies are very damaging to a developing child and may result in lifelong sequelae. Therefore, to improve outcomes and lessen toxicities, innovative, targeted therapies and reliable preclinical models are needed. Oncolytic herpes simplex virus therapy (oHSV) is a novel approach at targeting pediatric sarcomas. HSV has been successfully engineered to introduce mutations that prevent a productive infection in normal cells while maintaining the virus' oncolytic activity against cancer cells. In addition to killing cancer cells directly, the virus stimulates an anti-tumor immune response.
Objectives: We sought to determine whether virotherapy with M002, an oHSV that produces murine interleukin-12 in physiologic relevant amounts during replication to enhance the anti-

tumor immune response, could target pediatric sarcomas.
Design/Method: Using two newly described murine models of undifferentiated sarcoma (SARC28 and SARC45), we performed flow cytometry to measure the expression of nectin-1 (CD111), an adhesion molecule found in a variety of tissues that is the primary HSV entry molecule. In vitro sensitivity of the cell lines to M002 killing was measured by the alamarBlue assay. Survival was measured in BALB/c immunocompetent mice with flank tumors that received 1-3 intratumoral injections of M002 or saline.
Results: Both sarcomas had very high expression of CD111 (>87%), suggesting that oHSV should be able to readily enter the tumor cells, and were highly sensitive to in vitro killing by M002 with an LD50 ranging from 0.7-1.7 plaque-forming units (PFU)/cell. In tumor-bearing mice, intratumoral M002 slowed tumor growth and significantly prolonged survival compared to control mice.
Conclusion: These results indicate that two new undifferentiated sarcoma murine models are sensitive to oHSV M002 suggesting that pediatric sarcomas may be an excellent target for oncolytic immunovirotherapy. Future studies will explore the immune response to this therapy and ways this response may be augmented for therapeutic benefit.

Poster # 406

DIFFERENTIATED THYROID CANCER OUTCOMES IN THE PEDIATRIC/ADOLESCENT POPULATION: A LONGITUDINAL REVIEW FROM A SINGLE CENTER

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Background: Differentiated thyroid cancer (DTC) is the most common cancer in the adolescent and young adult (AYA) population. Optimal management remains controversial. In 2015, the American Thyroid Association (ATA) published guidelines for the management of pediatric DTC.
Objectives: We report our interdisciplinary experience in management of children and adolescent patients with DTC at a single institution against the framework of the new ATA guidelines.
Design/Method: Retrospective analysis of all patients diagnosed with DTC at Cincinnati Children’s Hospital Medical Center from 2008-2016 was performed. Demographics, histology, staging, molecular genetics, treatment and follow up were assessed.
Results: Of the 32 patients who underwent treatment, 29 (90.6 %) had papillary and 3 (9.4 %) had follicular carcinoma. Median age at diagnosis was 15 years (range 5-20). Classified by ATA risk stratification; 16 (50%), 10 (31.3%), and 6 (18.7%) patients had low, intermediate and high risk disease respectively. All patients underwent total or completion thyroidectomy. Ten of sixteen (62.5%) with low risk disease and all intermediate/high risk patients received I-131. For low risk patients treated prior to 2012 vs subsequently, I-131 dosing dropped from an average of 1.5 mCi/kg to 0.57 mCi/kg and percentage of patients who did not receive I-131 increased from 20 to 40%. Patients were monitored with recombinant thyrotropin-stimulated and unstimulated thyroglobulin concentrations and I-123 scans, and cervical MRI and chest CT as indicated.

Patients had one-year post-operative TSH concentrations below (41%), within (34%), or above (25%) goal range as defined by the ATA guidelines. Of 6 patients with molecular analysis, 1 patient each had a PTN variant, ALK STRN-ALK fusion, and BRAF V600E/TET2 fusion. Three additional patients had germline DICER1 mutations including 2 siblings. Persistent or recurrent disease was present only in high risk patients. Two patients with iodine refractory disease received trametinib for radio-iodine sensitization. All patients were alive and well at last follow-up (median 4 years).
Conclusion: Data is needed to determine outcomes of pediatric/adolescent DTC patients managed by ATA approaches. Recent reduction of I-131 use in low risk patients are consistent; however routine neck ultrasound has not been universally adopted. TSH concentrations within ATA targets were not universally achieved; thyroid replacement dosing, symptoms of thyroid imbalance, and patient medication adherence deserve further attention. Continued observation in patients with high risk disease may ultimately prove inadequate considering their relatively longer life span; further investigation into the role of molecular targeted therapy in this group is warranted.

Poster # 407

ESOPHAGITIS IN THE MULTIMODALITY TREATMENT OF THORACIC EWING SARCOMA: INCIDENCE, RISK FACTORS, AND MANAGEMENT

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Background: Ewing sarcoma of the thoracic spine and chest wall is frequently treated with concurrent chemotherapy and radiation (RT). Acute esophagitis related to multimodality treatment may lead to hospitalization and delays in treatment.
Objectives: The aim of this study was to analyze the incidence, risk factors, and management of esophagitis in pediatric patients with Ewing sarcoma of the thoracic spine and chest wall.
Design/Method: This study was a single institution retrospective review of patient's age 1-20 years treated at the University of Florida and Nemours Children's Specialty Clinic in Jacksonville, Florida, United States between 2006-2016. Medical records were reviewed for patient and treatment characteristics associated with CTCAE grade 2 or higher esophagitis. RT plans were reviewed and various esophageal dose metrics were analyzed.
Results: Twelve of 37 patients (32%) who received chemoradiation developed acute esophagitis. The median time to onset of symptoms was 3 weeks. Four patients had grade 2 esophagitis, 7 patients had grade 3 esophagitis, and 1 patient had grade 4 esophagitis. All 12 patients developed dysphagia and 8 (67%) also experienced odynophagia. Weight loss was observed in 11 patients (92%); 25% of patients lost >10% of their body weight. During RT, all patients received chemotherapy with vincristine/cyclophosphamide or vincristine/ifosfamide. However, patients who also received ifosfamide/etoposide had higher incidence of esophagitis (56% vs 25%, $p=0.01$). Neutropenia (ANC < 500 K/mcL) was associated with an increased risk of esophagitis (60% vs 14%, $p<0.01$). Although esophagitis was observed in three patients who received little or no RT to their esophagus, RT significantly contributed to the incidence when maximum

esophageal dose was > 47Gy (69% vs 5%, p<0.0001) and esophageal D5cc was > 15Gy (67% vs 9%, p<0.001). All 12 patients with esophagitis were initially managed with oral opioid analgesics. Nine patients with persistent symptoms received subsequent fluconazole for empiric fungal treatment and each had decreased need for opioid analgesics within 2-5 days. Seventy percent of patients had resolution of esophagitis within one month of completing RT.
Conclusion: Approximately a third of patients with Ewing sarcoma of the thoracic region will develop acute esophagitis. If radiation oncologists can keep the esophageal D5cc dose <15Gy and maximal esophageal dose <47Gy, the rate of acute esophagitis may be less than 10%. However, our cases observed in the absence of esophageal radiation, as well as the association with neutropenia and consistent response to antifungal therapy, suggest chemotherapy associated toxicity and an infectious component as part of the process.

Poster # 408

CLINICAL AND GENOMIC CHARACTERIZATION OF PROSTATE LESIONS IN MULTIPLE ENDOCRINE NEOPLASIA 2B

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Background: Multiple Endocrine Neoplasia (MEN) 2B is a hereditary disorder characterized by medullary thyroid cancer (MTC), pheochromocytoma, mucosal neuromas, and other non-tumor manifestations. Few cases of prostatic neuroendocrine tumors are reported in patients with MEN2B, however the significance of these lesions is yet to be elucidated.
Objectives: To describe and characterize prostate lesions in MEN2B.
Design/Method: We performed a retrospective review of imaging, pathology, and clinical characteristics of boys with MEN2B enrolled in a natural history study (NCT01660984). DNA from prostate lesions, thyroid, lymph node and normal tissue were analyzed by a custom capture next-generation sequencing panel. Bioinformatics analyses identified single nucleotide variants (SNV) and copy number variants (CNV). Cluster analysis determined the relationship between thyroid, lymph node, prostate lesions and normal tissue.
Results: Fourteen male patients (median age at enrollment 15.5 years, range 9-22) with the RET p.Met918Thr germline mutation and MTC were analyzed. Images from pelvic CT, MRI, and FDG-PET were available for 14, 10 and 12 patients, respectively. Prostate lesions were noted in four patients. Three lesions were found incidentally, and one was identified during investigation of pelvic pain. All four patients with prostate lesions had persistently elevated calcitonin after resection of primary MTC. Two patients were on vandetanib for MTC. Prostate biopsies were available for patients #8 and #24. Prostate lesions were pathologically indistinguishable from primary MTC by morphology and stained positive for calcitonin, consistent with neuroendocrine tissue. Patient #8 shared 1009 of 1121 (90.0%) and patient #24 shared 725 of 763 (95.0%) SNVs between prostate and normal tissue. The lymph node metastasis of patient #8 and primary MTC lesion shared 766 of 828 (92.5%) SNV homology. Prostate lesions did not have any exclusive SNV homology with primary MTC or lymph node lesions in either patient. Prostate lesions of

patient #8 had 44.97% and patient #24 had 7.79% change in copy number compared to normal tissue. Cluster analysis of CNV showed closer relationship between primary MTC and lymph node metastasis than between the primary MTC and prostate lesions.
Conclusion: We identified prostate lesions in four of 14 boys with MEN2B and metastatic MTC. Our data imply that prostate lesions are more frequent than previously described and suggest that prospective studies to monitor the prostate may be warranted. Despite pathological similarities to MTC, our data suggest that prostate lesions may be primary neuroendocrine tumors rather than metastatic MTC. Further analysis of panel-sequencing data, whole exome DNA, and RNA sequencing are ongoing.

Poster # 409

EFFECT OF HYPOXIA AND LOW GLUCOSE MEDIA ON EWING SARCOMA CELL VIABILITY, CELL CYCLE, AND CANCER STEM CELLS

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Background: Ewing sarcoma (ES) is a malignancy with poor event free and overall survival due to relapse and metastatic disease. Tumor exposure to hypoxia is associated with increased malignant potential and therapy resistance, which are characteristics of cancer stem cells (CSC).
Objectives: Evaluate if ES cells resistant to hypoxia-induced apoptosis and nutrient deprivation (low glucose) have a CSC phenotype.
Design/Method: The ES cell line A673 was grown under variable conditions including normoxia (20%), 1% hypoxia, 2.5% hypoxia, and media glucose concentrations of 0.45, 0.9, 3.15, and 4.15g/L. An MTT assay was used to measure cell viability. Propidium iodide analysis for flow cytometry was performed to define cell cycle parameters under these conditions. A673 cells were grown in neurosphere media under normoxia and hypoxia (1% and 2.5%) and numbers of neurospheres formed over 7 days counted for each condition were used as a functional assay for CSC. The neurosphere assay was validated using flow cytometry markers for stemmness including CD133, side-population, and ALDHhi.
Results: Growing cells in high glucose concentrations (4.15g/L) and hypoxia (1% and 2.5%) there was a decrease in cell viability. No pellet was seen and no cells were visualized microscopically at the 0.45g/L glucose with 1% hypoxia suggesting the double insult of hypoxia and low glucose killed the cells. In normoxia and 4.15g/L glucose ES cells had decreased viability compared to lower glucose concentrations. At 0.9 and 3.15g/L glucose, hypoxic cells had greater viability than normoxic cells suggesting a window of glucose concentrations for growth of hypoxic cells. Cell cycle analysis showed 2.8% apoptosis at normoxia, 0.71% at 2.5% hypoxia, and 1.14% at 1% hypoxia. No significant differences in G or S phase were seen. Neurosphere assay showed a significant increase in sphere numbers in hypoxic versus normoxic conditions.
Conclusion: Hypoxia is a metabolic stressor which decreases cell viability in ES. Apoptosis is not increased under hypoxic conditions, therefore decreased viability is likely through other pathways such as necrosis or autophagy. Growth under hypoxia appeared to be optimal in normal or moderately high glucose concentrations. ES cells are likely adapted to thrive in these stressful metabolic conditions. The high sphere forming capacity in hypoxia suggests that low

oxygen enriches for CSC. Results of ongoing studies using a panel of stem cell markers and limiting dilution tumor growth in NSG mice will better define the effects of hypoxia and low glucose on CSC related tumorgenicity and potential vulnerabilities for therapy.

Poster # 410

PEDIATRIC MELANOMA: A RETROSPECTIVE REVIEW OF 26 CASES

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Background: Melanoma is the most common skin cancer in children, and its incidence is rising. The ideal treatment approach is unknown and existing treatment guidelines are extrapolated from adult standards.
Objectives: This study aims to describe the outcomes of pediatric melanoma and add to the current knowledge on the topic.
Design/Method: We retrospectively reviewed the medical records of melanoma patients aged less than 21 years at diagnosis and analyzed demographics, clinical presentation, diagnosis, treatment, and outcome.
Results: We identified 26 patients with melanoma diagnosed at a median age of 10.3 years (1.7-17.7) over a 20-year period. No male or female predominance was identified. Melanoma was most prevalent among whites (65%), then Hispanics (23%) and African Americans (12%). Common primary sites included the thigh (19%), face (19%), trunk (15%), and upper limbs (15%). The lesions were primarily amelanotic (27%) and had histopathological features of spitzoid melanoma (54%). Eight patients (30%) had stage 0-II melanoma and all were treated with wide excision; one patient received adjuvant high-dose interferon α-2b. All were alive at last follow-up without any evidence of disease. Fourteen patients (54%) presented with stage III melanoma and all were initially treated with wide local excision and lymph node dissection. Among them, five did not receive systemic therapy; four were alive without disease and one had developed lung metastases at last follow-up. Nine stage III patients were treated with adjuvant high-dose interferon α-2b; eight were alive at last follow-up and one developed local and distant recurrence and died despite treatment with high-dose interleukin-2, ipilimumab, and temozolomide. Three patients (11%) presented with stage IV melanoma. Two patients had primary CNS melanoma; 1 was treated with radiotherapy and was alive at last follow-up and the other died despite radiotherapy and temozolomide treatment. One patient with distant metastasis went into remission after treatment with high-dose interferon α-2b, high-dose interleukin-2, vinblastine, cisplatin, and bleomycin. One patient with intraocular melanoma developed distant metastasis and died despite enucleation. The 5-year overall survival of all melanoma patients was 82%. Sixty-four percentage of spitzoid melanoma patients had lymph node metastases and all of them were alive at last follow-up.
Conclusion: Children presenting with stage 0-III melanoma have favorable outcomes with wide excision of primary lesion and complete lymph node dissection in stage III patients. The need for adjuvant interferon α-2b in stage III patients is unclear. Patients presenting with stage IV melanoma have poor outcomes despite the use of systemic therapies.

Poster # 411

RADIATION-ADAPTED EWING SARCOMA XENOGRAFT MOUSE MODEL DEMONSTRATES DECREASED SENSITIVITY TO IONIZING RADIATION THERAPY

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Background: Ewing sarcoma (ES) is the second most common pediatric bone cancer and accounts for approximately 1.7-3.7% of all pediatric cancer diagnoses between the ages of 10-20 years old. Recent reports demonstrate five-year overall survival rates for both localized and metastatic disease combined of approximately 60%, but patients with relapsed/resistant disease have a dismal five-year overall survival rate of only 15-20%. Adequate local control is highly prognostic for rates of relapse and overall survival in patients with ES, and more investigations are needed to create better approaches with lower effective doses for patients who rely on radiation therapy for local control. However, very little has yet been done to elucidate mechanisms of radio-resistance in ES.

Objectives: This study establishes a radiation-adapted in vivo model to assess the molecular perturbations associated with ES response to ionizing radiation to provide insights and future approaches to relapsed/resistant disease.

Design/Method: Radiation-adapted cell populations were created in vitro by exposing Ewing sarcoma human cell lines to fractionated doses of ionizing radiation over a several week period. Assays to assess migration/invasion potential and cancer stem cell properties were performed on the radiation-adapted cells. Orthotopic intratibial in vivo investigations were performed with radiation-sensitive and adapted ES cells to generate tumors. Transplanted mice underwent whole body positron-emission tomography scans (PET) followed by fractionated ionizing radiation therapy (IRT) directed at the primary tumor. Mice were subsequently monitored for tumor regression and change in metabolic activity on PET.

Results: Exposure to repeated fractionated doses of ionizing radiation caused a statistically significant increase in migratory, invasive and stem cell properties for radiation-adapted ES cells compared to non-irradiated wild type controls. Transcriptome analysis from ES radiation-adapted populations revealed significantly decreased expression of forkhead box O1 (FOXO1) and increased expression of serum glucocorticoid regulated kinase 1 (SGK1) when compared to control ES cells. Radiation-adapted tumors demonstrated significantly less tumor regression ($p = 0.03$) on day of mouse death compared to wild type tumors. Wild type xenograft tumors also had significantly lower metabolic activity on PET after IRT compared to radiation-adapted xenograft tumors ($p = 0.03$).

Conclusion: In vitro investigations revealed increased migratory and invasive phenotypes and increased cancer stem cell subpopulation in radiation-adapted cell lines. In vivo investigations demonstrated increased metabolic activity and significantly decreased sensitivity to IRT as demonstrated by growth response curves and PET activity. In vivo and in vitro investigations identified possible radiosensitizing-dependent targets in SGK1 and FOXO1.

Poster # 412

GASTROINTESTINAL CANCERS, OSTEOGENIC SARCOMA AND MYELODYPLASTIC SYNDROME PREDOMINATE IN DIAMOND BLACKFAN ANEMIA

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Background: Diamond Blackfan anemia (DBA) is an inherited bone marrow failure syndrome characterized by red cell aplasia and congenital anomalies. We previously quantified the cancer incidence in the patients in the DBA Registry of North America (DBAR). This update reveals additional solid tumors (ST), in particular gastrointestinal tumors, and an alarming incidence of myelodysplastic syndrome (MDS).
Objectives: To report the types, ages, outcomes and hazard rates in DBA patients with neoplasia enrolled in the DBAR.
Design/Method: The patients/families and their physicians completed a detailed questionnaire which was verified through medical records and telephone interviews. The ratio of observed to expected (O/E) cancers was computed using SEER data, and the cumulative incidence and hazard rate of hematopoietic stem cell transplant (HSCT), acute myeloid leukemia (AML), ST, and MDS by age were calculated.
Results: There were 702 patients with 12,376 person-years of follow-up. Solid tumors were reported in 23 patients, acute myeloid leukemia (AML) in 3, and MDS in 8. The median age at diagnosis of a ST was 35 years (range, 11-63). There were 9 gastrointestinal carcinomas (7 colon, 1 gastroesophageal, and 1 esophageal), 4 osteogenic sarcoma (OS), 2 breast cancer and 2 squamous cell carcinomas (SCC; vaginal and oral) and 9 others, with 3 patients having more than one cancer. Cancer incidence in DBA was significantly elevated with an O/E ratio for all cancers combined of 4.75; significant O/E ratios were 352 for MDS, 45 for colon carcinoma, 42 for OS, and 29 for AML. Although the sample size is small it appears that the cancer risk by genotype correlates only with the relative incidence of that genotype in the DBAR cohort. By their mid-40s, 24% had received a HSCT, 23% had died, 2% had AML, and 12% had developed a ST. The median overall survival was 51 years and the actuarial risk of MDS in the absence of any competing risks was 50% by age 30 years. Also of note, there are 4 patients who had ST after HSCT excluded from the analysis (2 rectal carcinoma, 1 OS and 1 rhabdomyosarcoma).
Conclusion: Cancer risks in DBA appear to have reached those seen in dyskeratosis congenita (DC) but are still lower than in Fanconi anemia (FA). Furthermore, the type of STs in DBA (gastrointestinal carcinoma and OS) vs. FA (head and neck SCC) is quite different. The risk of MDS in DBA is also elevated, although not as high as in FA or DC.

Poster # 413

ASSOCIATION OF MYCN COPY NUMBER WITH CLINICAL FEATURES, TUMOR BIOLOGY, AND OUTCOMES IN NEUROBLASTOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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Background: High-level amplification at the MYCN locus (MNA) is associated with poor outcome and key clinical and biological features in neuroblastoma. Less is known about these associations in patients with low-level MYCN copy number gain.
Objectives: This study compares clinical characteristics, biologic features, and clinical outcomes of patients according to MYCN copy number.
Design/Method: In this retrospective cohort study, we categorized neuroblastoma patients as having MYCN wild-type, MYCN gain, or MYCN amplification. We used Cochran-Armitage tests of trend to investigate ordered associations between MYCN copy number category and variables of interest. We used log-rank tests and Cox models to compare event-free survival (EFS) and overall survival (OS) according to MYCN copy number.
Results: The analytical cohort consisted of 4,672 patients including 3,694 (79.1%) with MYCN wild-type tumors, 133 (2.8%) with MYCN gain, and 845 (18.1%) with MNA. We observed significant ordered trends in multiple clinical and biological features. We identified a non-linear association of 11q aberration with MYCN copy number, with highest rates in tumors with MYCN gain. Patients with MYCN gain had inferior EFS and OS. Patients with high-risk disease and MYCN gain had lower response rates to induction chemotherapy. Patients with non-stage 4 disease and patients with non-high risk disease with MYCN gain had significantly increased risk for death, a finding confirmed on multivariate testing, and these deaths were observed within the first year of diagnosis.
Conclusion: Neuroblastomas with MYCN gain demonstrate patterned clinical and biological features in a continuum with MYCN wild-type tumors and MYCN amplification, with 11q aberration a notable exception. Patients with MYCN gain have inferior outcomes compared to MYCN wild-type, especially in those with otherwise more favorable features.

Poster # 414

JUVENILE NASOPHARHYNGEAL ANGIOFIBROMA: EXPERIENCE OF A REFERRAL CENTER IN GUATEMALA

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Background: Juvenile nasopharhyngeal angiofibroma (JNPAF) is a pathological benign vascular tumor with aggressive and destructive behavior that usually affects male adolescents. Its treatment is not well defined although embolization, surgery and radiation are considered standard approaches. Lately the use of antiangiogenic therapies has been proposed. The selection of treatment depends on individual institutional resources and expertise. Here we describe the experience of Unidad Nacional de Oncologia Pediatrica (UNOP) in Guatemala in the treatment of JNPAF.
Objectives: To describe a 16 year institutional experience in treating JNPAF in Guatemala.
Design/Method: Retrospective review of patients treated for JNPAF at UNOP from January

2000 to June 2016.
Results: Over 17.5 years, an average of 350 pediatric oncology new diagnosis per year were seen at UNOP. Fifteen patients with JNPAF were found since 2,000 for and incidence of 0.2%. Two patients had incomplete information on staging and treatment and were not included in this analysis. All patients were male, with ages ranging from 8 to 17 years (mean 12.5 years). The most common presenting symptoms were nasal obstruction (n=14, 93%) and epistaxis (n=10, 67.6 %). Three patients (20%) presented with exophthalmos. CT scan was done for staging in all patients. Five patients were stage I (33%), 4 were stage II and 4 stage III (26% each). Treatment modalities used were: embolization followed by surgery (n=5, 38%), radiotherapy alone (n=5, 38.5%), partial resection followed by radiation (n=3, 23%). Embolization facilitated complete surgical resection in 4 cases and spare patients from radiation therapy. However, two patients (15%) had tumor relapse 7 and 12 months after surgery and were later treated with radiation therapy. Patients treated with upfront radiation therapy did not have tumor recurrence, although experience radiation related long-term side effects. Patients were followed for a mean of 24 months (range 1 – 60 months). At the time of last follow up all patients were alive without evidence of active disease.
Conclusion: JNPAF represents a small subset of all malignancies at UNOP however given the aggressive and destructive nature of JNPAF patients presented with diagnostic and therapeutic challenges. Surgery and/or radiation were the main treatment modalities. Arterial embolization was feasible with collaboration with other local institutions; Utilization of arterial embolization facilitated surgical resection and spare radiation in a small subset of patients. The use of antiangiogenic therapies such as Bevacizumab or Sirolimus has not yet been utilized in our setting but may represent an opportunity to decrease treatment related morbidity.

Poster # 415

INHIBITION OF ULK1-DEPENDENT AUTOPHAGY DECREASES TUMOR GROWTH AND PROLONGS SURVIVAL IN NSG MICE WITH NEUROBLASTOMA

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Background: Neuroblastoma is a childhood cancer of the nervous system that accounts for >10% of childhood cancer related mortality. Its poor prognosis is attributed to high rates of metastatic disease and a poor response to conventional chemotherapy. Autophagy is a lysosomal degradation pathway that is known to play critical roles in regulating tumor growth, metastasis and chemo-resistance in a variety of cancer types. However, the physiologic importance of autophagy in neuroblastoma tumor progression and therapeutic response remains unclear. Elucidating the role of autophagy in neuroblastoma will not only further our understanding of the underlying mechanisms driving neuroblastoma, but could also provide a novel target for therapeutic benefit.
Objectives: To investigate the role of autophagy through inhibition of ULK1 kinase in neuroblastoma growth, metastasis and discover new therapeutic strategies.
Design/Method: To investigate the effects of autophagy inhibition in neuroblastoma, we transduced SK-N-AS neuroblastoma cell line with a plasmid vector expressing a dominant

negative ULK1 gene (CMV-dnULK1) to inhibit the essential autophagy kinase, ULK1. An identical plasmid lacking dnULK1 (CMV-Empty) was generated as control. In addition, both the CMV-dnULK1 and CMV-Empty cell lines were transduced with a luciferase reporter gene for monitoring tumor growth and metastasis in vivo. After verifying dnULK1-mediated inhibition of autophagy, as evident by p62 accumulation and perturbed LC3 lipidation, SK-N-AS cells harboring the dnULK1 construct were injected subcutaneously in the flank of NSG mice to assess tumor growth in vivo. These cells were also injected through the tail vein into NSG mice to assess tumor metastasis.
Results: Mice bearing subcutaneous CMV-dnULK1 tumors displayed a significant reduction in tumor volume and weight as compared to CMV-Empty control mice ($p<0.01$). In addition, mice receiving tail vein injections of CMV-dnULK1 SK-N-AS cells displayed a significant reduction in tumor engraftment in the liver ($p<0.001$), as well as an increase in overall survival ($p<0.0001$). Furthermore, metastatic liver tumors harvested from mice bearing CMV-dnULK1 demonstrated significantly lower mitotic indices ($p<0.01$) in comparison to control mice.
Conclusion: Here, we demonstrate that inhibition of autophagy through inhibition of ULK1 kinase results in reduced tumor growth and prolonged survival of mice with metastatic neuroblastoma. The underlying mechanisms are currently under investigation, and may provide insight into the development of novel therapies for neuroblastoma.

Poster # 416

SALVAGE REGIMENS FOR PEDIATRIC PATIENTS WITH RELAPSED NASOPHARYNGEAL CARCINOMA

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Background: Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy has resulted in event-free survival rates of approximately 85% for children with nasopharyngeal carcinoma (NPC). Outcomes for children with relapsed NPC however are dismal, and no standard salvage regimen exists for these patients.
Objectives: To investigate salvage regimens used for children with relapsed NPC and identify agents with the highest activity in this setting.
Design/Method: Data were obtained by retrospective review of medical records from pediatric patients with relapsed NPC across three institutions, as well as collected from published literature.
Results: Fourteen pediatric patients were diagnosed with relapsed or progressive NPC at a median age of 16 years (range 11-18 years). All patients had stage III or IV disease at initial diagnosis, and were treated with cisplatin-based chemotherapy and radiation. The median time to first relapse was 9 months (range 4 – 27 months). Sites of initial relapse included bone (n=8), lung (n=4), lymph node (n=3), soft tissue (n=2), and 1 each in liver, nasopharynx and eyes. Seven patients were treated with carboplatin plus a taxane (paclitaxel or docetaxel), and two of these patients also received gemcitabine. Six of these seven patients had disease progression, although three remained alive without disease after subsequent treatment with autologous EBV-specific T lymphocytes (EBVSTs). Two patients were treated with oxaliplatin in combination

with doxorubicin or gemcitabine. Both patients treated with oxaliplatin regimens had a complete response to therapy, and were alive without disease at last follow-up. One patient with isolated occipital bone relapse was alive without disease after surgical resection followed by vincristine, doxorubicin, cyclophosphamide and irinotecan chemotherapy. One patient achieved a complete remission and remains alive without disease after nivolumab monotherapy. Three patients received other regimens and died after disease progression. Overall, seven patients were alive after a median follow-up of 43 months. Three-year event-free and overall survival were 34% and 44% respectively.
Conclusion: These data demonstrate that disease remission and long-term survival are possible for some pediatric patients with relapsed NPC. Although definitive recommendations for salvage chemotherapy cannot be determined based on outcomes from 14 patients who received varied regimens, an oxaliplatin-containing regimen in combination with gemcitabine would be a reasonable choice for first line treatment for children with relapsed NPC. Consolidation with autologous EBVSTs should be considered for patients with EBV-positive NPC, although availability of this treatment is currently limited. The role of immune checkpoint inhibitors in this setting should also be investigated in future studies.

Poster # 417

MXI1 and MXI0 DIFFERENTIALLY AFFECT N-MYC EXPRESSION IN NEUROBLASTOMA

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Background: Neuroblastoma (NB) is the most common extracranial malignancy of childhood. The Myc family of proteins regulates cell growth and proliferation and has been implicated in the etiology of many cancers, and MYCN amplified NB is associated with a poor prognosis. Investigating specific tumor pathways will further our understanding of neuroblastoma pathogenesis and lead to future therapeutic options. Mxi1 is a member of the MAD family that inhibits N-Myc activity. Mxi0 is an alternatively spliced variant of Mxi1 that lacks the inhibitory activity of Mxi1. In fact, preliminary studies indicate that Mxi0 promotes N-Myc activity. Furthermore, N-Myc shifts the balance of expression from Mxi1 towards Mxi0 suggesting it protects its function in NB.
Objectives: Investigate how Mxi1 and Mxi0 modulate N-Myc expression using inducible cell lines.
Design/Method: We created native NB cell lines (SH-SY5Y (low MYCN) & IMR-32 (high MYCN)) with inducible expression of Mxi1 or Mxi0. Cell proliferation and survival following Mxi1 and Mxi0 induction were quantified using BrdU and MTT assays, respectively. The effect of Mxi1 and Mxi0 on N-Myc expression was measured by RT-PCR and immunoblot analysis. Finally, we utilized RNA Sequencing (RNASeq) to assess the impact of Mxi1 and Mxi0 expression on N-Myc-regulated genes.
Results: As expected, overexpression of Mxi1 inhibits NB cell viability (41% of control). Conversely, overexpression of Mxi0 in NB cell lines leads to increased cell viability (180% of control), indicating divergent effects of Mxi0 and Mxi1. In addition, we observed that MYCN

mRNA and N-Myc protein levels decrease in response to Mxi1 expression and increase when Mxi0 is expressed. Examination of the downstream impact of Mxi1 and Mxi0 expression by RNASeq analysis showed a clear augmentation of N-Myc-regulated genes, notably those involved in transcription and metabolism, and downregulation of the PTEN in response to Mxi0 induction.
Conclusion: Overexpression of Mxi1 in NB cell lines leads to inhibition of N-Myc-mediated cell proliferation, while Mxi0 promotes N-Myc dependent proliferation. These effects are partially due to alterations in N-Myc expression. Mxi1 decreases N-Myc expression, thus amplifying its inhibitory effects. In contrast, Mxi0 enhances N-Myc expression, potentiating its effects. Mxi0 expression also increases expression of N-Myc-regulated genes. A better understanding of the interactions among Mxi1, Mxi0 and N-Myc and how their relative expression levels affect NB physiology may aid in developing more effective targeted therapies to improve outcomes in pediatric NB patients.

Poster # 418

A MULTICENTER RETROSPECTIVE REVIEW OF PEDIATRIC LEYDIG CELL TUMOR OF THE TESTIS

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Background: Leydig cell tumors (LCTs) are rare tumors arising from testosterone-producing Leydig cells and are the most common hormone-secreting testicular tumors. While LCTs are usually benign, malignancy has been reported in 10% of cases, and local recurrence or metachronous tumors of the contralateral testis have been described in a few patients. Radical orchiectomy is the current standard of care.
Objectives: To describe the clinical presentation, diagnosis, treatment, and outcome of pediatric patients diagnosed with LCTs.
Design/Method: Retrospective analysis of patients with LCTs diagnosed between 1990 and 2016.
Results: Eight children were identified with a median age of 8.1 years (4.2 - 11.9 years) at diagnosis. Primary presenting symptoms included precocious puberty (n=5), palpable testicular mass (n=2), and/or scrotal swelling (n=1). Scrotal ultrasonography was the initial diagnostic modality and the lesions were described as a heterogeneous mass with a peripheral hyperechoic and central hypoechoic nature with increased vascularity. Lesions were observed in the right testis in four patients and left testis in four patients. Serum alpha-fetoprotein, β-human chorionic gonadotropin, and lactate dehydrogenase were within normal limits. Preoperative serum testosterone was elevated while luteinizing hormone and follicle-stimulating hormone were suppressed in all 5 patients presenting with precocious puberty. In four of these five patients, bone age was advanced (> 2 standard deviations above chronological age). Except for elevated testosterone in one patient, hormone levels were not tested in the three patients without precocious puberty. One 10-year-old patient presented with scrotal pain secondary to testicular torsion; while the pain and torsion resolved within 3 weeks, a lesion remained on ultrasound and surgical enucleation was performed. Radical orchiectomy was performed in the remaining seven patients. None of the patients had evidence of metastasis at diagnosis. Serum sexual hormone

levels rapidly returned to the normal prepubertal range after surgery with subsequent stabilization or regression of pubertal symptoms. While pubertal symptoms resolved in one patient following orchiectomy at age 4.2, he later developed central precocious puberty at age 9.5 and was treated with a gonadotropin-releasing hormone analog. All patients were alive at last follow-up without evidence of local recurrence or metastasis (median follow-up 2.7 years, range 0.3 - 12.2 years).
Conclusion: LCTs are rare in pre-pubertal patients and have an excellent prognosis. When feasible, enucleation may be considered instead of radical orchiectomy as the surgical treatment in pre-pubertal patients. The need for surveillance scans post-surgery is debatable and requires further study.

Poster # 419

DFMO MAINTAINS REMISSION IN RELAPSED/REFRACTORY HIGH RISK NEUROBLASTOMA

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Background: While most patients with High Risk Neuroblastoma (HRNB) will initially attain remission, approximately half of patients will relapse within five years of diagnosis. Those who relapse following front-line therapy, or who are refractory to initial therapy, often respond to additional interventions but have a high rate of subsequent relapse, generally 80-90% within 2 years.
Objectives: The objective of this study was to evaluate the effectiveness of the ODC inhibitor difluoromethylornithine (DFMO) to prevent subsequent relapse in patients with relapsed/refractory HRNB who had achieved remission after salvage therapy.
Design/Method: This study was a single agent, multicenter study, enrolling from June 2012 to February 2016. Patients received 27 four-week cycles of oral DFMO at a dose of 750 ± 250 mg/m2 twice daily. Event free survival (EFS) and overall survival (OS) were determined on an intention-to-treat basis.
Results: A total of 39 patients received DFMO, and all were eligible for the intention-to-treat (ITT) analysis. For all patients, EFS was 52% (± 8%) and OS 85% (±6%) at two years with a median follow up time of 2.9 years. The median survival time is not yet defined (>4.5 years). For the subgroup of patients (n=21) who were refractory to upfront therapy but subsequently achieved remission prior to starting this study, the two year EFS was 65% (± 11%) and OS 95% (±5%). For the subgroup of patients (n=18) who had initially achieved remission with standard therapy and were in 2nd or subsequent remission following relapse, the two year EFS was 39% (± 11%) and OS 70% (±13%). The refractory cohort has an improved EFS and OS over the relapse cohort with marginal statistical significance (EFS p=0.06, OS p=0.03). High risk features, including MYCN, were not prognostic of worse EFS/OS. DFMO was well tolerated: 62% of patients had no related adverse events, Grade 2 transaminitis was the most common toxicity (occurring in <10 % of patients), and there was only a single Grade 3 AE of reversible

hearing loss and no Grade 4 or 5 AEs.
Conclusion: DFMO at 750 +/- 250 mg/m2 BID as maintenance therapy following completion of relapse/refractory therapy for HRNB is safe and associated with a high EFS and OS. Patients with refractory disease appear to have a better outcome than the relapsed cohort. DFMO is currently in a prospective confirmatory trial with each cohort evaluated separately for a better comparison and with additional safety and pharmacokinetic analysis.

Poster # 420

LEPTOMENINGEAL MELANOMA AND NEUROCUTANEOUS MELANOCYTOSIS

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Background: Neurocutaneous melanocytosis is a disorder of excessive proliferation of melanocytes in the leptomeninges and brain parenchyma. Leptomeningeal melanocytosis rarely transforms to leptomeningeal melanoma. The prognosis for children with leptomeningeal melanoma is poor with no reported survivors. Recent reports of genetic mutations in leptomeningeal melanoma have renewed interest in the use of targeted therapy in these patients.
Objectives: To describe outcomes of leptomeningeal melanoma treatment while adding to the knowledge of the clinical features of leptomeningeal melanoma and neurocutaneous melanocytosis in the pediatric population.
Design/Method: We retrospectively reviewed the medical records of patients aged less than 21 years with a diagnosis of leptomeningeal melanoma and antecedent neurocutaneous melanocytosis over a 20-year period, and analyzed demographics, clinical presentation, treatment, and outcome.
Results: We identified four patients with neurocutaneous melanocytosis who subsequently developed leptomeningeal melanoma at a median age of 2.8 years (range 2-4 years). Three were female. Three were Hispanic, and one was African American. The presenting symptoms were intractable vomiting in one, bilateral lower extremity weakness in one, abdominal distention in one, and one patient was diagnosed during a surveillance scan. The patient with abdominal distension had abdominal metastases presumably seeded by ventriculoperitoneal shunt tubing. Mutation analysis of the tumor tissue was available for three patients, and all three had NRAS p.Q16K mutation. Two patients had tumor debulking surgery at diagnosis and subsequent craniospinal irradiation. One of those patients subsequently received cyclophosphamide, sorafenib, and temozolamide with partial response, but had eventual disease progression and died 8 months after diagnosis. The other patient was treated with ipilimumab, but developed progressive brain metastases and died 5 months after diagnosis. Two patients were treated initially with systemic therapy. The patient with intraabdominal metastasis was treated with vinblastine, dacarbazine, and cisplatin; he experienced local progression of the tumor five months later and died shortly after. The other patient is currently receiving first cycle of combination therapy with ipilimumab and nivolumab.
Conclusion: The prognosis for leptomeningeal melanoma in the setting of neurocutaneous melanocytosis is poor. NRAS mutation is present in all patients tested, and use of NRAS pathway inhibitors and immunotherapy may be considered for first line therapy in this rare

disease with poor prognosis. More research is needed to improve outcomes for children with leptomeningeal melanoma.

Poster # 421

TARGETING THE METABOLIC PATHWAY OF NEUROBLASTOMA

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Background: Neuroblastoma is characterized reduced dependence on oxidative phosphorylation and an increased dependence on glucose. Lowering blood glucose levels and/or inhibiting the cancer cell's ability to metabolize glucose is a promising therapeutic strategy. Ketogenic diet (KD), a high fat, low carbohydrate diet originally developed for children with epilepsy, has been shown to lower blood glucose levels. KD results in an increase in ketone bodies however the effect of ketone bodies on tumor cells remains controversial. Exogenous ketones have shown to have both anti-tumorigenic and pro-tumorigenic effects.
Objectives: Investigate the individual and combined effects of ketone bodies and glycolytic inhibition on neuroblastoma cell lines.
Design/Method: Neuroblastoma cell lines SMSR, NB1691 (N-MYC amplified) and SK-N-AS, SVBM15 (N-MYC non-amplified) were treated with increasing concentrations of the glycolytic inhibitor 2-deoxy glucose (2-DG) (0.01-2mM) or the ketone bodies: acetoacetate (AA), and beta-hydroxybutyrate (βHB) (both at 1-20mM). Cell viability was determined at 72 hours of treatment using MTS assay. To determine the effects of AA on cancer stem cell self-renewal properties, we performed neurosphere-forming assays using NB1691 derived stem cells. These cells were propagated in neurosphere media and demonstrate multiple stem cell marker expression.
Results: AA induced a dose dependent increase in cell death in all cell lines however the sensitivity varied greatly with SVBM15 being the most sensitive and SK-N-AS being the least sensitive. Compared to non-treated controls, 10mM AA induced cell death by 20-80%. βHB on the other had not significant effect. Combining AA and with 2-DG was more effective than either treatment alone suggesting an additive effect. Treatment of neuroblastoma stem cells with AA significantly reduced neurosphere formation at concentrations as low as 1mM. Treatment with10mM AA inhibited neurosphere formation >90%.
Conclusion: Our results demonstrate NB cell lines are sensitive to glycolytic inhibition as well as the effects of AA but not βHB. Ketogenic diet has shown promise in cancer treatment however compliance remains a major obstacle. Here we demonstrate that exogenous AA can induce neuroblastoma cell death and reduce neuroblastoma stem-cell self-renewal properties. This data suggests that neuroblastoma patients might benefit from combined AA and glycolytic inhibitor treatment.

Poster # 422

PRIMITIVE NEUROECTODERMAL TUMOR ARISING FROM PILOCYTIC ASTROCYTOMA IN A CHILD WITHOUT ANTECEDENT RADIOTHERAPY

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Background: Pilocytic astrocytomas (PA) are common, typically indolent pediatric gliomas. When cerebellar in location, recurrence following gross total resection (GTR) is rare. Progression from PA to pilomyxoid glioma is reported, and transformation to anaplastic glioma is much less common in children than adults. Primitive neuroectodermal tumors (PNET) are composed of undifferentiated neuroepithelial cells capable of both glial and neuronal differentiation. Transformation from gliomas to histologically distinct PNETs is rare, and reported in one child following prior radiation therapy.
Objectives: To describe transformation of PA to PNET in a young child undergoing chemotherapy.
Design/Method: Review of patient medical records, radiographic imaging, histopathology, and published literature.
Results: A previously healthy 3-year-old girl presented with progressive headache, vomiting and dizziness. Magnetic radiographic imaging (MRI) showed a large, circumscribed, gadolinium-enhancing cerebellar mass. Spinal MRI was normal. Tissue obtained after gross total resection (GTR), confirmed by post-operative MRI, showed bipolar neoplastic cells with long cytoplasmic processes and Rosenthal fibers consistent with juvenile pilocytic astrocytoma. Surveillance MRI 5 months later showed locally recurrent mixed cystic-solid gadolinium-enhancing mass, prompting repeat GTR. Pathology showed highly cellular tumor with moderately pleomorphic glial cells but no Rosenthal fibers consistent with pilomyxoid astrocytoma (PMA), a more clinically aggressive glioma variant. She began treatment with monthly carboplatin/vincristine chemotherapy. Following course 6, brain and spine surveillance MRI showed new gadolinium-enhancing nodular leptomeningeal tumor dissemination. Despite changing chemotherapy to thioguanine/procarbazine/CCNU/vincristine, within 1 month she experienced intractable headache, emesis and status epilepticus. MRI showed marked widespread leptomeningeal disease progression with obstructive hydrocephalus. Despite surgical decompression and external ventricular drain placement, she died of uncal herniation 2 days later. Tumor tissue from limited autopsy showed small, round cells with higher nuclear:cytoplasmic ratio. Immunohistochemical stains were positive for synaptophysin but negative for glial fibrillary acidic protein (GFAP) diagnostic of primitive neuroectodermal tumor (PNET).
Conclusion: To authors' knowledge, this is the first report of transformation from low-grade glioma to highly aggressive PNET in a radiation-naïve child. The existing sparse literature, primarily adult-oriented, reporting glioma to PNET transformation potentially implicates radiation-induced genetic changes, including multiple chromosomal abnormalities possibly consistent with radiation-induced DNA changes. In the absence of radiation exposure, acquired mutations in oncogenes, tumor suppressor genes or DNA repair genes could produce a similar genotype. Although rare, transformation to PNET should be considered in in young children undergoing chemotherapy for low grade glioma who experience rapid disease progression.

Poster # 423

TRANSFUSION SUPPORT TO MAINTAIN HIGHER HEMOGLOBIN LEVELS DECREASES ANTI-GD2 MONOCLONAL ANTIBODY THERAPY-RELATED

ADVERSE EVENTS IN PATIENTS WITH HIGH-RISK NEUROBLASTOMA-A CASE SERIES

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Background: Neuroblastoma is the most common extra-cranial solid tumor in children. Patients with high-risk features continue to have poor outcomes despite intensive therapy. The addition of a chimeric monoclonal antibody targeting GD2, an antigen over-expressed on neuroblastoma cells, combined with GMCSF and IL-2 improves event-free and overall survival in children with high-risk neuroblastoma. This immunotherapy, however, is associated with adverse events, including pain and capillary leak syndrome. Interventions that mitigate these effects are vital to permit patients to successfully complete this immunotherapy regimen.
Objectives: We describe our experience using red blood cell (RBC) transfusions, targeting a hemoglobin greater than or equal to 10 gm/dL, in patients with neuroblastoma receiving immunotherapy and the impact of this intervention on treatment-related adverse events, including ICU transfer, pain, and capillary leak syndrome.
Design/Method: This study is a retrospective case series involving 14 patients with high-risk neuroblastoma treated with anti-GD2 monoclonal antibody based immunotherapy from 2011-2016 at Nationwide Children's Hospital in Columbus, Ohio, for a total of 76 hospital admissions for antibody administration. During 37 of these hospital stays, RBC transfusions were given to maintain a hemoglobin greater than or equal to 10gm/dL (group 1). During the other 39 hospital stays, patients were transfused to maintain hemoglobin of 7gm/dL or for symptomatic anemia (group 2). We reviewed the charts for information regarding side effects and ICU transfers/admissions, and then used two sample t-tests to examine the differences in the means of the two groups in these categories.
Results: Respectively, groups 1 and 2 showed differences in mean days with a narcotic drip for pain (3.57 vs 4.28, p=0.03), incidence of capillary leak (20 vs 27, p=0.18), mean number of lasix doses (1.11 vs 1.64, p=0.24), and number of ICU admissions (1 vs 6, p=0.06). Our study showed a mean length of stay of 6.65 and 6.41 days for groups 1 and 2 respectively (p=0.84), and a mean weight change of +1.03kg and +1.01kg (p=0.96).
Conclusion: Patients with high-risk neuroblastoma undergoing immunotherapy in whom hemoglobin was kept greater than or equal to 10 gm/dL had a statistically significant reduction in days with a narcotic drip for pain, and a nearly statistically significant reduction in ICU admissions. This group also had a clinically significant reduction in lasix doses and incidence of capillary leak. Larger studies are necessary to further demonstrate the association between RBC transfusions and reduction in adverse effects with anti-GD2 immunotherapy as suggested by our case series.

Poster # 424

PEDIATRIC PRIMARY PULMONARY SYNOVIAL CELL SARCOMA: A SINGLE INSTITUTION CASE SERIES

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Background: Synovial cell sarcoma, the most common non-rhabdomyosarcoma soft tissue sarcoma in children, accounts for 7.7% of pediatric soft tissue sarcomas. The most common anatomic locations are the lower extremity followed by the upper extremity. Trunk wall, visceral, and head and neck sites are less frequent. At diagnosis, distant metastases are rare with the lungs being the most common site. There are no reported pediatric cases of primary pulmonary synovial cell sarcoma.
Objectives: To report three cases of primary pulmonary synovial cell sarcoma and discuss the unique challenges of this disease.
Design/Method: Case series
Results: A 15 year old female was admitted to hospital for persistent cough for several months. Her cough worsened despite treatment for reactive airway disease and gastroesophageal reflux. Chest CT revealed a large mediastinal lesion (5.4 cm x 9.5cm). Biopsy of mass lesion revealed synovial cell sarcoma. She received 3 cycles of standard sarcoma chemotherapy (Doxorubicin, Cyclophosphamide, Ifosfamide, Etoposide). Gross resection was unsuccessful and repeat CT revealed metastatic pleural lesions. Refractory sarcoma chemotherapy regimen consisting of Vincristine, Cyclophosphamide, and Topotecan was started but the disease progressed, resulting in respiratory failure and death 9 months after diagnosis.A 12 year old female with new onset tremor and hallucinations developed acute left-sided chest and shoulder pain. CT chest demonstrated a left upper lobe nodule measuring 2x4cm. PET-CT of the lesion revealed enhanced uptake without metastasis. Left upper lobe wedge resection established a diagnosis of monophasic synovial cell sarcoma, with negative margins. Next generation sequencing (NGS) confirmed the pathognomonic SS18-SSX2 fusion translocation. Since the pulmonary lesion was < 5cm, completely resected, and without metastasis, we elected to observe with imaging every 3 months. She is now 9 months from surgery with no evidence of disease. Following tumor resection her neurologic symptoms improved.A 14 year old male presented with a 3 week history of progressive left-sided chest and abdominal pain and a progressive cough with dyspnea x3 days. Chest CT showed two areas of increased density along the left pleural surface and a rounded, hypodense lesion in the left upper lobe. Biopsy of pleural lesions was consistent with metastatic monophasic synovial cell sarcoma. NGS revealed the SSX 18-SSX2 fusion translocation. He underwent multimodal therapy including resection, radiotherapy, and chemotherapy with near complete response. He is now on pazopanib for maintenance chemotherapy.
Conclusion: The 3 presented cases highlight the need for clinicians to consider synovial cell sarcoma in pediatric patients presenting with primary pulmonary lesions.

Poster # 425

A PHASE 1/2 STUDY OF VALPROATE IN COMBINATION WITH INTERFERON ALPHA IN RELAPSED, RECURRENT OR PROGRESSIVE NEUROBLASTOMA

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Background: Novel treatment approaches are needed to improve outcomes and decrease toxicity in neuroblastoma. Histone deacetylase (HDAC) inhibitors cause growth arrest, differentiation and apoptosis in a wide range of tumors. Valproic acid is a HDAC inhibitor that has been extensively used in the pediatric population. We and others have shown that the combination of HDAC inhibition and treatment with interferon alpha has an anti-neuroblastoma effect in vitro and in vivo.
Objectives: The primary objective was to define the response rate of relapsed/refractory neuroblastoma patients to the combination of interferon alpha and valproic acid. Secondary objectives included evaluation of toxicities, assessment of time to disease progression, and overall survival.
Design/Method: This study was a Simons two-stage, multi-center, investigator initiated study, aiming to recruit 10 patients for an activity signal with an expansion cohort of 15 patients. The first 6 patients were evaluated as a safety cohort for dose limiting toxicity. Interferon was administered 3x per week subcutaneously (3MU/m2 per dose) and valproic acid was administered twice daily (to maintain trough at 525-700 μmol/L). Disease response was evaluated after two courses of treatment.
Results: A total of 9 patients were enrolled and treated between 2011 and 2015. The combination therapy was well tolerated. Grade 3/4 hematological toxicities occurred in 5 patients, and were unrelated to study drugs. One patient experienced grade 3 febrile neutropenia, and another experienced grade 3 self-resolving deranged liver function tests. One patient experienced a febrile reaction after the first dose of interferon with presyncope and delirium. This represented the only adverse reaction to interferon, was an expected toxicity, and the patient recovered without sequelae.No objective responses were seen for any patients enrolled on the study. All patients who had disease evaluation had disease progression prior to, or at the end of cycle 2. Disease progression was either detected clinically or radiologically. The study was terminated early due to lack of activity and slow enrolment. Despite this, the overall survival rate was 22% at 3 years, and 2 patients were long-term survivors and alive at their last evaluation (at 32 months and 63 months from study entry).
Conclusion: The combination of interferon alpha and valproic acid was well tolerated. Despite promising pre-clinical activity, the combination was not active in relapsed or refractory neuroblastoma patients. The two long-term survivors highlight the variability in time course in relapsed neuroblastoma, and the need for caution when using overall survival as an outcome measure.

Poster # 426

DESMOID TUMOR OCCURRING IN A PATIENT WITH VERY LONG CHAIN ACYL-CO-A DEHYDROGENASE DEFICIENCY (VLCADD)

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Background: Desmoid-type fibromatosis, also known as desmoid tumor, is a locally aggressive neoplasm sometimes associated with familial adenomatous polyposis (Gardner's syndrome). It is characterized by mutations in the APC or CTNNB1 genes, resulting in an increase in the β-

catenin protein that mediates adherens junction cell-to-cell adhesion. VLCADD is a rare disorder of lipid metabolism not known to be associated with neoplastic disease. Few patients with the very severe form of VLCADD have survived beyond infancy, because of recurrent episodes of rhabdomyolysis and hypoglycemia. Early identification of the condition, followed by strict metabolic and dietary control, is required. Patients with this condition are exposed to lifelong metabolic excess of very long chain fatty acids in tissues.
Objectives: We describe the occurrence of a large desmoid tumor in the abdominal wall of a patient with the very severe form of VLCADD.
Design/Method: Case Report.
Results: A 16 year-old female with very severe VLCADD developed a rapidly growing abdominal wall mass at the site of prior gastrostomies. She had known mutations in the ACADVL gene resulting in complete absence of the VLCAD enzyme, and requiring rigid dietary management. Biopsy of the mass revealed desmoid-type fibromatosis and the patient subsequently underwent complete surgical excision requiring abdominal wall reconstruction.
Conclusion: Few patents with the very severe form of VLCADD survive beyond infancy, so little is known regarding a predilection for malignancy in this disorder. Desmoid-type fibromatosis is more common in young women, often occurring at sites of previous abdominal surgery, as in this case. In our patient, the presence of chronic rhabdomyolysis, the excess of very long chain fatty acids, and the prior surgical tissue injury, may have contributed to the development of desmoid-type fibromatosis at the previous gastrostomy site. Genes involved in fatty acid metabolism are dysregulated in a variety of neoplasms. An excess of very long chain fatty acids in known to enhance cancer proliferation, and is associated with more aggressive phenotypes in lung, liver, and colorectal cancer. Loss of heterozygosity at 17p13, the location of the ACADVL gene, occurs in adrenocortical carcinomas, and down regulation of ACADVL is a feature that distinguishes adrenocortical carcinoma from adrenocortical adenoma. Down regulation of ACADVL is also associated with cervical squamous cell carcinoma. We speculate that this patient's disordered lipid metabolism, prior abdominal wall surgery, and chronic rhabdomyolysis may have contributed to the development, and subsequent aggressive clinical behavior, of her desmoid tumor.

Poster # 427

ROLE OF DLX HOMEOBOX GENES IN MOUSE AND HUMAN RETINOBLASTOMA - IMPLICATIONS FOR CELL OF ORIGIN AND DIFFERENTIATION-BASED THERAPIES

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Background: In humans, retinoblastoma is due to loss of function mutations of the retinoblastoma gene, Rb, but is insufficient to cause retinoblastoma tumors in mice. The retinoblastoma protein is a member of the pocket protein family of cell cycle regulators which also includes p107 and p130. Loss of function of two members of the pocket protein family is necessary to generate retinoblastoma tumors in mice. The distalless/DLX homeobox genes are required for proper development of the forebrain and retina. Loss of function of both Dlx1 and Dlx2 results in retinal ganglion cell (RGC) cell death, decreased RGC differentiation and altered

cell fates in the Dlx1/Dlx2 double knockout (DKO) mice. The cell of origin of human retinoblastoma has been determined to be cone photoreceptor progenitors whereas the cell of origin in the mouse is an inner nuclear layer interneuron (amacrine or horizontal cell progenitor).
Objectives: The goal of our research project was to determine the upstream regulation of members of the pocket proteins during retina development and identify the cell of origin of retinoblastoma in the mouse towards understanding how these tumors coopt normal developmental pathways.
Design/Method: We coupled chromatin immunoprecipitation (ChIP) of mouse embryonic tissues using our DLX2 poyclonal antibody with a CpG island DNA microarray to identify candidate DLX2 transcriptional targets for further characterization. We obtained unstained FFPE human fetal and retinoblastoma tumor sections and cryopreserved samples of human and mouse (Chx10BAC:Rb1;p107) retinoblastoma to assess expression of DLX2 in vivo.
Results: The ChIP/DNA chip assay identified over 100 candidate DLX2 targets, including p107. ChIP using embryonic retina and forebrain tissues showed DLX2 occupancy of the p107 promoter in vivo. Specificity of binding was confirmed by gel mobility shift and site directed mutagenesis of candidate homeodomain binding sites. Co-expression of a reporter gene with Dlx2 demonstrated activation of p107 expression in vitro; this was validated by quantitative PCR that showed decreased p107 expression in the Dlx1/Dlx2 DKO. DLX2 was expressed in all mouse retinoblastoma samples, 62/75 (82%) cases of human retinoblastoma and co-expressed with PAX6, syntaxin and PROX1 which are markers of amacrine and/or horizontal cells.
Conclusion: DLX2 directly binds to the p107 gene promoter and activates its expression. Expression of DLX2 in both mouse and human retinoblastoma is consistent with the partially differentiated state of these tumors and with an inner nuclear layer cell of origin in mouse retinoblastoma. Co-opting DLX2 transcriptional networks could augment current treatments by reintroducing differentiation-based therapies for retinoblastoma.

Poster # 428

HYPERCALCEMIA AND ELEVATED PTH-RP IN A 3 YEAR-OLD WITH HUMORAL HYPERCALCEMIA OF MALIGNANCY (HHM) AS THE PRESENTING FEATURE OF RELAPSED METASTATIC MALIGNANT ECTOMESENCHYMOMA

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Background: Hypercalcemia of malignancy is rare in children compared to adults. Hypercalcemia due to a paraneoplastic syndrome, mediated by parathyroid hormone-related peptide (PTHrP), is called humoral hypercalcemia of malignancy (HHM) and is far less prevalent.
Objectives: We present an 18 months old female with labial MEM that relapsed with distant pleuropulmonary metastasis and HHM
Design/Method: A review of the patient's medical record and available literature pertaining to hypercalcemia associated with cancer was performed.
Results: An 18-month old female was initially diagnosed with localized PAX3/7–FOXO1 fusion negative alveolar- RMS of the labia. Diagnosis was later changed to malignant ectomesenchymoma (MEM). She was treated according to ARST0531 and entered remission.

She relapsed with distant metastasis 15 months after completion of treatment. Symptoms on relapse include constipation, abdominal pain, tachypnea and labored breathing. Radiology imaging showed involvement of mediastinum, lung and pleura (malignant effusion). Histologic study of pleural fluid showed malignant cells.Laboratory test on relapse revealed hypercalcemia (13.6mg/dL), peaked on day 3 (14.8mg/dL) with elevated ionized calcium (2.13mmol/L). Phosphorus was slightly low (3.0mg/dL). PTH-related peptide was elevated (29, reference 14-27pg/mL). CT and bone scan ruled out other metastatic or primary site lesion.Hypercalcemia worsened despite treatment with hyper-hydration. Thus, pamidronate 15 mg IV was given on day 3. The calcium level normalized 2 days later, but continued to drop resulting in hypocalcemia, with lowest level (total 6.4mg/dL, ionized 0.96mg/dL) 5 days after pamidronate. The hypocalcemia was treated with calcium supplementation and normalized after 2 days.Patient also received salvage chemotherapy with cyclophosphamide, vinorelbine, and temsirolimus (ARST0921). She had partial response with viable residual disease in right lung after completion treatment. Second salvage chemotherapy with topotecan, cyclophosphamide, cisplatin, and etoposide failed and developed disease progression 18 months after relapse.Hypercalcemia was not seen during initial diagnosis. She also had no recurrence of hypercalcemia despite persistent disease after relapse and during disease progression.
Conclusion: We described a unique presentation of a rare clinical entity, HHM associated with release of PTHrP. This is the first reported case of MEM presenting with HHM. Absence of hypercalcemia at initial diagnosis and later disease progression suggests heterogeneity of MEM within the same patient. Treatment with pamidronate and chemotherapy is effective. But need close monitoring is needed to ensure hypocalcemia which is a likely adverse effect of pamidronate.

Poster # 429

EPIDEMIOLOGY OF RETINOBLASTOMA AMONG HAITIAN CHILDREN TREATED AT A HAITAIN PEDIATRIC HOSPITAL FROM 2010 TO 2015

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Background: Retinoblastoma is a malignant tumor of the retina found mostly in young children. In Haiti, it is the third most common pediatric cancer after the leukemias and Wilms tumor.
Objectives: The main objective of this study is to describe the epidemiology of children with retinoblastoma treated at a Haitian pediatric hospital.
Design/Method: This is a retrospective study on the cases of retinoblastoma admitted in the Oncology department of Saint-Damien hospital in Port-au-Prince, Haiti from January 2010 to December 2015. Among the key variables considered for this study figured: age, gender, family history of retinoblastoma, eye affected, signs and symptoms, delay of diagnosis, staging and outcome.
Results: Thirty-nine cases of retinoblastoma were diagnosed and managed during the study period. Twenty-three cases (58.97%) were males and 16 cases (41.03%) females. The mean age at diagnosis is 31.8 months [9 – 76 months] and the mean delay of diagnosis is 7.4 months [15 days – 26 months]. Two children (5.13%) had a known family history of retinoblastoma. Thirty-five children (89.74%) had unilateral retinoblastoma and 23 (58.97%) an extraocular extension.

The most common signs were leucocoria (79.49%) and exophthalmia (58.97%). In terms of therapeutic outcome, 16 children (41.03%) were lost to follow up, 14 (35.90%) died, 6 (15.38%) were in remission and 3 (7.69%) relapsed. Twenty-one of the 30 children (70%) who were lost to follow up or deceased were diagnosed at stage III or IV of the St Jude classification.
Conclusion: Retinoblastoma is overall diagnosed in St Damien Hospital at a late stage, which results in high mortality and loss to follow up as outcome. National awareness as well as better access to cancer care are mandatory in Haiti for an optimal management of retinoblastoma.

Poster # 430

LYMPH NODE METASTASES IN PEDIATRIC AND YOUNG ADULT NON-RHABDOMYOSARCOMA SOFT TISSUE SARCOMA: FINDINGS FROM CHILDREN'S ONCOLOGY GROUP STUDY ARST0332

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Background: Prognosis in metastatic non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) is poor, but little is known about the clinical features and outcomes of pediatric NRSTS patients with lymph node (LN) metastases.
Objectives: To better define the clinical features and outcomes of young NRSTS patients with LN metastases treated in a standardized fashion, we performed a subset analysis of Children's Oncology Group clinical trial ARST0332, which was designed to evaluate a risk-based treatment strategy for young patients with all stages of NRSTS.
Design/Method: Patients <30 years of age with newly diagnosed NRSTS and LN metastases enrolled on ARST0332 were studied. Diagnostic pathology and baseline imaging studies were centrally reviewed. Regional lymph node sampling was required for patients with epithelioid sarcoma or clear cell sarcoma, as well as those with enlarged lymph nodes on imaging or physical exam. ARST0332 allocated patients to 4 treatment arms (surgery only, surgery/radiotherapy, surgery/radiotherapy/chemotherapy, or neoadjuvant chemoradiotherapy/delayed surgery) based on tumor features and extent of resection prior to study entry. Lymph node dissection was recommended at the time of primary tumor resection; radiotherapy to a dose of 64.8 Gy was recommended for unresectable nodal metastases.
Results: Between 2/5/07 and 2/10/12, 550 eligible patients were enrolled on ARST0332. Of these, 22 had LN metastases, which were found most often in patients with parachordoma (n=1 of 5; 20%), epithelioid sarcoma (n=5 of 29; 17%), angiosarcoma (n=1 of 6; 17%), and clear cell sarcoma (n=1 of 7, 14%). Larger tumor size (11.2 cm±6.3 cm vs. 7.6 cm±5.3 cm, p=0.002), unresected tumor (72.7% vs. 33%, p=0.0003) and distant metastases (54.5% vs. 11.3%, p<0.0001) were more common in patients with LN involvement than those without. LN involvement was evident on pre-treatment imaging in all patients except one who did not undergo LN imaging. Events in patients with LN involvement were: metastatic recurrence (n=14), local recurrence (n=1), and second malignant neoplasm (n=1). At 4.6 ± 1.7 years mean follow-up, patients with LN metastases had a 5-year overall survival of 40.9% (95% CI: 20.9, 60.1).
Conclusion: Regional LN involvement by tumor occurs in about 4% of childhood NRSTS, is

limited to a few histologic subtypes, and is associated with larger tumor size, unresectable tumor, and the presence of distant metastases. LN sampling may be unnecessary for patients without imaging evidence of nodal involvement. Overall outcomes are poor in NRSTS patients with LN metastases and novel therapies are urgently needed.

Poster # 431

SAFETY AND EFFICIENCY OF CHEMOTHERMOTHERAPY CTT) FOR INTRAOCULAR RETINOBLASTOMA USING SINGLE AGENT CARBOPLATIN THROUGH PERIPHERAL INTRAVENOUS INFUSION

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Background: Satisfactory tumor reduction occurs with systemic chemotherapy regimens combined carboplatin associated with other systemic agent (vincristin,etoposide)and local therapies for retinoblastoma. However, significant chemotherapy-associated systemic toxicity has been reported and theses regimens requires an oncology hospital.
Objectives: An alternate approach for treatment of group B retinoblastoma is chemothermotheraphy (CTT) involving a single agent Carboplatin administered through a peripheral intravenous without a venous access device and combined with thermotherapy. The advantages of CTT include, a single neoadjuvant instead of multi-agent chemotherapy, reduced systemic chemotoxicity and the peripheral vein is a good alternative for ophthalmologists managing Group B retinoblastoma without immediate access to an oncology center.
Design/Method: This retrospective study evaluated 20 eyes (20 patients; age, 8 days to 28 months) with newly diagnosed group B retinoblastoma with no previous treatment. Treatment involved intravenous carboplatin (18 mg/kg/dose) for patients less than 36 months old, and 560 mg/kg/dose for patients over 36 months old, followed by laser diode thermotherapy 2 hours later. CTT was performed once-every-4-weeks with a maximum of 6 courses at a tertiary care eye hospital (mean, 2.8 courses;range, 1 to 6 courses). Acute systemic illnesses were ruled out prior to therapy.
Results: Nineteen (95%) eyes had an excellent response (type III and IV regression) after CTT. One (5%) patient had a poor response requiring enucleation and referral to an oncology center. No patients developed extraocular disease. Twelve (60%) patients had a median follow-up beyond 5 years (range, 2 to 10 years) with a disease free survival of 100%.Two (10%) patients with a good clinical response to CTT had an event-free survival without enucleation but disease recurred several months later, warranting referral to oncology. Sixteen (80%) patients had an event-free survival without enucleation or systemic treatment. Only one patient required prolonged hospital-based antiemetic treatment with dexamethasone and ondansetron for 24 hours followed by outpatient oral ondansetron for a few days. There were no cases of extravasation or adverse events. No patients developed fever and neutropenia after CTT. The chemotherapy schedule was not delayed in any case due to carboplatin-associated bone marrow suppression. All repeat hemograms indicated a neutrophil count>1000, hemoglobin level>10 g/dl, platelets>250000 and normal renal and hepatic functions.
Conclusion: CTT for Group B retinoblastoma is an efficient first-line therapy with remarkably less toxicity and good patient tolerance compared to systemic multiagent chemotherapy

regimens. CTT is a good alternative for an ocular oncologist treating retinoblastoma in a non-oncology hospital setting.

Poster # 432

RHABDOMYOSARCOMA WITH CENTRAL NERVOUS SYSTEM METASTASES: MORE COMMON THAN WE SUSPECT? A SINGLE-INSTITUTION'S EXPERIENCE

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Background: Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma of childhood, accounting for approximately 3.5% of cancer cases in children aged 0-14 years. Prognosis is variable and depends upon risk stratification. More than 70% of children with localized RMS are cured of their disease, and pulmonary metastases along with local recurrences constitute most of the therapy failure cases. Here we report a surprisingly high incidence of central nervous system (CNS) post-treatment recurrences in a consecutive group of our patients that was not reflected before in the literature with RMS.
Objectives: To describe a series of five patients diagnosed within two years with RMS at the Children's Hospital of Michigan who developed progressive leptomeningeal disease.
Design/Method: We retrospectively reviewed all of the patients diagnosed with RMS at our institution from January 1, 2015 to December 31, 2016.
Results: Seven patients were diagnosed with RMS during the study period. Five developed progressive disease isolated to the CNS including two patients with alveolar RMS (ARMS) with FOXO1 rearrangement and three patients with embryonal RMS (ERMS) with parameningeal primary tumors. Four patients had stage IV disease and one had stage III/group III disease. All three with ERMS had negative cerebral spinal fluid cytology. All five patients were treated per Children's Oncology Group intermediate- or high-risk protocols with good initial response; however, each patient developed progressive CNS disease with leptomeningeal metastases within two to 14 months after initial diagnosis (median time six months). Following progression, four patients were treated with chemotherapy. One patient received chemotherapy and cranial-spinal irradiation. All five patients subsequently died within three months of their leptomeningeal progression (median two months). Two patients with ERMS were negative for TP53 mutations. Additional testing for TP53 is in process.
Conclusion: Therapy failures in RMS with leptomeningeal metastases may be underreported and more common than previously thought in a subset of patients (parameningeal primary or ARMS with FOXO1 rearrangement) based on our institution's recent experience. Data is lacking regarding the prevalence of CNS metastasis as a cause of therapy failure, but prognosis seems extremely poor with current treatment. We feel additional monitoring for CNS disease in a subset of patients may be necessary, and research to determine the actual prevalence of CNS involvement and to explore novel treatment options is warranted.

Poster # 433

FOCAL ADHESION KINASE INHIBITION DECREASES TUMORGENICITY IN PATIENT-DERIVED XENOGRAFT MODELS OF METASTATIC WILMS TUMOR

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Background: Wilms tumor (WT) is the most common pediatric renal tumor. About 12% of patients with WT will have metastatic disease at diagnosis with a 4-year-relapse-free survival rate of 70%, and those who relapse with metastatic disease have an even graver prognosis. Clearly children with metastatic WT need a concentrated research effort. Limited cell lines are available for the study of metastatic WT and long-term passaged cell lines do not accurately represent the human condition. We have developed patient-derived xenograft (PDX) models of metastatic WT for in vitro and in vivo studies. Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that controls a variety of cellular pathways involved in tumorigenesis. Inhibition of FAK has been found to decrease cell survival and proliferation in a number of renal tumors, including WT. To date, the role of FAK in metastatic WT has not been investigated.
Objectives: To investigate the role of FAK in PDX models of metastatic WT.
Design/Method: Cells from two PDXs of metastatic WT, COA 16, a lung metastasis, and COA 42, a liver metastasis, were utilized. Short tandem repeat (STR) analysis and immunohistochemistry were used to characterize these PDXs. Immunoblotting was performed for FAK expression and phosphorylation on COA 16 and COA 42 PDX protein lysates. Cells from COA 16 and COA 42 were treated with small molecule FAK inhibitors, PF-573,228 (PF) and 1,2,4,5-benzenetetraamine tetrahydrochloride (Y15), for 24 hours at increasing concentrations. Cell viability and proliferation were assessed with alamarBlue and CellTiter 96 assays, respectively. Results were compared with student's t-test and $p \leq 0.05$ was considered significant.
Results: STR analysis and immunohistochemical staining confirmed the two cell lines recapitulated the human tumors from which they were derived. FAK expression and phosphorylation were detected by immunoblotting in both PDXs. FAK inhibition with PF (10 μM) decreased cell viability by 53% and 63% and proliferation by 75% and 83% in COA 16 and COA 42, respectively, compared to untreated control cells. Y15-induced FAK inhibition similarly decreased cell survival and proliferation. Y15 (10 μM) diminished cell viability by 58% and 72% and proliferation by 49% and 68% in COA 16 and COA 42, respectively, compared to untreated control cells.
Conclusion: FAK protein is expressed and phosphorylated in human metastatic lung and liver WT PDXs. FAK inhibition with two small molecules led to decreased tumor cell viability and proliferation. These findings suggest FAK inhibition should be explored as a novel therapeutic for metastatic WT.

Poster # 434

SURGICAL MANAGEMENT OF PEDIATRIC, ADOLESCENT AND YOUNG ADULTS WITH STAGE I HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) is an aggressive hepatic neoplasm that is often chemoresistant. Complete surgical resection remains the mainstay of therapy, however, most patients present with unresectable disease. The role of liver transplantation in pediatric HCC is in evolution. The advantage of adjuvant chemotherapy for stage I disease is unknown.
Objectives: To retrospectively review the clinical and pathological characteristics and to report outcomes of children, adolescent and young adults (AYA) with Evan's stage I HCC treated with surgery alone at our institution from 2004-2015.
Design/Method: Single institution case series.
Results: Ten patients (male=4, female=6) with stage I HCC treated with surgery alone were identified. Median age was 10.5 years (range 1-17). Two patient had non-cirrhotic liver with HCC (fibrolamellar-HCC=1, de novo early HCC=1). Four patients had non-cirrhotic liver with early and/or well differentiated HCC in the context of portosystemic shunts (2 existing congenital portal systemic shunts, 1 mesocaval shunt, and 1 portal vein thrombosis). The remaining 4 patients had well differentiated HCC in the context of pre-existing liver disease (progressive familial intrahepatic cholestasis type 2=2, alpha-1 antitrypsin deficiency=1, Alagille syndrome=1) with cirrhosis. Median serum alpha fetoprotein level at diagnosis was 2.15 ng/mL (range 1-17043.3 ng/mL). The maximal tumor diameter by imaging ranged from 0.6-12.6 cm. PRETEXT stage was I (1), II (6) and IV (3). None had portal vein, inferior vena cava/hepatic vein, caudate lobe, or extrahepatic involvement. Seven patients were treated by liver transplantation (6 with multifocal disease; 1 with central/hilar disease). Four exceeded the Milan criteria. One patient underwent segmentectomy and two underwent hemihepatectomy. All ten patients had a complete response without any neoadjuvant or adjuvant chemotherapy. One patient had radiofrequency ablation prior to surgery. All ten patients are alive without evidence of recurrence with a median follow-up of 36.5 months.
Conclusion: Many types of pediatric and AYA Stage I HCC can be effectively treated with complete surgical resection without chemotherapy, especially those with HCC developing in the setting of either anatomic or genetic predisposition.

Poster # 435

MIR-16 SUPPRESSES GROWTH OF THE KIDNEY RHABDOID TUMOR CELL LINE WT-CLS1

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Background: Malignant rhabdoid tumor of the kidney (MRT) is a highly aggressive pediatric cancer characterized by inactivation of SMARCB1, a core component of the SWI/SNF chromatin remodeling complex. Outcomes remain poor despite ongoing research into SMARCB1-driven tumorigenic pathways. In contrast to the more common pediatric kidney

cancer Wilms tumor, MRTs display large nuclei containing distinct nucleoli and absence of SMARCB1. HMGA2, SALL4, and Cyclin D have been shown to be driven by loss of SMARCB1 and are essential for rhabdoid tumor growth, but these genes have not been therapeutically targeted in MRT. Notably, the 3'UTRs of these genes contain well-conserved let-7 and miR-16 binding sites, which could be exploited in future therapeutic regimens.
Objectives: To characterize the WT-CLS1 cell line and identify novel miRNA-based therapeutic options.
Design/Method: We characterized WT-CLS1 by whole-exome sequencing, RNA-seq, and xenograft histology. Additionally, the effect of inducible let-7 and miR-16 expression on WT-CLS1 cell proliferation and gene expression was observed.
Results: WT-CLS1 was derived from a renal tumor arising in a 5 year-old female and has previously been described as Wilms tumor. We found evidence suggesting that WT-CLS1 should be reclassified as MRT. WT-CLS1 xenografts demonstrated histological hallmarks of MRT: large nuclei, prominent nucleoli, and loss of SMARCB1 staining. Sequencing demonstrated a homozygous nonsense mutation in SMARCB1, resulting in a premature stop codon. By gene expression, WT-CLS1 clustered with rhabdoid tumor samples rather than Wilms tumors. Having established that WT-CLS1 represents MRT, we sought to use WT-CLS1 to identify novel therapeutic strategies in MRT. It was previously shown that SMARCB1 inactivation in rhabdoid tumor leads to overexpression of HMGA2, SALL4, and the Cyclin D family, and inhibition of these genes impairs growth. Because the tumor suppressor miRNAs let-7 and miR-16 are both predicted to target these transcripts, we used a tet-dependent system to inducibly overexpress each of these miRNAs in WT-CLS1. Indeed, we found miR-16 overexpression decreased cell density 4-fold. This was accompanied by repression of miR-16 target genes, a decrease in proliferation markers, and an increase in apoptosis markers.
Conclusion: The loss-of-function SMARCB1 mutation found in WT-CLS1, in conjunction with histochemical and gene expression analysis, warrants reclassification of this cell line as one derived from a primary rhabdoid tumor. Proliferation of WT-CLS1 is significantly abrogated by overexpression of miR-16. Further studies are necessary to gain insight into the potential use of miR-16 as a novel therapeutic option in malignant rhabdoid tumor of the kidney.

Poster # 436

USING HEPATOCELLULAR CARCINOMA TREATMENT STRATEGIES FOR THE TREATMENT OF REFRACTORY RELAPSED HEPATOBLASTOMA, CASE REPORT

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Background: Hepatoblastoma (HB) is the most common pediatric liver cancer. Patients who have relapsed disease, especially with multiple relapses, have a poor prognosis. There is limited evidence about effective chemotherapy strategies. Utilizing hepatocellular (HCC) treatment may prolong life with minimal toxicities.
Objectives: We report a patient with refractory–relapsed HB who had response to HCC regimens, specifically sorafenib and gemcitabine-oxaliplatin (GEM-OX).
Design/Method: Case report.
Results: An 11-year-old male with Stage 2 HB, initially treated with cisplatin, 5 fluorouracil,

vincristine, and doxorubicin (C5VD). After 2 cycles of C5VD, alpha-fetoprotein (AFP) was increasing. Imaging showed multiple lesions in all remaining liver segments, which was biopsy-confirmed HB, but no extrahepatic disease. He was changed to cisplatin, doxorubicin and sorafenib, with sharp decline in AFP. Prior to liver transplant, his AFP was 8.2 ng/dL. Post-transplant, he was unable to tolerate much chemotherapy due to poor kidney function and gastrointestinal toxicities, and only received one cycle of vincristine and irinotecan. His immunosuppression was switched from tacrolimus to sirolimus. Sorafenib was given for one year. He tolerated administration of sorafenib with sirolimus with sorafenib dose reductions due to dermatologic symptoms. He remained disease-free with normal AFP until 1 year off sorafenib, when a solitary lung nodule was seen and confirmed HB. He underwent microwave ablation and sorafenib was resumed. AFP was normal for 6 months before it rose again. Another solitary pulmonary nodule was seen but could not be ablated. Docetaxel 100 mg/m²/dose IV every 21 days, was started. AFP continued to climb. After 3 cycles, repeat scans showed multiple new and growing pulmonary nodules with enlarged hilar lymph node. Treatment was changed to gemcitabine, 1000 mg/m²/dose, and oxaliplatin, 100 mg/m²/dose, IV every 14 days. Patient wished to delayed surgery, so received 4 months of GEM-OX with falling AFP. He underwent pulmonary nodule resection but hilar lymph node was unresectable. He enrolled on phase 1 molecular guided clinical trial. He had rising AFP and radiographic progression, after 6 weeks of therapy. He was switched to bevacizumab, oral irinotecan, and temozolomide, with continued rise in AFP during all cycles. Because he did not have progression on GEM-OX, he was switched back, now with declining AFP. He is now 4-1/2 years from diagnosis, with measurable disease, but excellent quality of life and minimal toxicities from chemotherapy.
Conclusion: Hepatoblastoma, especially in the older children, may respond to HCC treatment strategies, including percutaneous ablation, sorafenib, and GEM-OX.

Poster # 437

OUTCOME OF WILMS TUMOR PATIENTS WITH BONE METASTASIS ENROLLED ON NATIONAL WILMS TUMOR STUDIES 1-5: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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Background: Wilms tumor (WT) is the most common renal tumor in children. The most frequent sites of WT metastases are to the lung and liver, but bone and brain metastases have been reported. No cohort studies have descriptively related bone metastases to other clinical factors or described their management.
Objectives: This study aims to describe the outcomes for patients with Wilms tumor that metastasized to bone (WTBM) to assist clinicians in decision making for these uncommon patients.
Design/Method: A retrospective study was conducted of patients enrolled on the National Wilms Tumor Study (NWTS 1-5) who were coded as having bone metastases, either at diagnosis or recurrence. The clinical characteristics of the patients, including age, gender, tumor histology, radiation therapy treatment and chemotherapy regimen were assessed and correlated with survival.

Results: Thirty-eight patients (0.44%) were identified with WTBM of 8,609 patients enrolled on the NWTS 1-5 clinical trials between 1969 and 2002. Bone metastasis most commonly occurred at relapse (66% - 25/38 patients). There was no gender predeliction. Overall, 13% (5/38) of patients with WTBM survived. Of those who died, the median survival following presentation of bone metastasis was 10.9 months (range 0.46 to 75 months). Half (4/8) of patients with bone metastasis presenting at diagnosis, 0% (0/5) with disease progression (defined as within 6 months of diagnosis), and 4% (1/25) upon relapse (beyond 6 months) survived. Twenty-two percent (4/18) of patients with favorable histology, 13% (1/8) with diffuse blastemal (all diagnosed pre-chemotherapy), and 0% (0/12) with anaplasia survived. Twenty percent (3/15) of patients with only axial bone metastasis, 0% (0/9) with only appendicular metastasis, and 14% (2/14) with both axial and appendicular metastases survived. Of the 5 survivors, median follow up was 14 years (range 6.7-23.8); one surviving male was still living with disease at last report. Radiation was confirmed to be used in 4 of 5 survivors. All survivors were registered on either NWTS 4 or 5. No consistent chemotherapeutic approach appeared to be associated with disease outcome.
Conclusion: Bone metastases in the setting of favorable histology Wilms tumor, and presence of bone metastasis at diagnosis, rather than at disease progression or relapse, were found to be the most important indicators of survival. We could not identify a consistent chemotherapeutic strategy associated with survival.

Poster # 438

ANTAGONIZING PROLACTIN INDUCED JAK/STAT SIGNALING IN OSTEOSARCOMA

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Background: Osteosarcoma (OS) is the most common pediatric bone cancer in the world. It is a highly aggressive cancer characterized by rapid progression, invasiveness, metastasis, resistance to chemotherapy, and recurrence after surgery. Despite medical treatment advances in other cancers, there has not been any newer efficacious treatment for OS. For the last two decades, we still rely on the same chemotherapy treatment (methotrexate, cisplatin, and doxorubicin). Reluctantly, there has been no true advancement in the overall survival in metastatic OS which remains less than 30%. Furthermore, patients are subjected to harmful adverse effects of chemotherapy that can result in hearing loss, impaired cardiac functioning, and renal injury due to the inability to selectively target cancer cells. There is an urgent need to identify and characterize key molecular targets involved in the pathogenesis of OS with the hope of blocking these pathways with targeted agents.
Objectives: To characterize the effect of antagonizing prolactin signaling pathway in osteosarcoma
Design/Method: OS cells (KHOS, MG63, SJSA, & OS3) were grown to 70-80% of confluency and treated with curcumin and prolactin. ERK phosphorylation, Jak2, and STAT5 were evaluated by western blot. The growth of OS cell lines was measured by hexosaminidase assay

and clonogenicity, respectively. Pancosphere formation was used to identify effects on stem cells. Immunohistochemical staining was performed for PRLR in normal bone vs OS.
Results: We identified prolactin receptor to be overexpressed in OS. When prolactin (PRL) binds its cognate receptor (PRLR), it induces various downstream events including the JAK-STAT and ERK MAPK pathways. In OS cell lines, we observe that PRL treatment induces dose- and time-dependent JAK2, STAT5, and ERK1/2 phosphorylation. Downstream pathway STAT-activated by PRL also was found to be a pathway target for OS. We hypothesize that PRL signaling enhances the pathogenesis of OS, and therefore decided to target it for therapeutic intervention. We developed a homology model for the C-terminal intracellular region of the receptor and performed a virtual screening in silico with compounds. One compound, derived from the plant Curcuma longa called curcumin was found to interact with the region of the receptor. Curcumin reduced cellular proliferation in all 3 OS cell lines and decreased colony formation. Curcumin in combination with doxorubicin decreased expression PRLR. Curcumin reduced spheroids suggesting an effect on cancer stem cell reduction.
Conclusion: PRL signaling through its cognate PRL receptor is critical for aggressive OS cancer behavior and therefore may be an effective therapeutic strategy.

Poster # 439

IMPRESSIVE RAPID RESPONSE TO ALKYLATING/TOPOISOMERASE-BASED THERAPY FOR RELAPSED WILMS TUMOR WITH HEMATOGENOUS METASTASIS THAT FAILED DOXORUBICIN-BASED SALVAGE THERAPY

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Background: The survival rate of low risk favorable histology Wilms tumor (WT) is excellent. However, for those that do relapse, optimal management is debated.
Objectives: To describe the surprising rapid response to cyclophosphamide/etoposide (CPM/ETO) in a patient with WT relapsing after treatment with Vincristine/Actinomycin-D and Doxorubicin/Vincristine.
Design/Method: Case report
Results: An eight month-old male was diagnosed with Wilms tumor of the left kidney. He underwent complete surgical resection and was found to have favorable histology Wilms tumor, stage 1, with no LOH at 1p or 16q, consistent with low risk disease. Accordingly he started treatment with regimen EE-4A (vincristine/Actinomycin-D). MRI after 6 weeks of treatment showed an area of enhancement in the tumor bed, initially thought to be a post-operative hematoma. Chemotherapy was continued with intermittent imaging demonstrating stable area of enhancement. Following completion of EE-4A therapy, end of therapy scans delayed for ten weeks due to poor compliance, showed overt disease recurrence in the tumor bed, retroperitoneal lymph nodes, liver, mediastinum and liver. Repeat biopsy demonstrated Wilms Tumor with favorable histology. Regimen I (Doxorubicin/Vincristine/Cyclophosphamide/Etoposide) was initiated as per NWTS5 (POG9444/CCG4942) relapse (stratum C) starting with doxorubicin/vincristine per protocol guidelines. Immediately after CPM/ETO was given a repeat scan demonstrated further progression. Family requested a second opinion at Cincinnati

Children's Hospital at which time a short-interval repeat body CT scan demonstrated an impressive response with 50 - 75% reduction of tumor burden just 7 days after CPM/ETO. Treatment was modified to complete 2 cycles of CPM/ETO to include mid-cycle/recovery stem cell collection (in case of need) followed by alternating cycles CPM/Carboplatin/ETO and CPM/Topotecan, along with radiation therapy. At the end of 6 cycles, whole lung radiation was given with boost to mediastinum, and whole abdomen with boosts to liver and renal fossa. Due to radiation-induced liver toxicity and pneumonitis, only one additional cycle of chemotherapy with CPM/Carboplatin/ETO was given after radiation. Now at 24 months after completion of therapy, he remains in complete second remission, and he is growing and developing well, although uses hearing aids.
Conclusion: Our patient had an impressive complete response to CPM/ETO within 7 days after failing Doxorubicin-based therapy.

Poster # 440

IFOSFAMIDE WITH AND WITHOUT ETOPOSIDE FOR RECURRENT OSTEOSARCOMA - THE MD ANDERSON EXPERIENCE

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Background: Ifosfamide based chemotherapy regimens, with and without etoposide, have been used to treat patients with recurrent osteosarcoma. Whether etoposide accentuates the response seen with high dose ifosfamide remains unknown.
Objectives: The objectives of this study were to estimate the progression-free (PFS) and overall survival (OS) in patients with recurrent osteosarcoma who received therapy with high dose ifosfamide (I) vs high-dose ifosfamide in conjunction with etoposide (I/E).
Design/Method: This study is an IRB approved, retrospective analysis of 65 patients with recurrent osteosarcoma treated with I(1.8-2.8 g/m2/day for 5 days) vs I/E(I: 1.8-2.8 g/m2 per day for 5 days. E: 100 mg/m2 per day for 5 days). OS time and PFS time were estimated using the Kaplan-Meier method and the comparison between or among patients' characteristics groups was evaluated by log-rank test.
Results: Of 65 patients, 37 patients received I alone and 28 patients received I/E. Mean number of chemotherapy cycles delivered was 4.43. No association between patient characteristics (gender, surgery/radiotherapy prior to relapse, primary site, site of relapse, number of cycles) and treatment group was found to be significant(all p-value > 0.05), aside from age at treatment($p = 0.03$) with I(mean age 18.2) vs I/E(mean age 15.07) In analysis of OS, 32 patients died. Median OS time was 3.47 years(95% CI: 1.54-NA); median follow-up time was 6.20 years(95% CI: 2.28-6.90). OS at 1, 2, and 5 years for patients who received I alone was 76%, 43%, and 32%, respectively. OS at 1, 2, and 5 years for patients who received I/E was 76%, 53%, and 35%, respectively. No statistically significant difference in OS between the two arms was noted($p = 0.5093$). In analysis of PFS, 56 patients had progression. The median PFS time was 0.56 years(95% CI: 0.28-NA). The PFS at 0.5, 1 and 2 years for patients who received I alone was 42%, 25%, and 17%, respectively. The PFS at 0.5, 1, and 2 years for patients who received I/E was 44%, 33% and 0%, respectively. No statistically significant difference in PFS between the two arms was noted($p = 0.2001$).

Conclusion: No statistically significant difference in PFS or OS was seen in patients with recurrent osteosarcoma who were treated with I alone versus I/E. This confirms results from older studies which have similarly shown that the addition of etoposide to high dose ifosfamide does not improve outcomes in patients with recurrent osteosarcoma.

Poster # 441

CURCUMIN: A NOVEL THERAPEUTIC FOR MEDULLOBLASTOMA

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Background: Medulloblastoma is the most common pediatric central nervous system cancer, and despite an overall favorable prognosis with intensive multimodal treatment, children are especially at risk for significant negative effects of these treatments. There is a need for treatments that are less toxic with fewer negative long-term sequelae. Curcumin, the active component of the dietary spice turmeric, has shown promising anti-cancer effects in vitro and in preclinical models of many types of cancer, including medulloblastoma. Along with its potent anti-cancer effects, a low toxicity profile and wide therapeutic window make curcumin an ideal candidate for a novel therapeutic for pediatric cancer. A major barrier to achieving curcumin's potential is poor bioavailability.
Objectives: To address this challenge we are focusing on two approaches: Meriva and TRB-N0224. Meriva is a curcumin-phosphatidylcholine complex shown to have 18-fold higher absorption than unformulated curcumin, while TRB-N0224 is a chemically modified curcuminoid. Our objective is to demonstrate therapeutic efficacy in an animal model of medulloblastoma.
Design/Method: In vitro studies were conducted using the primary cell lines IMB226 sonic hedgehog-type cells (SHH) and D425MED group 3 medulloblastoma cells. Animal studies were performed using 2 models: a D425MED orthotopic xenograft model in immunocompromised mice and an orthotopic transplant model of group 3 medulloblastoma (Myc + DN-p53) in syngeneic C57BL/6 mice.
Results: We have demonstrated in vitro efficacy of both Meriva and TRB-N0224 against SHH and group 3 medulloblastoma cells. The study using the D425MED model revealed negligible efficacy of Meriva using either oral or intraperitoneal administration. A pilot study with the Myc + DN-p53 model revealed a dose-dependent trend toward therapeutic efficacy of both Meriva and TRB-N0224. Experiments with larger cohorts are in progress.
Conclusion: Our study shows that Meriva and TRB-N024 have efficacy against medulloblastoma in vitro. Preliminary animal studies with these curcumins suggest a trend toward therapeutic efficacy and point to a possible immunomodulatory role of curcumin in the control of tumor growth.

Poster # 442

SIMULTANEOUS BILATERAL OPEN THORACOTIMES FOR PULMONARY METASTASES IN OSTEOSARCOMA TO REDUCE DELAY IN SYSTEMIC THERAPY

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Background: Osteosarcoma (OST) is the most common type of primary bone malignancy in children and young adults. Approximately 10-15% of patients will have primary metastases, and 66% will have recurrence with 90% involving the lungs (JCO 2002; 20(3):776-90, COG Can 2009; 115(22):5339-48). Aggressive surgical resection of all metastatic sites has a known survival advantage (J Ped Surg 2006; 41(1):194-9). Bhattasali et al. surveyed 183 surgical and medical CTOS members on management of metastatic OST. Respondents endorsed thoracotomy for all scenarios (69%-81%) with one exception, an untreated isolated nodule (58%) (Can Med 2015; 4(4):523-31). Preference for staged versus simultaneous open thoracotomies for bilateral metastases has not yet been studied. Although Chen et al. describes 8 of 12 OST patients with bilateral disease who underwent simultaneous thoracotomies, no data on delays in chemotherapy was available (Eur J Card thor Surg 2008; 34(6):1235-39). In a retrospective analysis of 10 children who underwent simultaneous bilateral thoracotomies, Häcker et al. reported no increased risk (Eur J Ped Surg 2007; 17(2):84-9).
Objectives: Simultaneous bilateral open thoracotomies in pediatrics have not been described in detail. Our goal is to report our experience with simultaneous bilateral open thoracotomies in young OST patients.
Design/Method: We reviewed all patients with bilateral OST lung metastases at our institution in the last 20 years. Delay time was calculated by subtracting pre-surgery from post-surgery cycle start dates.
Results: Among the 9 patients reviewed, 44% (n= 4) received simultaneous versus staged bilateral thoracotomies. Age ranged from 8-29 years with 6 males and 3 females. Of the patients who underwent simultaneous thoracotomies there were 1, 10, 21 and 23-day delays (Mean: 13.75 days, Standard Deviation (SD): 10.24). Of the patients who underwent staged thoracotomies, there were 16, 62, 75, and 121-day delays (Mean: 81.00 days, SD: 48.23). An independent t-test comparing simultaneous versus staged bilateral thoracotomy was computed (t= 2.70, p-value= 0.030).
Conclusion: Simultaneous bilateral open thoracotomies appear to be a safe approach for resection of metastatic OST lung disease with a potential benefit of decreased delay in chemotherapy in young patients.

Poster # 443

SURVEILLANCE MRIS IN CHILDREN WITH BRAIN TUMORS: HOW LONG SHOULD WE CONTINUE IMAGING?

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Background: Most children with cancer, including those with brain tumors, undergo surveillance imaging up to 5 years from diagnosis. Unlike children with other malignancies, however, children with brain tumors at some centers undergo continued imaging beyond 5 years from diagnosis. While there have been publications describing surveillance imaging practices among pediatric oncologists for children with various types of brain tumors, none focus on the utility of imaging beyond 5 years from diagnosis. We hypothesized that the yield of imaging surveillance beyond 5 years from diagnosis is low.
Objectives: To determine the frequency and yield of surveillance imaging in patients with brain tumors who are progression-free and greater than 5 years from diagnosis.
Design/Method: Children were eligible if they were diagnosed with a primary brain tumor between 1990 and 2005 and were free of recurrence 5 years from diagnosis. This was a retrospective review of the medical record. Information about age, brain tumor type and grade, gender, ethnicity, treatment type (surgery, radiation therapy, and/or chemotherapy), frequency of imaging, symptoms at the time of imaging, and whether there were any abnormalities appreciated on such surveillance imaging were obtained.
Results: Of the 265 children diagnosed with a primary brain tumor during the study interval, 77 were progression-free at 5 years from diagnosis. Their diagnoses were low grade glioma (36), medulloblastoma (20), high grade glioma (10), and other (11). All tumor types were non-metastatic. Of these 77 patients, 14 (18%) had changes noted on MRI. Five (6%) had changes that were not suspicious for recurrence and were followed; the MRI findings remained stable or resolved. The remaining nine (12%) had MRI findings concerning for recurrence of disease. The median time to development of changes in these nine patients was 113.2 months (61-226). Their initial diagnoses were low grade glioma (6), medulloblastoma (2), and high grade glioma (1). Six patients underwent surgical procedures: two had recurrent GBM, two had secondary tumors (meningioma, PNET), and two had presumed complications of radiation (cavernoma, gliosis). Three patients were followed via imaging alone and are alive, with their lesions remaining either stable or diminished. Four of the 14 children died.
Conclusion: A clinically significant proportion of children with brain tumors had evidence of disease beyond 5 years from diagnosis. The results of this small study suggest that imaging surveillance should continue beyond 5 years from diagnosis, even for children who are doing well and had been progression-free.

Poster # 444

IMPLEMENTATION OF COMPUTER-BASED IMAGE PATTERN RECOGNITION ALGORITHMS TO INTERPRET TUMOR NECROSIS; A FIRST STEP IN DEVELOPMENT OF A NOVEL BIOMARKER IN OSTEOSARCOMA

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Background: In light of failed efforts to intensify treatment based on tumor necrosis after 10-weeks of chemotherapy, a novel biomarker to predict or measure response is critically needed to

develop new therapies for patients with osteosarcoma.
Objectives: We hypothesize that such a biomarker can be discovered by combining the emerging virtual microscopy technology of whole-slide digital imaging with computer-based image pattern recognition algorithms. Initial development of the biomarker would be based on histological features of tumor response.
Design/Method: We retrieved data from resection specimens of 50 osteosarcoma patients treated at Children's Medical Center Dallas between 1995-2015. We implemented a multi-step process to develop an automated image analysis protocol for histological features that involved digitalization of all slides, development of an image visualization and navigation tool, and an image segmentation and processing module for extracting major features within an image.
Results: Tumor preparation: all resected tumors were prepared for histological evaluation with standard procedures that are briefly summarized. After surgical resection, each patient tumor was bisected in the plane predicted to provide the largest surface area for histology slide preparation. Using a pre-determined grid, each area within the grid was harvested to produce one slide (20-50 slides/patient). Using an Aperio scanner, we digitalized all histology slides for each patient, within which digitalized slides retain histological details from 2x to 20x magnification (each 20x image = 1 tile). Since each digitalized whole slide has approximately 4000 tiles, each patient whole tumor is represented by approximately 200,000 tiles.Main image processing algorithm development: Two-hundred image tiles were specifically identified from 3 patients' cases, to represent the main tumor features. An image segmentation pipeline was then designed and implemented to differentiate tumor from non-tumor and viable tumor from non-viable tumor based on color, shape, and cellular density characteristics. Implementing Color segmentation for chromatically distinct regions, and threshold segmentation using Multi-Otsu with clustering and contouring of segmented images for shape and density analysis, we completed the initial image analysis protocol. Using a flood-fill algorithm applied to pixels, cell counts, and cell density, we identified viable tumor and coagulative necrosis with 100% accuracy, fibrosis with 93% accuracy, and tumor osteoid with 89% accuracy. We then identified 2,500 tiles based on a stratified random sample approach to train and validate a set of machine learning algorithms. These efforts are ongoing.
Conclusion: We have completed the first phase necessary to automate the interpretation of histological features of tumor response in osteosarcoma.

Poster # 445

IRINOTECAN AND BEVACIZUMAB IN CHILDREN WITH MALIGNANT GLIOMAS AND RECURRENT/REFRACTORY CENTRAL NERVOUS SYSTEM TUMORS

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Background: The combination of Bevacizumab and Irinotecan has been described in adults and children with various types of brain tumors including low grade and high grade gliomas and embryonal tumors. The effectiveness of this regimen is still not fully established.
Objectives: To evaluate the overall response, time to progression and side effects of patients with Low Grade Gliomas (LGG), High Grade Gliomas (HGG) and Embryonal tumors (ET) receiving Bevacizumab and Irinotecan.

Design/Method: Retrospective chart review of children with brain tumors who received Bevacizumab/Irinotecan therapy at a single institution between 2010 and 2016.
Results: We reviewed the records of 25 patients (11 male and 14 females). Five had low grade gliomas, ten had high grade gliomas and ten had embryonal tumors (4 medulloblastomas, 3 ATRT, 1 PNET, 1 ETANTR and 1 Sarcoma). Patients received bevacizumab 10mg/kg every 2-4 weeks and Irinotecan 125g/m2 intravenously every 2 weeks.In the LGG group, patients were between 9 months and 10 years old. The average length of the therapy was 10 months. 100% of the patients had stable disease. Two patients did receive a different regimen after completing therapy (Everolimus and Vincristine/Carboplatin). In the HGG group, age of presentation ranged between 1 and 19 years old. Therapy varied between 2 to 60 months with an average of 19.5 months. Time to progression of the disease from the beginning of therapy was between 2 and 60 months with an average of 22 months. Three patients in the HGG group had continued complete response. These patients had an average therapy of 37 months. The longest follow up was more than 72 months since the beginning of therapy. In the ET group, patients were between 10 months old and 3 years old. Therapy was given between 3 to 24 months with an average of 9.3 months. Only 3 patients had progressive disease and time to progression was between 4 to 18 months from the beginning of therapy. Six patients had continued complete response and the longest follow up off therapy was 8 years. In our review, one patient experienced severe nausea, anorexia and emesis, one patient developed hypertension that responded well to medications and one patient developed transient heart failure 6 months into therapy.
Conclusion: The combination of Bevacizumab/Irinotecan was well tolerated in children with brain tumors. Stable disease was seen in all of the patients with LGG and good responses were seen in patients HGG and ET.

Poster # 446

GENOMIC CLUES TO THE PATHOGENESIS OF A UNIQUE SUBSET OF LOW-RISK WILMS TUMORS OF INFANCY

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Background: We previously identified 5 subsets of favorable histology Wilms tumor (FHWT) based on gene expression patterns that differed in their histology, nephrogenic rest status, and clinical outcomes. Subset 1 (S1; ~5% of FHWTs) were epithelial tumors without nephrogenic rests arising in infants, none of which relapsed. They showed a post-induction metanephric mesenchyme gene expression pattern. In comparison, Subset 5 (S5; ~70% of FHWTs) had a pre-induction gene expression pattern.
Objectives: Recent genomic studies have identified multiple pathogenic variants in high-risk FHWT. We now similarly study these unique low-risk S1 tumors.
Design/Method: Whole genome or exome sequencing (WGS or WXS) and copy number analysis (Illumina Quad-610) were performed on 2 and 5 S1 tumors, respectively. Gene expression (Affymetrix U133A) was analyzed in 11 S1 tumors, 158 S5 tumors, 5 perilobar nephrogenic rests (PLNRs) and 15 clear cell sarcomas of the kidney (CCSKs). Targeted sequencing (Illumina HiSeq2500) of genes recurrently mutated in WT was performed on 11 S1

tumors. Global methylation (Illumina 450K) was analyzed in 5 S1 tumors.
Results: WGS and WXS revealed no recurrent variants in 2 S1 tumors. Targeted sequencing in 11 S1 tumors revealed no variants in genes previously reported to be recurrently mutated in WT (WT1, WTX, CTNNB1, SIX1/2, DICER1, DROSHA, DGCR8, XPO5, or MLLT1). Global segmental DNA copy number analysis performed in 5 S1 tumors lacked recurrent segmental gains and losses. Strikingly, all 5 S1 tumors showed copy number neutral loss of heterozygosity (CN-LOH) on 19q, with a common region of CN-LOH involving 19q13.32-q13.43. Methylation analysis of genes within this region failed to show consistent evidence of biallelic hypo- or hyper-methylation. Gene expression analysis of genes within this region revealed under-expression of TRIM28 and SICLE6 in 11 S1 tumors as compared with each comparison population (S5 tumors, PLNRs, and CCSKs). Of note TRIM28 plays a complex role in renal development and has also been shown to interact with WTX, a tumor suppressor implicated in WT development.
Conclusion: S1 tumors show a common region of CN-LOH on 19q which is being further investigated.

Poster # 447

ANTI-CANCER EFFECTS OF ATYPICAL ANTIPSYCHOTIC DRUGS ON BRAIN TUMOR CELL LINES

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Background: Primary malignant central nervous system tumors (CNS) are the second most common childhood malignancies and are the leading cause of death in children of which Medulloblastoma is the most common malignant brain tumor and Glioblastoma multiforme (GBM) the most malignant glioma type of brain cancer. Brain cancers are difficult to treat due to the lack effective chemotherapeutic agents able to cross the blood brain barrier (BBB). Antipsychotic drugs have been used for decades in various psychiatric clinical settings, additional to their proven ability to cross the BBB, antipsychotic drugs (APDs) are being used as treatment for chemotherapy/disease induced emesis, anorexia, delirium and psychological disorders. Recent data indicates that APDs can have direct anti-cancer effects on tumor cells. Risperidone (Res) and Quetiapine are atypical or second generations APDs and are currently used in the pediatric population.
Objectives: To determine if Risperidone and Quetiapine induce anti-cancer affects in pediatric brain tumor cell lines.
Design/Method: We conducted an in vitro study on brain tumor cell lines: SJ-GBM2 (derived from pediatric glioblastoma patient with progressive disease) and HDMB03 (derived from patient with metastasized Group 3 medulloblastoma). Cells were exposed to increasing concentrations (0.1-25uM) of Risperidone or Quetiapine for 3 and 6 days, viability was determined using MTS assay. A 10-day cell proliferation assay at 2uM concentration of Risperidone and Quetiapine was tested on HDMB03 cells. To determine the effect of APDs (1uM and 5uM) on brain cancer stem cells (CSCs), neurosphere-forming assay was conducted on GBM brain tumor stem cell line, Glio3.

Results: Both APDs reduced viability in a dose and time dependent manner; HDMB03 cells however were more sensitive. For the HDMB03 cells, Quetiapine was more effective when compared to Risperidone, (25uM: 62.8% vs 75.5% of non-treated controls, respectfully). Treatment with only 2uM of either APD for 10 days reduced cell proliferation by approximately 60%. Both APDs significantly reduced neurosphere formation compared to non-treated controls: Quetiapine 1uM 65.9%, 5uM 40.5% and Risperidone 1uM 81.7%, 5uM 38.1%.
Conclusion: Our data indicates that potentially clinically relevant concentrations (low micromolar) of APDs induce anti-cancer effects; decreasing cell viability, cell proliferation and CSC self-renewal properties. Of the medulloblastoma subgroups, Group 3 (MYC amplified) is associated with the worst prognosis and the prognosis for GBM remains poor. The APDs Quetiapine and Risperidone represent strong candidates as a chemotherapeutic adjuvant for these difficult to treat cancers. (Hastings et al, Wiley-Blackwell, 2012)

Poster # 448

IDENTIFICATION OF MOLECULAR ALTERATIONS IN PEDIATRIC SOLID TUMORS FOR TARGETED THERAPUTICS

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Background: Recent progress in genomic profiling of patient-derived primary malignant tissues has led to the development of numerous that selectively target cancer-associated molecular aberration(s). Targeted therapy works with specific gene alterations and may be grouped into classes based upon function – enzyme inhibitors, apoptosis-inducing drugs, and angiogenesis inhibitors. This allows for directed treatment of malignancies with the potential to mitigate effects. However, the majority of targeted therapy options are currently not available for childhood cancer. A subset of pediatric solid tumors carry unfavorable prognosis with conventional combinatorial therapy. Genetic profiling of pediatric patients may uncover novel, potentially actionable targets for therapy.
Objectives: To identify actionable targets for therapy in children with solid tumors
Design/Method: From August 2014-December 2016, we perfomed a validated comprehensive genomic profiling of pediatric solid tumors. This assay from FoundationOne (Foundation Medicine) interrogates the entire coding sequence of 315 cancer-related genes plus select introns from 28 genes often rearranged or altered in solid tumor cancers. Tumor samples were obtained at the time of diagnosis and/or relapse. Retrospective chart review of patients was conducted and genomic alterations were reviewed. A review of literature was then conducted.
Results: Nineteen tumor samples from 16 patients were tested for gene alterations during the study period. Gene alterations were identified in 18/19 samples (95%). The number of gene alterations ranged from 1-4. Gene alterations with identified therapies found were MET amplification, mutations of NF-1, EWSR1, TFE3, and BRCA2. Nine samples (50%) had potential targeted therapies currently available on the market. In our cohort, only one patient was treated using genomic profile results. A 17 year old male with signet ring cell adenocarcinoma that carried MET amplification, was treated with crizotinib, a dual tyrosine kinase inhibitor active against c-MET and ALK, for palliative therapy. He was treated for 8 months with good quality of life. Three patients had repeat testing at the time of relapse. There were no new gene

alterations identified with retesting.
Conclusion: Our cohort showed high incidence for the identification of genomic alterations in children with solid tumors. However targeted therapy options for our patients were limited at present time. It is promising that an increased number of pediatric patients tolerate targeted therapy, and that an improvement in outcomes have been reported in the literature. Promising data in adult counterparts indicates that research should continue into identifying potential targets for therapy, as well as developing future therapies.

Poster # 450

TRUCUT NEEDLE BIOPSIES OF PALPABLE MALIGNANT ABDOMINAL TUMOURS IN CHILDREN; EXPERIENCE AT THE CHILDREN HOSPITAL, LAHORE, PAKISTAN

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Background: The Children Hospital (CH) and Institute of Child Health (ICH) , Lahore is the largest referral center for paediatric malignancies in Pakistan. Malignant solid tumors presenting in advanced stage with apalpable abdominal mass comprise largest group of patients. Laparotomy for the sole purpose of establishing diagnosis of Abdominal Masses can be detrimental considering assosiated perioperative morbidity and mortality. Diagnosis of abdominal masses by Trucut biopsy provide an alternative approach. Trucut Needle biopsy offer an early, efficient and less invasive technique enabling early diagnosis.
Objectives: To determine the demographics, accuracy, and complications associated with trucut needle biopsy of palpable abdominal masses in children with suspected malignancies.
Design/Method: The study was conducted in Haematology and Oncology Department at The Children Hospital, Lahore. All children presenting with suspected malignant palpable abdominal masses from April 1st 2016 till October 30th, 2016 were included. Informed consent taken from the parents. Tru-cut biopsy Procedures was performed by consultant or fellow under ultrasound guidance using 16 gauge tru-cut biopsy needle. Ultrasound was done by experienced radiologist (consultant or designated fellow). The sample were reviewed and analyzed by the hospital senior pathologist. Data entered into SPSS 20 and frequencies and percentages calculated. Data regarding age, gender, suspected diagnosis, final diagnosis, sample adequacy, and associated complications was analyzed.
Results: Total 90 ultrasound guided tru-cut biopsies were done. Six patients excluded due to bx of site other than abdomen. Suspected diagnosis based on clinical and radiological findings was wilms tumor 44(52.4%), neuroblastoma 23(27.4%), Non Hodgkin Lymphmoma 10(12%), Germ Cell tumor 4(4.8%), misc 3(3.6%). There were 60(71.4%) boys, 24(28.6%) girls. Majority 52 (62%) were 1-5years of age, 20(24%) were 5-10years old. Eight (9.5%) patients were under 1 year and 4(4.8%) over 10 years. Main symptom was abdominal distension 64(76.2%) while fever with abdominal distension observed in 15(18%), respiratory distress in 4(4.8%) and haematuria in 1(1.2%) patient. There was palpable abdominal mass in 84(100%) patients. Final diagnosis was wilms tumor 32(38%), Neuroblastoma 22(26.2%), Burkitts/B cell Lymphoma 12(14.3%), Germ cell tumor 3(3.6%), while 6(7.1%) have misc diagnosis while diagnosis was inconclusive in 8(9.5%) patients. Complications observed were Pain 2(2.4%), Haemoperitoneum and oozing

at biopsy site observed in 1(1.2%) patient each. Biopsy was inadequate/tiny in 3(3.6%) patients while biopsy size was adequate but showed necrosis only in 5(6%) patients.
Conclusion: Ultrasound Guided Tru-cut biopsy is a safe and reliable method for palpable malignant abdominal mass. It's associated with minimal complications and yield correct histological diagnosis expediting management.

Poster # 452

RADIATION EXPOSURE FROM DIAGNOSTIC IMAGES IN PEDIATRIC PATIENTS WITH CANCER: TRACKING THE DOSES WITH RADIMETRICS

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Background: Estimating radiation exposure from diagnostic images (REDI) in medicine is a complex process involving multiple factors. In Pediatrics this process is further complicated by evolving factors such as age, weight, body surface area, radiation sensitivity etc. While radiology reports include dosimetric values, volume CT Dose index (CTDI vol) and dose-length product (DLP) they do not provide an accurate estimate of the effective dose of radiation exposure to individual patients.
Objectives: To compare the accuracy of two different systems used to estimate the effective cumulative doses of REDI from computed tomography scans (REDI-CT) in children with sarcoma, neuroblastoma and Hodgkin lymphoma. 1) Manual calculation based on a previously published formula/data 2) Calculation performed by Radimetrics® software incorporated into the picture archiving and communication system also known as PACS.
Design/Method: A retrospective review of the REDI-CT in patients with sarcoma, Hodgkin lymphoma, and neuroblastoma diagnosed from 2009 and followed up through 2015. All CT scans from different body regions were included. A manual calculation of the cumulative dose of effective REDI-CT was performed for each patient, the results of which were compared to the data generated by Radimetrics®.
Results: Twenty-five patients with sarcoma, 14 patients with neuroblastoma and 13 patients with Hodgkin lymphoma were evaluated. The average REDI-CT from manual calculation vs Radimetrics® generated data for each group were: Sarcoma 51.25 mSv vs. 56.5 mSV; Neuroblastoma 42 mSv vs 25 mSv; Hodgkin lymphoma 60.5 mSv vs 156.7 mSv. We found that manual calculation underestimate the REDI-CT in the Hodgkin lymphoma group and overestimated the REDI-CT in the neuroblastoma group. There was consistency between calculation methods in the Sarcoma group. We speculate that the reason for this variation is the ability of Radimetrics® software to correct for smaller weight/BSA in younger children.
Conclusion: Our study indicates that manual calculations are complex and laborious to perform and may be misleading in tracking REDI-CT in the pediatric patients with cancer. The Radimetrics® system facilitate the accuracy of the process. More importantly Radimetrics system ensures that REDI is tracked in real time.

Poster # 454

PERCUTANEOUS TUMOR ABLATION IN PEDIATRIC ONCOLOGY

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Background: In adults, there are several different types of percutaneous tumor ablation used in both benign and malignant tumors of bone, soft tissue, lungs, liver, and kidneys. In contrast to the frequent use and numerous publications in adults, there is little published experience on using tumor ablation in children, besides its use in osteoid osteomas.
Objectives: We report 3 pediatric patients who safely underwent percutaneous tumor ablation. Two had microwave ablation and 1 had cryoablation.
Design/Method: Case series.
Results: A 14 year old male with relapsed hepatoblastoma, who had attained disease remission with liver transplant, presented with rising alpha-fetoprotein (AFP). The only lesion seen radiographically was a 6 mm metastatic nodule in the right upper lung, which was biopsy-proven hepatoblastoma. Mother and patient wanted to avoid chemotherapy and surgery. Microwave ablation of the pulmonary nodule was performed without complications. His AFP normalized within 1 month and remained normal for several months. A 12 year old male with metastatic hepatocellular carcinoma, who was responding to chemotherapy, underwent microwave ablation of his primary liver lesion, as a less invasive local control alternative to surgical resection. He had pain, controlled with intravenous narcotics, and fevers, without other signs of infection, which was managed inpatient for 3 days post-procedure. He was monitored closely for bleeding and renal insufficiency, and had no other complications. During surgical debulking of the metastatic disease, done 6 weeks post-ablation, a needle biopsy of the lesion was performed and showed only necrotic tissue. Radiographically, over the next 18 months, the ablated lesion continued to involute, without evidence of active disease in the liver. A 12 year old female with an unresectable desmoid tumor in her left forearm, had continued tumor growth despite several oral treatment regimens. Due to concerns that further tumor growth would impair wrist function and motion, she underwent image-guided cryotherapy. Post-procedure, she was admitted for pain control and was discharged the next day with pain controlled on oral narcotics. She had no other complications. At 1 month post-ablation, her tumor was only painful when bumped and imaging of the tumor showed similar size but with intratumoral hemorrhage and necrosis.
Conclusion: Percutaneous ablation can be done safely in children. It can be considered for local control in pediatric patients with poor prognosis tumors or with locally invasive non-malignant tumors, as an alternative to chemotherapy, surgery or radiation.

Poster # 601

LYMPHOCYTE CELL SUBSETS POST EPSTEIN-BARR VIRUS REACTIVATION MAY PREDICT DEVELOPMENT OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN: CD8:CD20 RATIO AS A NOVEL MARKER

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Background: Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disease (PTLD) following allogeneic hematopoietic stem cell transplantation (HSCT) is a serious complication associated with significant mortality. Most commonly, there is expansion of EBV infected B cells in the setting of low or dysfunctional cytotoxic T cells.
Objectives: The goal of this study is to evaluate whether lymphocyte subsets and CD8:CD20 ratio post EBV viremia in children undergoing HSCT can predict development of PTLD.
Design/Method: A retrospective chart review of allogeneic HSCT recipients was conducted with available lymphocyte subsets post EBV viremia. Demographic and clinical data were collected. Absolute lymphocyte count, lymphocyte subset, and CD8:CD20 ratio at the time of EBV viremia was analyzed. We used CD8+ as a T cells marker and CD20+ as a B cell marker. Patients who were treated preemptively with rituximab for high EBV titres were excluded.
Results: A total of 26 patients were included in the analysis. PTLD group (n=5, four with proven and one with probable PTLD) and non-PTLD group (n=21, EBV positive patients with no PTLD or rituximab treatment). Lymphocyte recovery was slower in PTLD group compared to the non-PTLD group, with median CD4+ cell count 55 cell/uL and 331 cell/uL respectively((p value 0.003), median CD8+ 17 cell/uL and 551 cell/uL respectively, (p value 0.014), median CD3+ 82 cell/uL and 940 cell/uL respectively (p value 0.007) and median Gamma delta T cells 2 cell/uL and 43 cell/uL respectively (p value 0.004). CD8:CD20 ratio was significantly lower in PTLD group (median 0.15) compared to non-PTLD group (median 2.4, range) (p value 0.012). Using receiver operating characteristic (ROC) curve, cutoff for CD8:20 ratios were analyzed and 1 was used as a cut off value. In PTLD group, four out of five patients (80%) had a ratio less than 1 whereas in non-PTLD group, all 21 patients had a ratio more than 1.Using a CD8:CD20 cutoff ratio of 1, the sensitivity and specificity were 80% and 100% respectively and the negative predictive value and positive predictive value were 95% and 100% respectively.
Conclusion: Profoundly low T cells count and the CD8:CD20 ratio may be used to predict the development of PTLD in the context of EBV viremia in children post allogeneic HSCT. Patients having adequate lymphocyte recovery were at a low risk for developing PTLD and did not require rituximab treatment. Further prospective studies are needed to validate this finding.

Poster # 603

THE ROLE OF HISPANIC ETHNICITY ON OUTCOMES IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION AT A SINGLE INSTITUTION

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Background: Hematopoietic Stem Cell Transplantation (HSCT) is a potentially life-saving treatment for patients with both malignant and non-malignant disease processes. Ethnic disparities in HSCT outcomes have been described in both the adult and pediatric literature.
Objectives: To determine the differences in morbidity and mortality in Hispanics and Non-Hispanic Whites receiving HSCT at a single institution.

Design/Method: Retrospective chart review was performed for a cohort of 175 pediatric patients from 01/01/2000 to 06/31/16 at Children's Mercy Hospital. We employed descriptive statistics, Kaplan-Meier survival analysis, chi-square test, and Cox proportional hazard regression analysis.
Results: Of the 175 patients reviewed 27 were Hispanic and 148 Non-Hispanic White. Median age at HSCT was 8 years (range 0.1 to 20.7 years). Males represented 57.7% of the cohort. Sixty-four percent underwent HSCT for malignant etiologies and 35.6% for non-malignant diseases. There was a statistically significant difference in the stem cell source between Hispanic and Non-Hispanic Whites, with a greater number of Hispanic patients receiving cord blood (37% vs. 15.5%; P=0.026). Seventy-seven percent of the whites had a 100% match compared to only 59% of Hispanics (p=0.052). There was no significant difference in the incidence of graft-versus-host disease or veno-occlusive disease between the 2 groups. Hispanic patients were found to have an earlier time to mortality than Non-Hispanic Whites (P=0.035). The estimated 1 year overall survival rates for White-Non-Hispanic and Hispanics were 78.8% and 62% (standard error 0.034 and 0.095) and at 5 year overall survival was 66% and 48% (standard error 0.41 and 0.103)) respectively. When survival was analyzed using Cox proportional hazards regression analysis controlling for stem cell source, degree of mismatch and sibling donor, Hispanic race was significant (p=0.03 with a hazard ratio of 2.069; 95% CI of 1.072, 3.995). The median time of follow-up after HSCT for Whites and Hispanics was 2141 days (range 174 - 6005) and 1921 (range 158-4995) respectively.
Conclusion: Overall, Hispanic patients died earlier than Non-Hispanic Whites. The hazard of dying for a Hispanic patient was two times that of a Non-Hispanic White patient. Some of these results may be attributable to the stem cell source, which differed between the groups and it is well-documented that a greater degree of mismatch results in a potentially higher rate of HSCT complications. Other factors, such as language, cultural barriers and socio-economic status may contribute. Median time after HSCT was similar between the 2 groups.

Poster # 605

THE ROLE OF 18F-FDG PET/CT AS A NON-INVASIVE MODALITY IN THE DIAGNOSIS OF ACUTE GASTROINTESTINAL GRAFT-VERSUS-HOST-DISEASE (GI-GvHD) IN CHILDREN

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Background: Severe acute gastrointestinal graft-versus-host disease (GI-GvHD) is a serious early complication of allo-transplants. Endoscopic biopsies provide the best supportive evidence, but are invasive in patients who are already medically compromised. 18F-FDG PET/CT may be able to stratify patients who require endoscopy and biopsy.
Objectives: To evaluate the performance of 18FDG PET/CT in differentiating Stage 0-1 disease compared to Stage 2-4 disease in pediatric patients with suspected GI-GvHD.
Design/Method: Retrospective chart review of all paediatric allo-transplant patients referred for 18F-FDG PET/CT with suspected GI-GvHD from 2009 to 2015. Clinical follow-up, endoscopy and biopsy findings were correlated with 18F-FDG PET/CT. Regional SUV parameters were extracted by placing ROIs around stomach, duodenum, distal ilium, caecum, ascending, transverse, descending colon, recto-sigmoid colon and rectum. Regional, and average large and

small bowel SUV data were statistically compared between patients with Stage 0-1 GIT-GvHD versus Stage 2-4 disease. The clinical and biopsy-supported diagnosis of acute GI-GVHD was taken as the true positive.
Results: 50 scans in 34 patients, median age 9 years, were performed at median 71 days post BMT. There were 13 Stage 2-4 GI-GvHD and 37 stage 0-1 GI-GvHD. Transverse colon SUVmax was significantly higher in the stage 2 to 4 GI-GvHD compared to Stage 0-1 disease (Mann-Whitney-U $p<0.05$). There was a non-significant trend for whole bowel SUVmax to be higher in the Stage 2 to 4 group compared to Stage 0-1 group (4.16 vs. 2.94, Mann-Whitney-U $p=0.07$). On ROC analysis, SUVmax 2.74 had a sensitivity of 79% and specificity of 61% for detecting Stage 2-4 GI-GvHD.
Conclusion: 18F-FDG PET/CT is a feasible and potentially useful non-invasive tool in the diagnosis and monitoring of therapeutic efficacy in acute GI-GvHD.Whole Bowel SUVmax may be higher in patients with stage 2 to 4 GI-GvHD, and transverse colon SUVmax could have the ability to differentiate children with no or stage 1 GvHD from those with stage 2 to 4 disease. PET scan with SUVmax below 2.74 ("PET-negative") could serve as a criteria to avoid invasive endoscopic procedures and observe for the persistence of gastrointestinal symptoms before subjecting these patients to an image-guided biopsy. In patients too unwell for endoscopy, an SUVmax > 4 (ROC curve Specificity 75%) and a high SUVmax in the transverse colon could serve as supportive evidence for stage 2-4 acute GvHD, in the absence of biopsy findings. Pre-endoscopic 18F-FDG PET/CT serves to guide the proceduralist to sample areas with the best diagnostic yield.

Poster # 607

COMBINATION OF HIGH-DOSE METHYLPREDNISOLONE AND DEFIBROTIDE FOR VENO-OCCLUSIVE DISEASE IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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Background: Veno-occlusive disease (VOD) is a serious complication of hematopoietic stem cell transplant (HSCT). VOD is diagnosed clinically and defined by hyperbilirubinemia associated with weight gain or ascites, and painful hepatomegaly. Radiographic evidence of reversal of flow in the liver via Doppler ultrasound is typical. VOD results from injury to the sinusoidal endothelial cells of the liver following administration of chemotherapy or radiation usually as part of a preparative regimen for HSCT. Until recently, supportive care measures alone were available for patients with VOD, but defibrotide was approved by the Food and Drug Administration for the treatment of severe VOD in patients with renal or pulmonary dysfunction following HSCT. Our group previously published on the use of high-dose methylprednisolone (500 mg/m2/dose every 12 hours for 6 doses) in patients with VOD showing good success.
Objectives: Assess response to the combination of high-dose methylprednisolone and defibrotide in VOD.
Design/Method: Retrospective chart review.
Results: There were 25 patients with VOD during the study period of January 2010 through July

2016. Of these 25 cases, 15 were treated with the combination of high-dose methylprednisolone and defibrotide, seven did not receive defibrotide, and three were transfers from outside institutions midway through defibrotide therapy. All 15 patients treated with combination therapy were undergoing HSCT with VOD developing at a median of 17 days post-HSCT. Twelve of 15 patients had multi-organ failure with either renal and/or pulmonary dysfunction. Renal replacement therapy was needed in seven patients and eight required ventilator support with an additional three patients requiring supplemental oxygen. Of the 15 who received combination therapy, four died from VOD complications within the first 100 days post-HSCT with an overall Day +100 survival rate of 73%. Of the remaining 11 alive patients, 10 achieved complete resolution of VOD by Day +100 with a median time to resolution of 27 days.
Conclusion: Data from the phase 3 trial of defibrotide for treatment of severe VOD showed a Day +100 post-HSCT survival rate of 38.2% (Soiffer at al Blood 2016) and a recent CIBMTR study showed a Day +100 survival rate of 39% (Saber at al BBMT 2016). Our single center experience utilizing the combination of high-dose methylprednisolone and defibrotide showed a Day +100 survival rate of 73% and Day +100 VOD resolution rate of 66.7%. This retrospective chart review suggests that the combination of high dose steroids and defibrotide may be superior to defibrotide alone, and warrants further investigation.

Poster # 609

ADRENAL INSUFFICIENCY IS COMMON AMONG CHILDREN WITH HIGH-RISK SOLID TUMORS UNDERGOING AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Treatment for high-risk solid tumors, including neuroblastoma (NBL), medulloblastoma (MBL), Ewing's sarcoma (ES), and Hodgkin's lymphoma (HL), among others, often includes induction chemotherapy and external radiation therapy (XRT). Autologous hematopoietic stem cell transplantation (aHSCT) is increasingly utilized to provide stem cell rescue during treatment. Endocrinopathies often arise due to chemotherapy, XRT, and aHSCT; however the incidence of adrenal insufficiency (AI) among children with solid tumors undergoing aHSCT has not been well described.
Objectives: Evaluate adrenal function among children with high-risk solid tumors following induction chemotherapy +/- XRT, who are undergoing aHSCT.
Design/Method: Retrospective analysis of 166 children at our institution with high-risk solid tumors undergoing aHSCT between 2007 and 2016 was performed. Adrenal testing was performed on 76 (46%) subjects, following induction chemotherapy +/- XRT but prior to aHSCT. Those actively taking glucocorticoids were excluded. Median age was 4.8 years (range 0.5 – 29.7 years). AI was determined by serum cortisol <13 mcg/dL from timed morning sample (8AM) and/or peak serum cortisol <20 mcg/dL during ACTH stimulation testing.
Results: Among 76 subjects tested, 58 (76%) had normal timed or stimulated cortisol levels, whereas 18 (24%) demonstrated AI. Ten subjects with AI (56%) had NBL (27% of all NBL subjects tested). Only three of these received therapeutic MIBG prior to adrenal testing, and all had at least one intact adrenal gland. Three subjects with AI (17%) had brain tumors (17% of all

brain tumor subjects tested), 2 of whom received prior craniospinal XRT. The remainder of subjects with AI included those with HL (n=2), retinoblastoma (n=1), desmoplastic small blue cell tumor (n=1), and one with ES who had received skull base XRT. ACTH levels were performed in 8 subjects and elevated in 2 with NBL, demonstrating primary adrenal insufficiency. Among those with AI, concurrent use of megestrol, an appetite stimulant with glucocorticoid effects, occurred in 3 subjects (17%), which likely contributed to suppression of the HPA axis.
Conclusion: Our results demonstrate that AI (both primary and secondary) is common among children with high-risk solid tumors preparing for aHSCT, especially among those with NBL. Interestingly, only 6/18 (33%) of those with AI had XRT or therapeutic MIBG prior to adrenal testing, raising the possibility of direct effect from induction chemotherapy. Potential other contributors to AI include glucocorticoid withdrawal in brain tumor patients and HPA axis suppression from megestrol. We recommend screening for AI in all subjects with high-risk solid tumors undergoing aHSCT.

Poster # 611

USING ULTRASOUND ELASTOGRAPHY TO DIAGNOSE SINUSOIDAL OBSTRUCTION SYNDROME IN PEDIATRIC BONE MARROW TRANSPLANT PATIENTS

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Background: Sinusoidal obstruction syndrome (SOS) is a potentially fatal disease affecting children following bone marrow transplantation (BMT).Diagnosis of SOS is based on clinical criteria. Traditional ultrasound has poor sensitivity and specificity with portal vein flow reversal occurring well after the disease is clinically evident. Ultrasound elastography is a newer technology that measures liver stiffness, which should increase in SOS due to passive hepatic congestion.
Objectives: Our hypothesis is that quantitative shear wave ultrasound elastography will be more accurate in detecting this disease compared with conventional ultrasound parameters.
Design/Method: This is a single site prospective cohort study evaluating ultrasound elastography in BMT patients from December 2015 to January 2017. Patients under 21 years of age receiving allogeneic or autologous myeloabalative stem cell transplantation were included. Reduced intensity conditioning regimen and haplo identical transplants were excluded. SOS was defined using the modified Seattle/Baltimore criteria. Subjects had abdominal Doppler ultrasounds with shear wave elastography at two scheduled time points: one-week prior to conditioning regimen and day +14 of post-transplant. Other standard of care ultrasounds with elastography were included. At least ten elastography measurements were obtained in the right hepatic lobe. Patients were divided into two groups those developed SOS (Group I) and those who did not (Group II). Two tailed student t-tests were used to compare the two groups.
Results: 17 consecutive BMT patients (11 allogenic and 6 autologous) were included. 53% of patients were females and the mean age was 8.8 years (± 6.2).Three (18%) of the subjects developed SOS and one (33%) received defibrotide treatment in the SOS group. All three

patients with SOS received allogenic stem cell transplant and busulfan as part of their conditioning regimen. Patients with SOS had shear wave velocities that significantly increased 1.4 m/s +/- 1.2 m/s from baseline compared to patients without SOS had shear wave velocities that increased 0.1 m/s +/- 0.2 m/s from baseline (p=0.004).
Conclusion: Patients who develop SOS have significantly increased liver stiffness as measured by ultrasound elastography compared to patients who do not develop SOS. Patients who receive busulfan as a part of their conditioning regimen may be at increased risk of developing SOS.

Poster # 613

REDUCED FERTILITY POTENTIAL IN YOUNG FEMALES FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION DESPITE REDUCED INTENSITY CONDITIONING

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Background: Reduced intensity (RIC) hematopoietic stem cell transplantation (HSCT) is increasingly used for treatment of childhood malignancies and other genetic and immune disorders with the goal of maintaining therapeutic efficacy while limiting toxicity. Risk of infertility and primary ovarian insufficiency in females after more intense, myeloablative HSCT is high, but little is known of late endocrine and fertility effects after RIC HSCT.
Objectives: Longitudinally evaluate gonadal function and fertility potential in young females after RIC as compared to myeloablative HSCT.
Design/Method: A retrospective cohort study of female patients, presenting ≥ 1 year after a single HSCT was performed.
Results: Preliminary results from 33 female subjects enrolled in our ongoing study were obtained, 16 of whom were in puberty and had laboratory data available for review. Of these, 11 received myeloablative HSCT and 5 received RIC HSCT. Median age at HSCT was 12.2 years (range 9.1 – 23.1 years) for the myeloablative group and 20.6 years (range 13.3 – 34.3 years) for the RIC group. Median interval since HSCT was 5.2 years (range 2.1 – 13.3 years) for the myeloablative group and 2.2 years (range 1.1 – 11.3 years) for RIC. Laboratory evaluation of ovarian reserve via anti-mullerian hormone (AMH) and hypothalamic–pituitary–gonadal axis via LH, FSH, and estradiol was performed to determine fertility potential and late endocrine effects in RIC compared to myeloablative HSCT.All pubertal subjects in the RIC group had normal FSH, LH and estradiol post-HSCT. However, 64% (7/11) of subjects in the myeloablative group had elevated FSH and LH levels suggestive of primary ovarian insufficiency, and 71% of these (5/7) also had low estradiol levels. Regardless of conditioning treatment, AMH values were abnormally low in nearly all (94%, 15/16) patients studied. Only one subject, who had received RIC HSCT, had a normal AMH level at the time of our analysis.
Conclusion: Our results suggest that young females after RIC HSCT have a lower incidence of primary ovarian insufficiency compared to patients after myeloablative HSCT. However, low AMH values in nearly all subjects suggest that ovarian reserve and future fertility potential is

compromised with both conditioning regimens. Therefore, normal pubertal development and lack of primary ovarian failure does not ensure normal ovarian reserve following RIC HSCT. Risk of infertility should be discussed in counseling about RIC HSCT, and fertility preservation should be discussed and offered prior to HSCT. Additional studies to confirm these data in a larger cohort are underway.

Poster # 615

SAFETY AND FEASIBILITY OF GRANULOCYTE TRANSFUSION FOR HIGH-RISK ALLOGENIC STEM CELL TRANSPLANT RECIPIENTS

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Background: Bacterial and fungal infections contribute to morbidity and mortality in hematopoietic stem cell transplantation (HSCT) recipients. During the pre-engraftment neutropenic period, patients with prior infections are at particularly high risk of life-threatening infectious complications. Granulocyte transfusion (GT) is an adjunct to antibiotics for neutropenic oncology patients with active infections; data on GT for infection prophylaxis in HSCT recipients are limited.
Objectives: This study assessed the safety and feasibility of prophylactic GT in patients with prior bacterial and/or fungal infections undergoing allogeneic HSCT.
Design/Method: This was a retrospective cohort study of patients at Children's Hospital of Pittsburgh of UPMC (Pittsburgh, PA, US). From a consecutive sample of 102 HSCT recipients between August 2012 and October 2016, records of patients who received GT were reviewed. Unrelated, ABO-matched granulocyte donors were stimulated with corticosteroids; related donors (N=1) were stimulated with filgrastim. Recipients received premedication with acetaminophen, diphenhydramine, and methylprednisolone (0.5 mg/kg)
Results: The cohort comprised 12 patients, 3 female (25%), with a median age at HSCT of 7 years (0.7 – 40.3), receiving 60 GTs total. Indications for HSCT were leukemia/lymphoma (N=7), primary immunodeficiency (N=2), metachromatic leukodystrophy (N=1), and severe aplastic anemia (N=2). Indications for GT were prior bacteremia (N=5), bacterial pneumonia (N=5), or multifocal bacterial infection (N=2); 4 patients (33%) also had a history of proven fungal infections.The median number of GTs per patient was 7 (1 – 15). The mean rise in white blood cells post-GT was 1.3 (+ 2.2) x109/L; in patients with differentials performed, the mean rise in absolute neutrophil count was 1,560 (+ 3,173) x106/L. Transient dyspnea was reported during 3 of 60 GTs (5%), with 1 of these episodes (2%) requiring oxygen therapy and no ICU transfers. No transfusion reactions were reported.While receiving GT, 1 patient (8%) with a history of mixed bacterial/fungal pneumonia developed bacteremia and radiographic progression of chronic lung disease; new bacteremia occurred in 3 patients (25%). Cumulative non-relapse mortality at 100, 180, and 365 days post-HSCT was 17%, 33%, and 33%, respectively. Overall survival in the cohort was 50%. One patient (8%) died of disseminated cytomegalovirus. No patients died of bacterial or fungal infection.
Conclusion: GT was well tolerated. A minority of patients developed new or recurrent bacterial/fungal infections while receiving GT, and infection-related mortality was low. GT

appears feasible and may have a role in preventing infectious complications in HSCT recipients with prior bacterial/fungal infections.

Poster # 617

CLINICAL UTILITY OF RT-PCR TO MONITOR MOLECULAR MRD AND TO GUIDE THERAPEUTIC DECISIONS PRE AND POST-TRANSPLANT IN PEDIATRIC MLL-AML

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Background: MLL (KMT2A) gene rearrangements are potent oncogenes found in 10-15% of pediatric Acute Myeloid Leukemia (AML). Persistence of MLL fusion transcripts is strongly associated with pending AML relapse. The clinical utility of tracking molecular MRD (MMRD) pre and post-transplant for MLL-AML is not defined.
Objectives: To describe the outcome of children with positive MMRD before bone marrow transplant (BMT) for MLL-AML in first Complete Remission (cytological CR-1).
Design/Method: As of 2009, MLL chimeric fusion transcripts were serially tracked by nested RT-PCR in our center. We retrospectively report every MLL-AML transplanted in cytological CR-1 but with persistent MMRD.
Results: Four children were transplanted in cytological CR-1 with positive MMRD: case#1: 6 years, t(11;19); case#2: 7 months, t(9;11); case#3: 4 years, t(1;11); case#4: 4 months, t(11;17).Cytological CR were obtained after first induction for the two first children and second induction for others. Case#2 was MMRD negative after the first induction cycle but positive before transplant, the other children were never MMRD negative before transplant.Post-transplant evolutions were marked by:- case#1 always remained positive for MMRD and relapsed 55 days post matched-related BMT (MR-BMT). The patient was refractory to FLAG-IDA regimen, donor lymphocytes infusion (DLI), and succumbed from toxicity early after haplo-identical transplant.- case#2 achieved negative MMRD after MR-BMT but relapsed (cytology and MMRD) 105 days post-transplant. Molecular remission was achieved following re-induction, donor bone marrow infusions and 1-year of Interleukin-2 therapy. MMRD was sustained for 2 years off-therapy.- case#3 was MMRD positive after MR-BMT and achieved molecular remission after 2 consecutive DLI. MMRD relapse was detected 1 year post-transplant, persisted following Interferon-alpha treatment with cytological relapse 17 months post-transplant. Two courses of FLAG-IDA and haplo-identical transplant with a single post-transplant DLI led to CR with negative MMRD which remained negative 22 months after transplant.- case#4 underwent matched unrelated donor transplantation and achieved negative MMRD 53 days post-transplant with grade 3 cortico-sensitive cutaneous acute GVHD. Immunosuppression was tapered rapidly and the patient remains in molecular remission 16 months post-transplant.
Conclusion: All 4 children transplanted in cytological CR-1 for MLL-AML with positive MMRD relapsed after transplant. Three patients were rescued after relapse using combinations of chemotherapy and/or immunotherapies. Our local experience raises the possibility that close and serial MMRD tracking for MLL-AML enables early relapse detection and timely

intervention and questions whether negative MMRD prior to transplant would lead to improved outcomes in MLL-AML.

Poster # 619

AUTOLOGOUS STEM CELL TRANSPLANTATION FOLLOWING INDUCTION CHEMOTHERAPY, HiPEC SURGERY, AND WHOLE ABDOMINAL RADIATION IN PATIENTS WITH DESMOPLASTIC SMALL ROUND CELL TUMOR DEMONSTRATES LOW TREATMENT RELATED MORTALITY AND PROLONGED PROGRESSION FREE SURVIVAL

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Background: Desmoplastic Small Round Cell Tumor (DSRCT) is a rare, highly fatal disease with 3 year overall survival (OS) of approximately 30%. The use of multimodal therapy (chemotherapy, aggressive resection and irradiation) extends 3 year OS to 55%. Recently, autologous stem cell transplantation (autoSCT) or hyperthermic intraperitoneal chemotherapy (HIPEC) with aggressive surgical debulking have been added with some success. We combined autoSCT with intensive, chemotherapy, HIPEC, aggressive surgical debulking, and whole abdominal irradiation. We find this regimen is well tolerated and may lead to an increase in survival beyond previously published regimens.
Objectives: To review the toxicity and progression free survival of this novel regimen.
Design/Method: Retrospective review was preformed of patients with DSRCT at the University of Chicago between 2014 and 2016 treated with chemotherapy induction (vincristine, ifosfamide, adriamycin and etoposide), HIPEC, surgical debulking, irradiation, and autoSCT with busulfan (12.8mg/kg) and melphalan (140mg/m2) conditioning.
Results: Three patients (mean age 17.3 years) were diagnosed with stage IV DSRCT. Two patients completed treatment; one is currently undergoing treatment. The regimen was well tolerated. Major complications included grade III pleural effusion and central line associated infections, all during induction chemotherapy. The two patients who completed therapy demonstrated good immune recovery without infectious sequela following transplantation. Flow cytometric analysis of peripheral lymphocytes three months post transplantation revealed mildly low CD4+ T cell numbers and low immunoglobin levels. A large proportion of lymphocytes (>50%) are CD3+CD4+CD25+ CD8+. CD56+ cells were normal in number. One patient remains in complete remission 23 months off therapy. The other patient suffered relapse at 18 months off therapy and subsequently died of disease. Both patients had disease at the time of autoSCT. However, the patient who remains disease free had very good partial response while the patient with progressive disease had bulky tumor with unresectable peri-portal infiltration. The third patient has completed his induction chemotherapy, HIPEC and surgical debulking.
Conclusion: DSRCT is a rare, aggressive solid tumor that is refractory to intensive therapy. Combination of chemotherapy, HiPEC, aggressive surgical debulking, whole abdominal irradiation and autoSCT with busulfan/melphalan conditioning is well tolerated and may provide longer progression free survival (PFS) than previously published regimens. The addition of autoSCT may be a key factor as similar regimens without autoSCT report a 9-19 month PFS

while this has current mean PFS of 20.5 months. Additional patients and longer follow up are required to fully understand the implications and long-term sequela of this novel strategy.

Poster # 621

HOW LONG DOES IT TAKE TO FIND A MATCHED UNRELATED DONOR IN 2016?

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Background: Donor availability for hematopoietic cell transplant (HCT) has improved tremendously in the last 30 years. Adult unrelated donors (URD) have been effectively recruited and retained in registries, customized software has facilitated rapid donor identification, and use of cord blood (CBU) for HCT has increased. In contrast to URD and CBU, haploidentical donors are usually immediately available, making time to finding a donor important when balancing stem cell source choices.
Objectives: We sought to determine the time taken to identify a matched unrelated donor (MUD) at our center.
Design/Method: We reviewed our last 300 URD searches and recorded time to donor identification and workup.
Results: The cohort included 60% male and 77% Caucasian patients, with a median age of 6 years (range 10 days – 41 years). Donor search was performed for patients with immune deficiency/dysregulation (38%), malignancy (30%), bone marrow failure (20%), hemoglobinopathy (5%), or other disorders (7%). Median time from preliminary to formal search was 1 day (range 0-1854). Of 300 searches, 190 patients have undergone HCT; 162 with a MUD. For those who identified a MUD and proceeded to HCT, median time between formal search and date of confirmatory donor HLA testing was 16 days (range 3-540). Median time from formal search to donor information session was 58 days (range 1-645), formal search to start of preparatory regimen, 92 days (range 8-772), and formal search to infusion, 107 days (range 22-786). An alternative donor source was used for 28 patients [22 CBU, 5 matched sibling, 1 haploidentical] when no MUD was identified. Additionally, 110 patients did not undergo HCT. The reasons for not proceeding with HCT were patient death (27), HCT not indicated (25), alternate therapy chosen (19), no suitable donor (15), family preference (2), and patient deemed ineligible (1). Eleven patients are still undergoing diagnostic evaluation, 4 are undergoing pre-HCT evaluation, and 6 were lost to follow-up.
Conclusion: Our data show that under the best circumstances, a MUD can be identified quickly, with 44% of our patients moving from formal search to confirmatory donor testing within 14 days. Time to preparatory regimen and infusion is often influenced by variability in patients' condition. In cases where a donor is needed urgently but the search is not ideal, we have used haploidentical HCT. MUD could not be identified in only 5% of our last 300 searches and haploidentical HCT is of value in these patients.

Poster # 623

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR THE TREATMENT OF MUCOPOLYSACCHARIDOSIS

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Background: No
Objectives: Mucopolysaccharidosis (MPS)is a lysosomal storage disorder caused by deficient activity of the iduronate-sulfatase.This leads to accumulation of glycosaminoglycns(GAGs) in the lysosomes of various cells,which causes progressive multisystem invaolvement with ensuing death.The aim of this study was to exploit the effect of treatment with allogenic hematopoietic stem cell transplantation and administration of high doses of cyclophosphamide early after haploBMT in these cases.
Design/Method: We retrospectively reviewed data from 3 MPS patients (2 cases MPS Ⅱ, and 1 case MPS Ⅰ). The two MPS Ⅱ patients were 44-month-old and 35-month-old boy and the MPS patient is an 84-month-old girl at the time of transplantation. The reduced-intensity of Bu+Flu conditioning regimen in allo-HSCT for these patients was as follows: busulfan 4mg/kg at 5 to 2 days before transplantion,fludarabine 40mg/m2 at 6 to 3 days before transplantion.Graft-versus-host disease(GVHD) prophylaxis:rabbit antithymocyte globulin 2.5mg/kg daily at 5 to 3 days before transplantation,short-course methotrexate,posttransplantation high-dose cyclophosphamide on days +3 and +4 was followed by mycophenolate mofetil and cyclosporine.The donors all were their HLA-haploidentical father.
Results: These three patients' Neutrophil engraftment occurred on +14d , +12d and +15d after transplantation respectively,platelet engraftment occurred on day +14d, +10d and +15d after transplantation respectively.Complete donor type engraftment was confirmed by Short Tandem Repeat-Polymerase Chain Reaction(STR-PCR) on day 14 after transplantation.No regimen-related toxicity occurred,GVHD and graft failure were not observed.1 month after transplantation, the activity of the iduronate-sulfatase was increased to normal.The motion of metacarpophalangeal joints ameliorated,regression of hepatosplenomegaly,the neurocognitive function improved.
Conclusion: Allogeneic hematopoietic stem cell transplantation is an effective measure to treat patient with MPS at least MPS Ⅱ and MPS Ⅰ.The reduced-intensity conditioning regimen was helpful to decrease the regimen-related toxicity. Posttransplant cyclophosphamide approach successfully used and reduced the incidence of GVHD.

Poster # 625

IRON CHELATING AGENTS DELAY BUSULFAN CLEARANCE

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Background: Busulfan is used in combination with other chemotherapy agents in hematopoietic stem cell transplant (HSCT) preparative regimens. Elevated ferritin levels have been linked to increased incidence of sinusoidal obstructive syndrome (SOS) in HSCT patients. We report the case of a patient undergoing haploidentical HSCT who received deferasirox and deferoxamine for iron chelation prior to HSCT and developed severely delayed busulfan clearance.
Objectives: To discuss the interaction between iron chelating agents and delayed busulfan clearance
Design/Method: Presentation of a unique case
Results: High serum ferritin concentrations are associated with an increased risk of SOS. With the presumption that ferritin is a surrogate marker for iron overload, we treated our patient with deferasirox and deferoxamine for 4 weeks prior to HSCT with a successful reduction in serum ferritin. An initial test dose of busulfan (30.4 mg) was infused over 2 hours and produced elevated immediate, 1hr, 2hr and 4hr post-infusion levels (1400, 1096, 941 and 698 ng/mL respectively) with an atypical pharmacokinetic (PK) curve and an impaired clearance rate of 2.1 mL/min/kg. Unaware of a single prior report of deferasirox interfering with busulfan clearance, we discontinued fluconazole as that likely caused delayed clearance. Busulfan testing was repeated 10 days later. The results were nearly identical so a daily dose of 82 mg was calculated to achieve a goal daily AUC of 4400 μM-min. Because of the very unusual clearance, we repeated PK monitoring with the first 82 mg therapeutic dose. Monitoring demonstrated that busulfan clearance was delayed more than expected (1.44 mL/min/kg) and the actual AUC was much larger than expected (6184 μM-min). In order to compensate for this larger than expected busulfan exposure, the third and fourth doses were decreased to 30 mg. With this change, we reached an acceptable total busulfan exposure of about 18,500 μM-min, as confirmed by PK monitoring. The total busulfan dose to achieve this target was 7.2 mg/kg, less than half the typical dose. The patient successfully engrafted on Day +14 with no evidence of SOS.
Conclusion: One previous report shows a possible association between deferasirox and delayed busulfan clearance. Our report (1) confirms this finding, (2) suggests the possibility that the combination of deferasirox and deferoxamine may further delay and (3) worsens busulfan clearance. Since the value of iron chelation prior to transplant is theoretical, we recommend discontinuing those medications well in advance of busulfan administration to avoid the danger associated with excessive exposure to busulfan.

Poster # 627

ISOLATED TESTICULAR RECURRENCE OF AML IN PATIENTS WITH CHRONIC GVHD MORE THAN ONE YEAR FOLLOWING TRANSPLANT

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Background: Chronic graft-vs-host disease (cGVHD) is associated with reduced incidence of relapse in the myeloid leukemias. Although this may provide protection from systemic relapse, areas with intact blood barriers remain susceptible. We present two pediatric patients with cGVHD and isolated testicular relapse more than a year post-transplant.
Objectives: See Above
Design/Method: Case Series

Results: Two patients with acute myelogenous leukemia (AML) with isolated testicular relapse more than a year after hematopoietc stem cell transplantation (HSCT) despite cGVHD.Case#1Eighteen-year-old with CNS-negative AML diagnosed at 15 years of age. Cytogenetics demonstrated t(8q22;21q22), FISH + for RUNX1T1-RUNX1. He was treated per AAML 0531, and after Induction I his minimal residual disease (MRD) was 3% and FISH 1.6%; after Induction II MRD was not detectable. He received a 10/10 sibling marrow transplant with 1.87x10e8 total nucleated cells (TNC)/kg. Conditioning was AUC-targeted standard-dose myeloablative Busulfan/Cytoxan. Immunosuppression consisted of tacrolimus. He developed acute GVHD(aGVHD) with Stage III gut responsive to steroids. He subsequently developed extensive cGVHD of the GI tract with weight loss responsive to tacrolimus and prednisone, being weaned to budesonide only. RFLP's were all donor since day+100. At 32 months post-transplant he developed right testicular swelling, positive for recurrent AML with same markers as at diagnosis. PET-CT, bone marrow biopsy and CNS studies were all negative for disease.Case#2Seven-year-old with CNS positive AML diagnosed at 5 years of age. Cytogenetics demonstrated t(9;11), FISH + for MLL, negative for FLT3 ITD. He was treated per AAML 0531. He had no sibling donor. At the end of Induction I his MRD was 6.2%, declining to 1.2% after Induction II, 0.5% after Intensification I, and 0.06% after Intensification II, prior to transplant. He received a 5/6 unrelated cord transplant with 9.7x10e7 TNC/kg and 7x10e5 CD34+ cells/kg. Conditioning was AUC-targeted standard-dose myeloablative Busulfan/Cytoxan. Immunosuppression consisted of tacrolimus and prednisone. He developed aGVHD with Stage IV GI with ileus, responding to steroid pulse. He developed extensive cGVHD of the GI tract and was TPN-dependent for several months before tolerating GI feeds, being switched to sirolimus because of tacrolimus-associated seizures, and weaning steroids. RFLP's were all donor since day+100. At 14 months post-transplant he developed right testicular swelling, which was recurrent AML with same markers as at diagnosis. PET-CT, bone marrow biopsy and CNS studies were negative for disease.
Conclusion: Chronic GVHD is associated with reduced systemic relapse rates, but disease surveillance should be maintained for immune privileged sites as well.

Poster # 701

DECREASING THE RATE OF ASPARAGINASE REACTIONS DUE TO HYPERAMMONEMIA

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Background: The overall survival of childhood ALL has improved dramatically from about 30 % in the early 1970s to over 85 % in the year 2010. A crucial factor that has contributed significantly the improvement of outcome over the past five decades is the addition of asparaginase to pediatric treatment protocols. Reported adverse reactions to asparaginase include anaphylaxis and hyperammonemia reactions, which can be difficult to differentiate. Prevention of hyperammonemia related to asparaginase infusions may help minimize the discontinuation of this important drug and improve the overall outcome. Pharmacokinetics data suggests that asparagine and glutamine are removed from the blood 5 and 20 minutes after starting

asparaginase infusion respectively. Each molecule of asparagine or glutamine broken down by asparaginase creates one molecule of ammonia, creating a huge spike in levels within minutes. In a weaned pig model, slowing the initial infusion rate to 0.3ml/min optimizes the clearance of asparagine and glutamine without a large spike in ammonia production which should prevent hyperammonemia related infusion reaction.
Objectives: To determine the rate of infusion reactions to PEG-Asparaginase before and after the implementation of an alternative infusion method.
Design/Method: Retrospective chart review was performed on all patients who received PEG-Asparaginase between January 2014 and June 2016. The alternative infusion method was implemented in October 2016. The alternative method included a test dose of PEG-Asparaginase given initially, followed by a 10 minute observation period. If no reaction was observed the infusion was begun at a slow rate of 19.5ml/hr for 80 minutes. The final 30 minutes of the infusion was increased to 160ml/hr. All PEG-Asparaginase was given within 120 minutes. A second retrospective chart review was conducted in January 2017; 3 months after the alternative infusion method had been implemented.
Results: The initial chart review revealed infusion reactions in 18.75% (9/48) of our patients. This included both allergic and hyperammonemia reactions since attribution is difficult to assign with symptoms such as rash. In the 3 months using the alternative infusion method the reactions occurred in 7.69% (1/13) of our patients. The single observed reaction was anaphylaxis.
Conclusion: Though not yet statistically significant, our study shows that there is a trend toward decreased reactions to PEG-Asparaginase using the alternative infusion method.

Poster # 703

INTRAMUSCULAR ADMINISTRATION OF PEGASPARGASE IS ASSOCIATED WITH A SIGNIFICANTLY LOWER RATE OF ALLERGIC REACTION COMPARED TO INTRAVENOUS ADMINISTRATION. A SINGLE ACADEMIC MEDICAL CENTER EXPERIENCE

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Background: Pegaspargase is a crucial component in the treatment of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and lymphomas. It is FDA approved for intravenous (IV) and intramuscular (IM) administration. Several Children's Oncology Group protocols specifically recommend IV to decrease pain and for convenience. Because pegaspargase is derived from E.coli, it is highly immunogenic. Patients who experience anaphylaxis require treatment with epinephrine and steroids, hospital observation and change to Erwinia-asparaginase. Six doses of Erwinia-asparaginase are required to replace one dose of pegaspargase and dosing is 25,000 IU/m2/dose instead of 2,500 IU/m2/dose for pegaspargase, which is associated with increased cost and inconvenience due to clinic visits. The two modes of delivery have demonstrated comparable efficacy, but there is limited data regarding the incidence and severity of allergic reactions between the two. Smaller cohort studies have demonstrated higher rates of allergic reaction when pegaspargase was given IV compared to IM.
Objectives: The primary objective was to compare the rate of allergic reaction in patients who

received pegaspargase intravenously versus intramuscularly. The secondary objective was to evaluate additional cost associated with Erwinia-asparaginase treatment for patients unable to continue pegaspargase due to allergic reaction.
Design/Method: We conducted a retrospective chart review of all patients treated with pegaspargase at the University of Iowa Stead Family Children's Hospital between May 2009 and December 1, 2016. As of April 2016, IM pegaspargase has become the standard route of administration at our institution. Previously, the route of administration was based on patient and provider preference, with the majority receiving IV.
Results: A total of 106 patients were included. Thirty-five patients received pegaspargase IM and 71 patients received IV. The incidence of allergic reaction was higher in the IV group with 12 patients (16.9%) having signs/ symptoms of anaphylaxis compared to one patient (2.9%) in the IM group. Nine of the 12 patients who had an allergic reaction to IV pegaspargase required subsequent therapy with Erwinia-asparaginase. Based on average wholesale price, the average additional drug cost incurred with administration of Erwinia-asparaginase following an allergic reaction to pegaspargase was $136,758 per patient.
Conclusion: IM pegaspargase is associated with significantly fewer allergic reactions compared to IV and is well tolerated in pediatric patients. Overall cost of therapy was higher for patients who had an allergic reaction to IV pegaspargase and likely could have been mitigated by IM administration. The IM route should be preferred for all pediatric patients who require pegaspargase.

Poster # 705

PREDICTION OF OPIOID REQUIREMENT FOR MUCOSITIS BY GENOTYPE IN CHILDREN UNDERGOING HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Mucositis pain after hematopoietic cell transplantation (HCT) is a major burden on quality of life for pediatric patients. Adequate pain management is often delayed by trial and error of various agents and doses.
Objectives: To evaluate which host genetic polymorphisms predict pain perception, opioid efficacy, and opioid-induced adverse effects in HCT patients.
Design/Method: We genotyped 100 consecutive HCT patients (5/2013 – 10/2014) using pre-HCT samples and a panel of 46 single nucleotide polymorphisms (SNPs) in a set of candidate genes known to influence opioid effects. We collected demographics, HCT data, and detailed pain medication use from patient records.
Results: Our cohort included 65% male and 87% Caucasian patients; median age was 9.9 years (range 0.5-32.8). Seventy-six patients experienced mucositis a median of 3 days (range –2 to +17) post-HCT; 58 (76%) required PCA, and an additional 5 (7%) used scheduled IV opioids. We defined optimal pain control as time after which no further opioid increases were required. Our patients reached optimal pain control a median of 7 days (range 0-22) after opioid initiation. At optimal control, peak morphine-equivalent dose was 1.5 mg/kg (range 0.2-15.7). Patients

were on PCA for a median of 16 days (range 1-32). Eighteen patients (29%) on IV opioids required ≥1 medication change due to lack of efficacy. Thirty-two patients on IV opioids (51%) experienced ≥1 side effect (pruritus, over-sedation, excessive nausea/emesis). Twenty patients (32%) required opioid change due to toxicity. We found a strong correlation between common uridine diphosphate glucuronosyl transferase (UGT) 2B polymorphisms and race. The SNPs rs7668258 and rs7439366 demonstrated perfect linkage, and variants of UGT2B were present in 75% of Caucasians, but only 31% of non-Caucasians (p=0.0011). Patients with wild-type UGT2B alleles spent more total days on IV opioids compared with those with variant alleles (p=0.0299). This finding supports our observation that non-Caucasians had a higher incidence of mucositis than Caucasians (100% vs. 74%; p=0.0343). Non-Caucasians had more mucositis pain, as 92% required scheduled IV opioids, compared to 60% of Caucasians (p=0.028). We also found that those with rs4633 variants in catechol-O-methyltransferase (COMT) required more days to optimal pain control compared to wild type (p=0.0287), confirming increased pain sensitivity associated with this genotype, irrespective of race. We did not find any association between SNPs and opioid toxicity, as has been reported in different clinical contexts.
Conclusion: Our data suggest that prospective genotyping will improve achievement of optimal pain control in all pediatric patients undergoing HCT.

Poster # 707

FEASIBILITY OF AN AMBULATORY CENTRAL LINE CARE COACHING PROGRAM FOR PEDIATRIC ONCOLOGY AND STEM CELL TRANSPLANT FAMILIES

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Background: Background: Pediatric oncology (PO) and stem cell transplant (SCT) patients with central lines (CL) are at high risk for preventable central line associated bloodstream infections (CLABSI), increasing morbidity, mortality, and costs. A large portion of ambulatory external CL care is provided by families and caregivers in the home with limited opportunities to develop the needed skills and adhere to best practice line care.
Objectives: Objective/SMART Aim: To develop a coaching program by 12 months where >90% of families participate and achieve skill independence.
Design/Method: Methods: A quality initiative began June 2015 for families to demonstrate (teach-back) external line care with a nurse coach using a simulation model or patient during routine clinic visits. Tests of change using plan-do-study-act cycles were implemented to achieve performance and documentation in the medical record of participation and proficiency level. Run charts were used to track participation rates. Initial efforts consisted of assessing family interest in teach-backs and unstructured incorporation into routine care. Starting April 2016, targeted interventions included new dedicated personnel for scheduling, tracking, and coaching teach-backs; standardization of teaching content and approach; regular documentation of line care proficiency; development of a learning curriculum beginning > 48 hours prior to discharge and continuing in the ambulatory clinic until reaching independent proficiency; culture change

including an expectation of participation by all families, nursing incentives, and development of a job aid for coaches and to promote standardization; and wide dissemination of the program.
Results: Results: From June 2015-March 2016, monthly ambulatory participation did not reach >25%, with only 13% (23/176) of total eligible families participating. This was due to a combination of: family refusal; lack of nursing availability, space, or time; inability to approach prior to line removal. Fifty three percent (33/62) of eligible families in April 2016 had participated, reaching 93% (53/57) by June 2016 and sustaining monthly participation at >93% through September 2016. The total number of eligible families participating from April-September 2016 rose to 82% (90/110). During this time period, 96% (95/99) of families with documented proficiency during an ambulatory teach-back had achieved independence in at least the most commonly performed task, flushing the central line.
Conclusion: Conclusions: A CL teach-back program in a busy ambulatory PO clinic is feasible, but requires dedicated resources and culture change. Ongoing improvements are in place to ensure sustainability of the program and measure the impact of the program on family perception toward line care related-distress and ambulatory CLABSI rates.

Poster # 709

CHARACTERIZING POST-PROCEDURAL PAIN AND QUALITY OF LIFE IN PEDIATRIC ONCOLOGY PATIENTS UNDERGOING BONE MARROW PROCEDURES

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Background: Pediatric oncology patients undergo repeated bone marrow aspirations and biopsies (BMA/Bs) during treatment and off-treatment surveillance. BMA/Bs have been described in the literature as painful procedures for pediatric oncology patients. Exposure to repeated painful procedures can exacerbate anxiety and distress in children. There are no standardized clinical guidelines for management of pain associated with bone marrow procedures and practice varies among pediatric oncology centers. At Memorial Sloan Kettering Cancer Center (MSKCC) Department of Pediatrics, institutional practice has been to use the injectable anesthetic, propofol, which has amnestic but no analgesic properties, to provide anesthesia for our pediatric patients.
Objectives: The aim of this study was to observe and document the current process by which pediatric oncology patients undergo bone marrow procedures in order to collect baseline data, identify key drivers, and prioritize possible interventions.
Design/Method: A telephone survey was offered to all pediatric oncology patients undergoing BMA/B at MSKCC over a four week window. Survey questions assessed pain, medication usage, and activity level at 6 and 24 hours following BMA/B. All bone marrow procedures were performed with the current institutional practice of peri-procedural propofol.
Results: Twenty-six patients (ages 3 – 19 years) who underwent a BMA/B completed the survey. 18/26 (69%) patients had pain in the 24 hours following BMA/B. 8/26 (30.7%) patients required opioid analgesia within 24 hours of the procedure. 7 required post-procedural opioid and 1 received systemic opioid pre-procedurally. 15/26 (57.7%) patients had a reduced activity

level within 24 hours of the procedure. Parents used various terms to describe their children after the procedure such as “limping”, “sore”, “difficulty with diaper change”, "less playful", and “stayed in bed all day”.
Conclusion: Based on these data, we prioritized the addition of a local anesthetic with analgesic properties to our current practice. In order to ensure validity and sustainability, we designed and executed a prospective randomized clinical trial that is actively recruiting patients (ClinicalTrials.gov Identifier: NCT02924324). The SMART aim of this PDSA cycle is to determine whether local infiltration of the local anesthetic medication, ropivacaine, will reduce the percentage of pediatric neuroblastoma patients who require post-procedural opioid analgesia by 20% and improve quality of life as measured by an adapted PROMIS® (Patient-Reported Outcomes Measurement Information System) Parent Proxy Pain Interference questionnaire. The global aim of this project is to determine whether MSKCC should modify current institutional practice for pediatric patients undergoing bone marrow procedures.

Poster # 711

COMPLEMENTARY AND ALTERNATIVE MEDICINE: A SURVEY OF ITS USE BY PEDIATRIC ONCOLOGY PATIENTS INPATIENT VERSUS OUTPATIENT WITH COMPARISON OF PHYSICIAN DISCLOSURE RATE AND TYPE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE USE VARIATION IN BOTH SETTINGS

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Background: The percentage of Complementary and Alternative Medicine (CAM) users in pediatric oncology is as high as 87%. Patients use CAM because it is more in line with their own personal beliefs, values, and philosophies 1. Patients want physicians to incorporate CAM use. Cancer survivors would address the lack of attention paid to CAM therapies by their physicians 2. Despite the desire to include CAM only 20% - 65% of parents report discussing CAM use with their physician. This is a safety issue, particularly if CAM interacts with chemotherapy. In order to address CAM use physicians must understand CAM use. The incidence of CAM use inpatient when a patient is getting chemotherapy or acutely ill is not known.
Objectives: This study is designed to test the hypothesis that pediatric oncology patients are using CAM therapies, particularly ingested CAM, both inpatient and at home without disclosure to physicians.
Design/Method: Patients from Arkansas Children's Hospital were identified by chart review to confirm eligibility. Eligibility requirements included a diagnosis of cancer, hospital admission after January 1, 2013, and age less than 18 years of age. Type of cancer and physician/APRN documentation of CAM use were also noted. After eligibility conformation verbal consent was obtained at their oncology clinic visit and an anonymous survey was administered.
Results: 143 patients were surveyed out of 152 eligible patients. 68.5 % used CAM at home and 53.1% in the hospital. When any CAM therapy (from prayer to cannabinoid) was used at home, physicians were made aware 32.7% of the time and in the hospital 44.7% of the time. However, physicians/APRNs documented CAM use 10% of the time. The percentage of patients using ingestible CAM therapies was 41.3% at home and 19.6% inpatient. When CAM was ingested at

home, physicians were made aware 35.6% of the time and in the hospital 53.6% of the time. Physicians/APRNs documented ingested CAM use with 88.1% of home users and 14.3% with hospital users. Commonly ingested CAM included vitamins, supplements, guanabana peppermint, melatonin, specialized diets, and cannabis.
Conclusion: Pediatric Oncology patients use CAM therapies both at home and in the hospital without the documented knowledge of their physicians. This data demonstrates patients are also ingesting CAM products that may interfere with chemotherapy/medications or may cause side effects without physician knowledge while in the hospital.

1. Kemper, KJ, et al, Pediatrics, 2008.2. Zebrack, B, et al, J of Psych Oncology, 2014.

Poster # 713

IMPLEMENTING A TRANSITION TO ADULT CARE MODEL IN A MILITARY PEDIATRIC ONCOLOGY CLINIC

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Background: Long-term survivorship in pediatric oncology after the completion of treatment focuses on medical surveillance for late effects from the disease or treatment, recurrence or secondary cancers, and transition of care to primary care providers. Barriers to effective care for the late effects of childhood cancer therapy include survivor issues (lack of knowledge/understanding of treatment history, etc.) and care-giver issues (lack of knowledge about the late effects of cancer therapy, etc.). In addition our patients transition to the civilian medical system after losing military healthcare benefits, requiring additional considerations for the civilian health care marketplace.
Objectives: To incorporate a transition model into the survivorship process aimed at establishing a systematic approach to educate pediatric patients and their caregivers of the needs and skills required to transfer childhood cancer survivors to the adult care model in both military and civilian health care systems.
Design/Method: A transition process was developed based on nationally available tools modified for institutional use. Survivors between 12 and 18 years old were recruited to enroll in a transition process customized for each patient. The Plan-Do-Study-Act model of process improvement was applied to quickly modify any identified deficiencies. A key feature in this process was the use of COG long-term follow-up (LTFU) guidelines in the Passport for Care© (PfC©) tool, including the “Survivor portal”. Patients were monitored longitudinally for successful transition to adult care.
Results: Approximately 65 existing long term follow-up patients are now being managed through the modified survivorship program process. Risk-based survivorship care plans, entry of patient medical summaries into LTFU guidelines tool, and personalized educational plans based on the guidelines are implemented. Our experience indicates that the parent is the focus of the transition topics until teens reach the age of 16 or 17.
Conclusion: The PfC© Survivor portal provides less information in the treatment summary than will be needed for patient management by primary care providers. We recommend that PfC© consider revisions that would provide a detailed treatment summary accessible on the Survivor

portal to enhance this feature. In addition, to meet user concern over cybersecurity, communicating robust safeguards in place to protect the health care information of patients is necessary. The use of PfC© has resulted in reduced time required to develop transfer of care packets. The current use of this system are essential to patient buy-in. Establishing the transition program coupled with PfC© has resulted in a more effective survivorship program for our pediatric cancer survivors.

Poster # 715

CHILDHOOD CANCER IN WEST AFRICA

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Background: In rich countries, childhood cancer represents 1% of all cancers and is the second leading cause of childhood mortality. In Africa, infectious diseases like malaria, diarrhea, malnutrition, low acute respiratory infections, HIV etc. are the most prominent causes of childhood death. Still, cancer is now rapidly emerging as a significant cause of death in children. Unfortunately, at this stage there is no cancer registry in most sub-Saharan countries. As a result, the only epidemiological data available are those of national care centers. Unfortunately, these centers do not have the adequate medical expertise or equipment.
Objectives: We have made an inquiry in sub-Saharan Africa countries with pediatric cancer treatment center in order to make an inventory.
Design/Method: We sent a short questionnaire by email to the different centers. We completed our data with those available on the WHO website
Results: West Africa consists of 16 countries is an area of 6,138,000 km2, 332 million inhabitants, 44% under 15 years. The mortality rate is estimated at 82% with a life expectancy of 55 years. Only six countries (Benin, Burkina, RCI, Mali, Senegal, Togo, Ghana and Mauritania) have a national cancer plan. And among these 6 countries, only 3 have included childhood cancer in their national plan: Burkina Faso, Ghana and Mauritania. GFAOP has 6 pilot units in West Africa: Burkina Faso, Ivory Coast, Mali, Mauritania, Senegal and Togo. These countries together represent 50% of the total area of West Africa, and 23% of its population. There are 120 new cases on average per year.Tumor pathology in West Africa is dominated by lymphomas, retinoblastomas and Wilms tumors. The majority of cases are diagnosed at a late stage (75%). About the treatment, chemotherapy is available but access is expensive for parents (1000$).Surgery can be performed in most cases. However, treatment such as radiotherapy is only available in Mauritania for all the pathologies mentioned above, and now in Mali, though for retinoblastoma only. In the NHL, published studies have noted an overall survival rate of 61% for all stages and 75% in stage I and II with a decline of 3 years.In kidney tumors, overall survival is 75% and 55% without event.
Conclusion: Diagnosing childhood cancer in West Africa remains problematic. One of the main reasons for this is the fact that most of these countries are still struggling to cope with infectious diseases which are the most prevalent in terms of epidemiology.

Poster # 717

SUCCESSFUL IMPLEMENTATION OF A COMPUTERIZED PHYSICIAN ORDER ENTRY SYSTEM FOR PEDIATRIC CHEMOTHERAPY TREATMENT PROTOCOLS

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Background: Adoption of electronic health records (EHR) and computerized physician order entry (CPOE) systems in hospitals within the United States are rapidly expanding. Numerous studies demonstrate improvement in patient safety measures with implementation of CPOE, primarily by reducing medication errors and incorporating clinical decision support (CDS) tools within the platform. Complicated pediatric oncology protocols have the most to benefit from CPOE implementation; however, they are the most challenging to convert to CPOE. Even more so than adult protocols, pediatric chemotherapy protocols frequently use varying multiday, multidrug chemotherapy regimens that require complex dose calculations and include numerous supportive care medications. Guidelines and published experience regarding pediatric chemotherapy CPOE conversion and implementation are lacking.
Objectives: We describe our experience with pediatric oncology-specific CPOE implementation using Epic's Beacon platform at our institution. We highlight the unique needs of pediatric protocols as well as barriers to implementation of the system. In describing our experience, we propose a structure and timeline for pediatric chemotherapy CPOE implementation using the Beacon platform.
Design/Method: RI Hospital/Hasbro Children's Hospital is an NCI-designated Comprehensive Cancer Center that cares for 60-70 new pediatric oncology diagnoses per year. Pediatric chemotherapy CPOE using Epic's Beacon system was built over a 3 year intensive process.
Results: The 3 year build process proceeded through a series of phases: planning, build and validation, training, and Beacon activation. Approximately 400 pediatric-specific treatment protocols were built by a multidisciplinary team of clinicians, nurses, pharmacists, and information technology specialists. These chemotherapy treatment plans were produced through a standardized process using coordinated steps: protocol identification, initial protocol build, provider validation, protocol editing, team validation, and pharmacy testing. Following Beacon activation, improvements to the CPOE were made through a systematic approach and a framework was created for continued protocol review and future protocol builds.
Conclusion: Our 3 year experience implementing a pediatric oncology-specific CPOE using Epic's Beacon platform provides a guideline for other pediatric cancer centers which can be individually adapted to each institution. Commitment and coordination between a multidisciplinary team that bridges clinical expertise with health information technology expertise is essential. Involvement of personnel with experience in previous pediatric chemotherapy CPOE implementations is decidedly beneficial. Potential barriers include discordance with adult oncology CPOE build, improper CDS tools, and lack of a standardized build process. Pediatric chemotherapy CPOE systems offer the potential to minimize medication error and improve work flow in a highly complex and high risk clinical environment.

Poster # 719

MULTIDISCIPLINARY APPROACH TOWARDS IMPROVING NUTRITIONAL STATUS IN NEWLY DIAGNOSED PEDIATRIC ONCOLOGY PATIENTS: AIM FOR "OSCAR"

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Background: Children undergoing chemotherapy are at high risk for weight loss. Poor nutritional status impacts the course of disease and treatment-related morbidities. A baseline assessment of nutritional status in children who underwent chemotherapy at our institution between 2011-2012 showed that 69% of patients had >5% weight loss from baseline; 29% had 5-10%, 29% had 10-20%, and 11% had >20% weight loss. Most weight loss was noted at about 8 weeks from therapy initiation suggesting the need for early nutritional interventions.
Objectives: Our aims were to: 1. reduce the percentage of patients developing >5% weight loss during chemotherapy, 2. prevent >20% weight loss, and 3. identify and improve nutritional status of patients with weight loss over the study period of 1 year.
Design/Method: The DMAIC (Define-Measure-Analyze-Improve-Control) model was utilized for our quality improvement (QI) initiative with multiple PDSA (Plan-Do-Study-Act) ramps implemented in parallel. Baseline and periodic measurements, identification and analyses of factors contributing to gaps, and implementation of interventions were performed by a multidisciplinary team (physicians, nutritionists, nurses, and operations managers).
Results: Patient-related interventions included early introduction of baseline and periodic nutrition consults, improved patient education, regular assessment of nutritional status, early initiation of oral nutrition supplements, appetite stimulants, and nasogastric (NG)/gastrostomy-tube placements. Provider-related interventions included provider education and an action plan "OSCAR" (Order labs/nutrition consult, Schedule appointments within a week, Communicate: documentation, provider-nutritionist, and nutritionist-nutritionist, timely Action based on degree of weight loss, and Re-assess/Re-inforce). Charts of newly diagnosed patients between January-September 2016 (n=25; 18 male, 7 female) undergoing chemotherapy were reviewed. Median age was 8.4 years (range; 0.05-19.3 years). Diagnoses included brain tumors (n=7), leukemias (n=6), lymphomas (n=4), sarcomas (n=5), and other solid tumors (n=3). The majority (68%; n=17) had <5% weight loss of which 3 patients nearing 5% weight loss had NG-tube placed pre-emptively. No patient had ≥15% weight loss, while 24% (n=6) and 8% (n=2) had a 5-10% and 10-15% weight loss, respectively, with a maximum weight loss of 14%. Median time to nadir weight was 58.5 days (range; 6-70 days). Aggressive nutritional interventions were implemented including appetite stimulants (n=2), and NG-tube (n=5) within 1-7 days of the nadir weight. All 8 patients showed an improvement with post-intervention weights between 5% below- to 34.8% above baseline (median: 1.16 % above baseline).
Conclusion: Although the sample size is small, our QI efforts demonstrate a significant improvement in the nutritional status of pediatric oncology patients through early nutritional interventions and a team approach.

Poster # 721

IMPROVING ACCRUAL OF ADOLESCENTS AND YOUNG ADULTS AND

UNDERREPRESENTED MINORITIES WITH LEUKEMIA TO CHILDREN'S ONCOLOGY GROUP CLINICAL TRIALS: A NOVEL COLLABORATIVE APPROACH TO ADDRESS DISPARITIES IN LEUKEMIA

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Background: The dramatic decrease in mortality from ALL and AML in children is related to improved participation in NCI sponsored COG clinical trials. African-American (AA) and Hispanic children and particularly AYAs 15-39 years are under-represented in COG clinical trials. AA and Hispanic children with ALL and AML have worse survival than white children even with modern therapy (Bhatia PBC). Access to standard chemotherapy, socio–economic and insurance status, disease biology and pharmacogenetic variations play a role in these racial and AYA disparities. Insufficient cancer clinical trial enrollment treatment by non-pediatric oncologists is associated with inferior survival in AYAs. AYAs treated with pediatric “inspired” protocols have better outcomes than AYAs treated with protocols for adults (Stock JCO). In 2008,to improve access to a largely underserved population, two COG institutions (University of Illinois at Chicago (UIC) and Rush University) and a non-member hospital (Stroger Hospital of Cook County) created a unified COG program utilizing one IRB and research team.
Objectives: To assess the impact that the collaborative UIC/Rush/Stroger COG program had on clinical trial enrollment for minority underserved and AYA patients with leukemia.
Design/Method: A retrospective comparative analyses of COG enrollment data from 2002-2008 and 2008-2014 (pre vs. post-merger) for all patients with ALL and AML by race/ethnicity, age, insurance status, clinical trial type was completed. Information regarding primary oncologists of enrollees’ was collected.
Results: There was a three-fold increase in therapeutic leukemia (ALL and AML) trials open to enrollment and a 108% increase in total(all types)and 121% increase in therapeutic leukemia trial enrollments as a result of the merger. There was a 370% in Hispanic and 220% increase in AA patients enrolled. There was a 610% increase in AYAs (400% for ALL) enrolled post-merger. A total of 40 enrolments occurred at Stroger Hospital,a site with no access to COG trials prior to the merger. 39% of patients enrolled at Stroger were uninsured, 75% were AYA. Nine Pediatric and six Medical Oncologists and 3 Pediatric nurse practitioners were engaged in post-merger COG enrollments compared to 6 Pediatric and only 1 Medical Oncologist engaged pre-merger across the three institutions.
Conclusion: Significant increase in COG leukemia trial enrollment especially for under-represented (non-white, underinsured) minorities and AYAs was a result of the creation of the novel UIC/Rush/Stroger COG program. This Program serves as a model for improved collaboration between institutions and medical and pediatric oncologists to increase access to clinical trials for minority and AYA patients with leukemia.

Poster # 723

FACTORS AFFECTING FDG UPTAKE IN BROWN ADIPOSE TISSUE ON PET SCANS OF PEDIATRIC ONCOLOGY PATIENTS

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Background: Physiologic uptake of 18F-fluorodeoxyglucose (FDG) in brown adipose tissue (BAT) occurs in half of pediatric oncology patients undergoing positron emission tomography (PET) scans, and may confound interpretation by either mimicking or masking uptake in metastatic tumor. Strategies to reduce BAT uptake include fentanyl or propranolol premedication. While either intervention is relatively safe, understanding which patients are more likely to have uptake would allow more appropriate targeting of interventions and improve patient convenience and safety.
Objectives: We retrospectively reviewed PET scan results from pediatric oncology patients to identify factors most closely associated with BAT uptake.
Design/Method: We reviewed records from all pediatric oncology patients undergoing PET imaging from 2009-2016. Risk factors for BAT uptake that were investigated included age, gender, body mass index (BMI), disease type, and mean outside temperature on the scanning day. Generalized estimating equations (GEE) were used to model the odds of a scan having BAT uptake while adjusting for multiple scans for a particular individual and the best model was identified by forward selection and lowest QIC criteria.
Results: We reviewed 389 scans from 102 consecutively treated patients. Median age at first scan was 15 years (range 4 -32), and 65% were male. Diagnoses included sarcoma (52%), lymphoma (41%), and other (7%). BAT was identified in 51% of patients and on 26% of all scans. Eighty-two patients had multiple scans, and BAT findings were consistent throughout an individual patient's scans in only 44% of patients. On multivariable GEE analysis, neither gender nor diagnosis were associated with BAT uptake. However, age < 16 years (OR = 1.81, p=0.0240) and an outside mean temperature < 62 degrees (OR=1.71, p-value=0.0156) were independently associated with a higher risk of BAT uptake. Patients meeting NIH definitions of obesity also were more likely to have BAT uptake (OR = 1.79, p=0.08). In contrast to previous reports, patients < 10 years had a similar frequency of BAT uptake to that seen in older pediatric patients.
Conclusion: While there was considerable intrapatient variability, this larger data set confirms the importance of age, body size, and outside temperature in predicting which patients will have BAT identified on PET scans. The lowest risk for BAT uptake was seen in obese patients > 16 years old who were scanned on warmer days. We are now incorporating this data to make decisions on who should receive propranolol premedication prior to PET scan.

Poster # 725

SEASONALITY IN INCIDENCE AND TRENDS OF PEDIATRIC CANCER DIAGNOSES: A POPULATION BASED STUDY FROM MARITIMES, CANADA

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Background: Although seasonal trends in incidence and diagnosis of pediatric cancers have been widely investigated, the results have been inconclusive. There is modest support for a seasonal peak in the diagnosis of acute lymphoblastic leukemia and cutaneous melanoma, and in the birth of children with brain tumors. High incidence of cancer diagnosis in a particular season could overwhelm the capacity of health care teams, especially in smaller hospitals with limited resources. Any consistently observed trends would assist in plausible changes in health policy for managing staffing and resource allocation to adequately support the fluctuating patient volume and possibly provide etiological insights into pediatric cancers.
Objectives: This study aims to determine if there is a seasonal variation in cancer diagnoses in the pediatric population at the IWK Health Centre, a tertiary care center serving three Canadian provinces: Nova Scotia, New Brunswick, and Prince Edward Island.
Design/Method: All pediatric cancer patients aged 0-20 years diagnosed from 1995 to 2015 at our center were included in this study. The annual data was divided into four seasonal periods (December to February, March to May, June to August, and September to November). The cancer diagnoses were categorized as Leukemia, Lymphoma, Sarcoma, Brain Tumors, and Miscellaneous. Seasonal variation was assessed by a harmonic function in a Poisson regression model. The amplitude of multiplicative change in the incidence rate caused by the seasonal variation is expressed as the incidence rate ratio (IRR).
Results: For all cancer diagnoses for the entire cohort of 1200 patients the IRR was 1.03 (95% confidence interval (CI) 0.96-1.13). None of the IRRs for the cancer groups indicated a statistically significant seasonality of cancer diagnosis: Leukemia 1.11 (95% CI 0.96-1.28); Lymphoma 1.17 (95% CI 0.93-1.47); Sarcoma 1.29 (95% CI 0.99-1.69); Brain Tumors 1.16 (95% CI 0.97-1.38); Miscellaneous 1.09 (95% CI 0.93-1.27).
Conclusion: The present study did not show a seasonal variation in the various cancer types in the pediatric population at the IWK, possibly due to the relatively small sample size. Further studies using national level data are needed.

Poster # 727

QUALITY OF LIFE AMONG CANCER DISEASED CHILDREN SURVIVORS IN A DEVELOPING COUNTRY: A SINGLE CENTER STUDY IN SOUTH EGYPT

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Background: Successful treatment of cancer has resulted in increased demands on survivors and had diverse effects on the Quality of life (QOL) of diseased children and their families.
Objectives: In this study we aimed to detect the QOL in survivors of childhood cancer in a cancer treatment center in south Egypt.
Design/Method: A model of quality of life questionnaire containing aspects of physical, psychological, social, and spiritual well-being has been applied to illustrate the multidimensional needs of cancer survivors and the necessity of comprehensive care extending over the long term.
Results: A clear defective psychological and social support to the cancer survivor's children and

their families were detected.
Conclusion: Our data demonstrate the multidimensional needs of cancer survivors and the importance of comprehensive, multidisciplinary care. This may better be achieved by the cooperation between researchers, clinicians, and the true experts in that field.

Poster # 729

EVALUATION AND ENHANCEMENT OF THE INFORMED CONSENT PROCESS IN PHASE III PEDIATRIC ONCOLOGY CLINICAL TRIALS

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Background: Outcomes for many pediatric malignancies have improved substantially. This is largely due to coordinated research efforts of consortia, such as the Children's Oncology Group. A continuing commitment to research is imperative to further improve treatment, and many patients are offered phase III clinical trials at diagnosis. Research participants should understand the nature of the research they have been offered when they decide about participation. However, prior studies demonstrate that parents deciding about participation do not always understand key concepts of phase III clinical trials.
Objectives: Our objective is to understand the difficulties parents face with key concepts of phase III clinical trials, including randomization, clinical equipoise and voluntariness, and to create an intervention to improve understanding.
Design/Method: We developed a survey tool that uses primarily open-ended questions to assess parental understanding. The survey was administered in person in the days following the informed consent conversation. All participants were parents of a child who was newly diagnosed with a malignancy and eligible for a phase III clinical trial. After the first four participants, we refined the survey for clarity. Using the information from the survey, interviews with physicians who obtain consent, and a review of the literature, we are now working with Michigan Multimedia to develop a Google Slides-based intervention aimed at improving understanding.
Results: To date, we have administered the final version of the survey to five participants. As anticipated, participants understood some concepts of phase III clinical trials better than others. All participants understood that participation in the trial was voluntary. Most reported that they do not think that researchers a priori know which arm will have better outcomes and/or fewer side effects. Three participants understood the rationale underlying the use of the standard arm, but only one understood the rationale underlying the experimental arm. Only two understood how randomization occurs. We are now developing a Google Slides-based intervention explaining phase III clinical trials and what to expect during the informed consent conversation.
Conclusion: Parents in our limited sample understood that participation in a phase III clinical trial is voluntary, and about half of the participants at least partially understood clinical equipoise. Randomization proved more difficult to understand. These findings reinforce previous research conclusions that there is a need for improvement of parental understanding. Our proposed intervention to explain key concepts of phase III clinical trials will be tested as a tool to increase parental understanding prior to deciding about research participation.

Poster # 731

IMPLEMENTATION OF A SAFETY BUNDLE TO PREVENT VENOUS THROMBOEMBOLISM AS A HOSPITAL ACQUIRED CONDITION

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Background: The Children's Hospitals Solutions for Patient Safety Network (SPS) is a network of hospitals working together to eliminate harm to children caused by healthcare. Venous thromboembolism (VTE) is the second largest contributor to harm across this network. In 2013, among other Hospital Acquired Condition groups, we launched a VTE Prevention Committee as part of the SPS network.
Objectives: The global aim for this initiative was to eliminate all VTE safety events on the general pediatric floor and pediatric intensive care unit. Smart aims by October 2016 included 1) Reduce the number of VTE events by 40% from a baseline rate of 0.23 events/1000 patient days, and 2) Achieve sustained safety bundle reliability of >90%.
Design/Method: The VTE event rate was defined per the SPS network operational definition. Key drivers for the above smart aims were 1) Increasing staff knowledge of VTE risk factors, 2) Establishing a reliable process to screen for high risk patients, and 3) Reliable use of VTE prevention and treatment guidelines. We took advantage of noncompetitive sharing of outcomes and best practices within the SPS network, and created an evidence-based VTE screening bundle to be applied for patients >12y at admission. The bundle included an automatically populating smart phrase in the electronic medical record which outlines a risk scoring system and paired recommended interventions. A VTE lecture was integrated into the housestaff education series, then repeated every six months with anonymous surveys for feedback. VTE presentations were also held for nursing staff and the hematology & oncology department. Multiple Plan-Study-Do-Act (PDSA) cycles took place based on audit data and housestaff feedback.
Results: All VTE events during our reporting period of October 2015 to October 2016 were central catheter associated. The VTE event rate increased to 0.73 events/1000 patient days. Sustained bundle reliability of >90% over >6 months was achieved.
Conclusion: Our institution's experience mirrors that of other children's hospitals within the SPS network. VTE incidence increased over the monitoring period, presumably due to increased screening, which was a key driver for our initiative. Reliable implementation of the VTE bundle was challenging and required multiple PDSA cycles. Staff feedback suggests this was likely due to a lack of awareness of VTE as a top contributor of harm in pediatrics and provider hesitancy with pharmacologic intervention for high risk patients. Staff education and active feedback were the most important interventions employed to achieve sustained reliability of the VTE bundle at our institution.

Poster # 733

PROJECT STOP-BLEED: SLASHING TIME OF FACTOR PRODUCT REPLACEMENT IN SEVERE BLEEDING DISORDERS IN THE EMERGENCY DEPARTMENT

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Background: For children with severe bleeding disorders, the emergency department (ED) represents an integral and indispensable part of the medical home for emergent and after-hours care. Unfortunately, delays in factor administration are common and may lead to poor outcomes. Prompt factor administration results in rapid cessation of bleeding, faster time to disposition and improved patient satisfaction. Numerous algorithms have been developed to reduce time for medication administration in the ED, including antibiotics for febrile neutropenia, and these algorithms may be suitably adapted to improve timeliness to factor administration.
Objectives: Our SMART-Aim was to reduce time of factor administration in the ED from 123 minutes pre-intervention to less than 60 minutes post-intervention, as well as to increase the proportion of children receiving factor in under 60 minutes from less than 15% to greater than 90%.
Design/Method: This physician-led quality improvement initiative began November 2015 at Cincinnati Children's Hospital Medical Center with the creation of a task force made of Pediatric Hematologists, ED physicians, pharmacists, Hemophilia nurses and ED nurses. An in-depth investigation into existing health care delivery processes (i.e. febrile neutropenia pathway, on-call processes, etc.) was conducted and modified for this specific population, with the most significant key driver being standardization of pre-arrival processes to ensure factor orders placed and filled by pharmacy prior to patient arrival. Additional key drivers included utilization of vascular access nurses for children with mediports or known difficult venous access, creation of ED-specific electronic medical record templates, streamlining of pharmacy processes, and education of ED nursing staff via implementation of mandatory nursing modules. The process was launched June 2016, and children with severe bleeding disorders including Hemophilia A or B of any severity, Type 3 Von Willebrand disease and Glanzmann Thrombasthenia were eligible. Data was obtained from computer-generated reports and medical chart review.
Results: 130 patient encounters were available for analysis, 80 prior to intervention and 50 following the intervention. During the first six months of the study, time to factor administration was reduced from 123 minutes to 78 minutes, and the percentage of children receiving factor in less than 60 minutes increased from 15% to 45%. When home factor was used, average time to administration of factor was 52 minutes.
Conclusion: Modifying pre-existing algorithms and utilizing ED infrastructure are feasible and effective strategies to reduce time to factor administration in individuals with severe bleeding disorders. Multi-disciplinary engagement and PDSA cycles are ongoing to improve processes.

Poster # 735

QUALITY IMPROVEMENT IN THE CARE OF PATIENTS WITH ASPLENIA: FOCUS ON DIMINISHING RISK OF INFECTION

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Background: Patients with asplenia (PWA) are at risk of life threatening bacterial infections (1). Overwhelming post-splenectomy infection (OPSI) has a mortality rate of 50% (2). A series published in 2001 reported on 72 cases in 4 years of potentially preventable OPSI in patients aged 3 months to 87 years (3). Seventy-four percent of patients were not prescribed antibiotics (neither prophylactic nor for treatment use) (3). Only 1/72 individuals was issued an alert card for asplenia (3). We presume the disregard for appropriate management of PWA was due to the unrecognized importance of the condition.
Objectives: The objective of this study was to enhance recognition and understanding of asplenia and to promote preventative measures for infection for PWA.
Design/Method: A quality improvement initiative was conducted in the hematology clinics at St. Michael's Hospital. An interdisciplinary team of stakeholders facilitated the development of a medical alert card and educational booklet for PWA. These resources were used to record vaccination status and schedules, and provide instructions for fever onset. We administered a baseline questionnaire and distributed our materials to PWA. A follow-up questionnaire was completed by the patient at their next presentation. Primary outcomes included change in number of PWA aware of their: condition, vaccination status, need to present for medical attention at the onset of fever and type of prescribed antibiotic. Secondary outcomes included: change in number of patients appropriately vaccinated and patient satisfaction. This initiative was formally reviewed by institutional quality improvement authorities and deemed to not require Research Ethics Board approval.
Results: The baseline questionnaire was completed by 17 PWA. Thirteen out of 17 (76%) of patients had an unknown vaccination status, 14/17 (82%) patients were unaware of the need to present for medical attention during febrile episodes and 17/17 patients were unaware of a prescribed antibiotic. Preliminary analyses suggest improved awareness of vaccination status and appropriate management of fever.
Conclusion: Our intervention was associated with improved awareness and understanding of asplenia. We anticipate these preventative measures will arm patients with the knowledge to facilitate their safe medical management. Given the successful outcomes and apparent need, we are extending this intervention to pediatric PWA and their caregivers. We are collaborating with specialists in infectious diseases, hematology and surgery at The Hospital for Sick Children to adapt our tools for the care of pediatric patients with asplenia.1. Winkelstein, Arch Intern Med, 19772. Bisharat, et al., J Infect, 20013. Waghorn, J Clin Pathol, 2001

Poster # 737

AN UPDATE ON THE FEVER AND NEUTROPENIA CLINICAL PATHWAY: FOCUSING ON THE INDIVIDUAL

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Background: Fever with neutropenia (F&N) is a common cause of morbidity and mortality in pediatric oncology patients. Time to antibiotic administration (TTA) is a quality-of-care (QOC) measure used to evaluate interventions aimed at improving clinical outcomes in this patient population. A retrospective review previously reported by our institution showed a significant improvement in median TTA (141 minutes vs 103 minutes) after implementation of an

emergency department (ED) fever and neutropenia clinical pathway (CP), which provided notification to the appropriate staff and automatically triggered labs and antibiotics to order. Several studies have shown improvements in TTA, but few achieved a TTA < 60 minutes in greater than 50% of patients.
Objectives: The global aim of this study is to show a continued improvement in TTA after implementation of the CP and to increase the percentage of patients who receive antibiotics within 60 minutes of ED arrival. The SMART aim is to provide education to staff physicians in order to decrease TTA to < 60 minutes in 75% of pediatric oncology patients who present to the ED for fever and neutropenia after 4 months of intervention. Key drivers include prompt physician feedback and corrective education when goals are not met.
Design/Method: A retrospective chart review was performed from January to December 2016 to evaluate median TTA in pediatric oncology patients presenting with fever and neutropenia. This information was compared to historical data collected in 2013. The 2016 data also compared median TTA and percentage of patients with TTA < 60 minutes in the 8 months prior to and the 4 months after implementation of physician feedback and education. Interventions included monthly newsletters (tips, education, and statistics), division meetings, and direct feedback regarding delayed patients.
Results: Six months after initiation of the 2013 ED clinical pathway for F&N, the median TTA was 103 minutes. In 2016 the median TTA was 59 minutes. After four months of interventions, the median TTA improved to 50 minutes. During this time, the percentage of patients receiving antibiotics in less than 60 minutes of presentation increased from 52% to 81%.
Conclusion: Implementation of a clinical pathway has shown lasting effects on TTA prior to any additional interventions. However, despite a median TTA of 59 minutes, only 52% of patients received antibiotics within 60 minutes. By incorporating physician feedback and education, there was a 29% increase in patients who individually received antibiotics within 60 minutes of arrival to the ED.

Poster # 739

TIME TO ANTIBIOTICS (TTA) IN PEDIATRIC FEBRILE NEUTROPENIA PATIENTS

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Background: Febrile neutropenia (FN) is an emergency in patients with a malignancy. Chemotherapeutic interventions lead to immune compromised status in both children and adults. Mortality rates are higher for pediatric patients when compared to older patients (2). Time to antibiotics (TTA) in patients with fever and neutropenia is an important quality measure for oncology centers.
Objectives: In this study we aim to review the time to antibiotics in pediatric patients with febrile neutropenia. We will also assess the impact of this duration with respect to length of hospital stay, rates of ICU transfers and mortality.
Design/Method: We retrospectively collected data on a cohort of pediatric patients seen in the emergency department (ED) over 10-weeks during April to June 2016 after approval from the

hospital's Institutional review board (IRB). Time from triage to antibiotic administration and the related clinical details were recorded.
Results: There were 111 patients identified with febrile neutropenia. Male to female ratio was 78:33. The most common diagnosis seen was pre-B-leukemia n=72 (64.9%) followed by sarcoma n=17 (15.3%). The median time from triage to antibiotic administration was 83 minutes (range: 3 – 319). Twenty-seven patients (24.3%) received antibiotics within 60-minutes. Majority of the patients did not have a central line n=101 (90.9%). Patients presenting to the ED had a mean absolute neutrophil count (ANC) of 0.07 (range: 0-0.99). The median length of stay in the hospital was 5 days with no increase seen in patients with delayed antibiotic administration. There were 2 (1.8%) deaths in the 113 patients treated for FN at our center. Out of the 111 patients seen for FN, 2 (1.8%) were sick enough to need ICU care.
Conclusion: Standard risk pre-B leukemia followed by solid tumors are common diagnoses treated at our institution. There is delay in TTA when compared to the standards followed in the developed world (1). Most of our patients had TTA more than 60 minutes; when compared to those with TTA less than 60 minutes we did not see an increase in mortality or hospital stay. As a quality care benchmark we recommend and attempt within our resources to administer antibiotics to pediatric febrile neutropenic patients within the first hour of presentation to the ED (1).1) Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011

Poster # 741

MANAGEMENT OF FEBRILE NEUTROPENIA IN PEDIATRIC ONCOLOGY PATIENTS IN CENTRAL TEXAS

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Background: Febrile neutropenia (FN) remains a frequent reason for hospitalization of pediatric oncology patients. Less than half of children show a clinical or microbiological focus of infection during FN, and the incidence of severe adverse outcomes is low. Thus, patients meeting low risk (LR) criteria can receive shorter courses of intravenous antibiotics and transition to oral antibiotics prior to absolute neutrophil count (ANC) recovery. The completion of oral antibiotics in the outpatient setting correlates with lower costs and shorter hospital stays.
Objectives: To evaluate the management of LR FN patients prior to implementation of a standardized protocol and to determine if discharge with oral antibiotics and/or absolute neutrophil count (ANC) recovery status impacted readmissions.
Design/Method: Retrospective chart review of oncology patients admitted to our tertiary medical center for FN between January 1, 2013 and December 31, 2015. Inclusion criteria for LR FN: ANC less than 500/mm3, fever above 38°C, and oncologic diagnosis. Exclusion criteria: age less than 1 year; trisomy 21; AML; ALL at diagnosis, relapse, or not in remission; focal source of infection or signs of end-organ failure. ANC recovery was defined as ANC greater than 500/mm3 or at least two consecutive increasing ANC values with last ANC above 100/mm3. Fisher's exact test was used to compare the groups.

Results: Of 303 incidences of FN, 100 met LR criteria (32 females, 68 males, median age 5.46 years). Fifty-eight had blood cancers and forty-two had solid tumors, including brain neoplasms. Of the patients who did not have ANC recovery and were discharged with antibiotics, 0% (n=0/7) had recurrence of fever compared to 6.9% (n=2/29) who were discharged without antibiotics (p=1.00). Median length of hospital stay was 2 days (IQR 2-3) without ANC recovery.
Conclusion: LR FN patients without ANC recovery who received oral antibiotics upon discharge were less likely to have fever recurrence and readmission compared to those discharged without oral antibiotics. These results support the safety and efficacy of rapid transition to oral antibiotics in LR FN patients without evidence of ANC recovery, which will decrease length of hospitalization at our institution. As this is a preliminary report describing a three-year period to be included in a long-term study to describe management of LR FN in Central Texas, a prospective study powered to determine the differences between groups since implementation of a standardized protocol is needed.

Poster # 743

IMPROVING TIME TO ANTIBIOTIC DELIVERY: A QUALITY IMPROVEMENT PROJECT

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Background: Rapid delivery of antibiotics for pediatric oncology patients admitted to the hospital with fever and neutropenia is associated with decreased morbidity and mortality.
Objectives: The aim of this quality improvement project was to improve time to antibiotics (TTA) for pediatric oncology patients hospitalized with fever and neutropenia, with a goal of 60 minutes. The target population was patients directly admitted to the hospital, as baseline data indicated this group had the longest wait for antibiotics. A multidisciplinary team including pharmacists, nurses, Advanced Care Practitioners, a pediatric resident, and a faculty physician was convened March 2010, with active improvement work through 2012 and continued monitoring for sustainability through 2016.
Design/Method: The Model for Improvement was the performance improvement framework used for this project, along with PDSAs for rapid cycle tests of change. Initially the team reviewed baseline data, using QI tools such as a Pareto Chart and process flow mapping which allowed recognition of steps in the process of antibiotic delivery, identified key factors impacting TTA, and determined areas to focus improvement efforts. The team met biweekly to discuss PDSA cycles, both learning and outcomes, and data review. Hospital admission lists were used to identify patients meeting criteria with data gathered by retrospective chart review. Run charts were used to display and analyze data using time series analyses.
Results: Overall results indicated improvement from baseline median TTA of 90 minutes to 16 minutes, n=155. Baseline TTA administration from October 2010 through January 2011 (n=29) ranged from 20 to 270 minutes with a median delivery time of 90 minutes. Multiple PDSA cycles were run to improve TTA with a primary process change of antibiotics placed in an automated dispensing machine in February 2011. February 2011 through April 2012 (n=42) the TTA ranged from 15 to 70 minutes with a median delivery time of 44 minutes, significantly

improved from baseline and below the goal of 60 minutes. Changes in work flow/process for orders occurred with electronic medical record implementation in March 2013 that resulted in continued improvement with a decreased median TTA time to 16 minutes. Improvements have been sustained through October 2016 (n=84), delivery time ranged from 0 to 148 minutes. Outlier cases are primarily related to issues with line access causing delays.
Conclusion: TTA administration was successfully improved and sustained. Significant multidisciplinary work contributed to work flow/process change and standardization to improve care of our pediatric oncology patients.

Poster # 745

USE OF A STANDARDIZED CLINICAL PATHWAY IMPROVES TIME TO ANTIBIOTIC ADMINISTRATION IN FEBRILE PEDIATRIC ONCOLOGY PATIENTS: RESULTS OF A SINGLE INSTITUTION QUALITY IMPROVEMENT PROJECT

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Background: Pediatric oncology patients are at increased risk for invasive bacterial infections due to chemotherapy-induced neutropenia as well as the frequent use of indwelling central venous catheters (CVC). Previous studies have demonstrated that promptly administering broad-spectrum antibiotics can decrease morbidity and mortality from invasive bacterial infections.
Objectives: We assessed the effectiveness of a newly implemented clinical pathway at a single institution designed to improve the time to administration (TTA) of broad-spectrum antibacterial coverage in febrile pediatric oncology patients with a CVC.
Design/Method: The new clinical pathway was applicable to all pediatric oncology patients with a CVC presenting with fever (temperature >38.3 Celsius or 101 Fahrenheit). Upon presentation two blood cultures were obtained from the CVC as well as a complete blood count (CBC). While awaiting CBC results patients were administered Ceftriaxone 75mg/kg through their CVC. Patients with absolute neutrophil count (ANC) <500cells/mm3 were immediately administered broader coverage with Cefepime and admitted to the hospital. Patients with ANC >500cells/mm3 and well appearing were discharged home. If the patient was known to have ANC <500cells/mm3 prior to Ceftriaxone administration they were immediately administered Cefepime and admitted to the hospital. A retrospective chart review analyzed patient data for 12 months prior to and after implementation of the new protocol. In addition to TTA each encounter for fever had data collected regarding: location where patient presented; type of CVC used; patient's ANC; presence of bacteremia; sensitivity of bacteria to Ceftriaxone; and any complications associated with Ceftriaxone administration.
Results: Data was collected on 185 consecutive episodes of encounters for fever. Seventy-six episodes occurred in the 12 months prior to clinical pathway implementation while 109 occurred after implementation. There was a significant improvement in TTA after clinical pathway was implemented (mean 139.1 and median 126.5 minutes before vs. mean 69.4 and median 55 minutes after, P<0.0001). No adverse events occurred with Ceftriaxone administration in either time period. There were 6 (3.2%) cases of bacteremia (3 before vs. 3 after, P=0.65). Bacteremia was documented in 2.7% of patients with ANC <500cells/mm3 and 5.1% of patients with ANC

>500cells/mm3 (P=0.61). Fifty percent of isolates were sensitive to Ceftriaxone.
Conclusion: Implementing a new clinical pathway significantly improved TTA in this single institution. Ceftriaxone appeared to be a safe and reasonable option to use for empiric coverage while awaiting ANC results. In this study bacteremia was present at similar rates regardless of whether severe neutropenia was noted.

Poster # 747

IMPROVING TIME-TO-ANTIBIOTICS FOR PEDIATRIC PATIENTS WITH FEBRILE NEUTROPENIA, A QUALITY IMPROVEMENT PROJECT

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Background: Rapid initiation of empiric antibiotics in patients with fever and neutropenia has been shown to reduce morbidity and mortality. Current practice guidelines call for the initiation of antibiotics in these patients within sixty minutes. Many institutions, including our own, face barriers to meeting this time limit.
Objectives: Our objective is to implement a quality improvement intervention to reduce the time-to-antibiotics for pediatric febrile neutropenia patients who present to the Emergency Department (ED) at our institution.
Design/Method: We evaluated the efficacy of our current practice algorithm for pediatric oncology patients undergoing active chemotherapy who present to the ED with febrile neutropenia at a large, academic tertiary-care hospital. Outcomes from a twelve-month retrospective review included the percentage of patients receiving antibiotics within sixty minutes of arrival, the mean time to antibiotic administration, and the accuracy of triage acuity. We gathered a multidisciplinary team and identified key drivers that will be targeted in our intervention. Following pre-intervention data collection and analysis, a standardized triage card is being created for patients to present upon arrival in the ED. Along with the implementation of this tool, educational sessions are being designed for the triage team and resident staff in the ED. Pre- and post-intervention antibiotic delivery times will be compared.
Results: A total of thirty-three encounters for febrile neutropenia were captured in our pre-intervention data review. The mean time to antibiotic delivery in this cohort was 135 minutes, or seventy-five minutes greater than the standard of care. Only one patient received antibiotics within sixty minutes of arrival. Many patients were not clearly identified to providers by the triage team as being febrile and neutropenic.
Conclusion: We have identified a clear need for improvement in time-to-antibiotics at our institution's ED. We have also identified specific barriers to achieving this goal. We are actively implementing a quality improvement measure that empowers patient families to direct appropriate triage in the ED, and that simplifies treatment protocol for ED providers. We expect to identify an improvement in time-to-antibiotics from the pre-intervention to the post-intervention period.

Poster # 749

HOSPITAL BASED INITIATIVE TO MINIMIZE THE TIME TO ANTIBIOTIC ADMINISTRATION IN FEBRILE IMMUNOCOMPROMISED PEDIATRIC PATIENTS

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Background: Fever in immunocompromised pediatric oncology patients can have serious implications and warrants immediate interventions. Studies have shown early antibiotic administration, within the first hour of fever (golden hour), significantly improved the outcomes. Our study aims to reduce the time to antibiotic delivery using a unique admission strategy.
Objectives: 1. To evaluate the effect of a unique admission strategy for febrile pediatric oncology patients on the time to administration of first antibiotic dose.2. To study the impact of our interventions on adverse health outcomes.
Design/Method: We utilized the Plan-Do-Study-Act (PDSA) approach to implement Quality Intervention (QI) directed to reduce the time of administration of antibiotics. Health care providers were educated on the significance of prompt antibiotic administration. Preregistration for direct floor admission was initiated upon provider notification of fever. Order sets with labs and medication was activated in the EMR and transmitted to the pharmacy enabling delivery of antibiotics prior to patient's arrival. The first dose of antibiotic was administered immediately after drawing pertinent labs. Data was compared between the Pre QI and Post QI. T-test was used for the continuous data. Chi-square test was used for categorical data. p-value was considered as significant for less than 0.05. All analysis was performed using SAS 9.4.
Results: There were 29 patients in the Pre-QI and 45 patients in the Post QI group. The baseline characteristics were similar in both groups (p=0.44). The primary objective was statistically achieved by administering the antibiotic within the first hour of admission in nearly 82% of patients in Post QI compared to only 27% in the Pre QI period (p=0.0019). Mean time taken to administer the antibiotic was 79±183 minutes and 358±1233 minutes in the post and pre QI groups respectively. There was no significant difference in the duration of fever, incidence of failure of first line antibiotics or length of stay. None of the patients progressed to severe sepsis in the Post QI group compared to nearly 7% in the Pre QI group, though it was not significant(p=0.07)
Conclusion: The implementation of a simple hospital based initiative has drastically reduced the time for antibiotic delivery at our Institution. Moreover, our strategy successfully prevented progression to severe sepsis. Our goal is to utilize this PDSA cycle to achieve universal antibiotic administration within the golden hour.

Poster # 751

MULTI-CENTER QUALITY IMPROVEMENT COLLABORATIVE TO IMPROVE MEDICATION EDUCATION AT HOSPITAL DISCHARGE

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Background: Medication adherence, a crucial factor contributing to the efficacy of a therapeutic regimen, may be increased by improved understanding of one's medications. The American Society of Clinical Oncology-Oncology Nursing Society Chemotherapy Safety Standards state that hospital discharge education must include instruction on medication storage, handling, preparation, administration, and disposal; concurrent treatment and supportive care medications; drug and food interactions; and the plan for missed doses. To improve compliance with hospital discharge medication education, we completed an ASPHO-sponsored, multi-institutional quality improvement (QI) pilot project.
Objectives: Our primary aim was to improve the percentage of patients that received comprehensive home medication instruction over 6-months. Secondary aims included: evaluate the impact of the project and basic QI education course on participant QI knowledge self-assessment, improve multi-site QI collaboration, and provide Maintenance of Certification part-4 (MOC4) credit for participants.
Design/Method: Home medication education compliance was tracked through all-or-none measurement and included instruction on: (1) storage, handling, preparation, administration, and disposal of medications; (2) concurrent treatment/supportive care medications; (3) drug and food interactions; (4) plan for missed doses. Participant QI knowledge was assessed at baseline and upon project completion utilizing an existing QI knowledge assessment tool. The model for improvement was used to design, test, and implement changes in the participating institutions. Common key drivers included: standardized education process for all discharges, clearly defined roles and responsibilities, reliable tool to identify drug/food-drug interactions, reliable process to identify upcoming discharges. Individual site interventions included creation of medication education information sheets that were shared amongst centers, a “hard stop” to hold discharge until education was completed, and utilization of checklists amongst others. Monthly conference calls were conducted and an online forum was created to provide opportunity for collaboration and shared learning.
Results: Six institutions participated in the project (2 small, 2 medium, and 2 large). From March-August 2016, the median percentage of patients receiving adequate education in the 6 centers increased from 0% (baseline was 0% in all centers on providing instruction on all four components) to 72% (range= 0-100%). 5 of 6 centers maintained >60% compliance. In the 18 providers that completed the pre- and post-QI knowledge assessment, the mean QI knowledge increased amongst the 9 topics from 5.8 (out of 9) to 7.7 (p=0.0001). 36 ASPHO members received MOC4 credit at the completion of the project.
Conclusion: This project enhanced ASPHO member collaboration, QI learning, enabled membership access to MOC4 credit and improved patient care through education.

Poster # 753

HEALTH-RELATED INTERNET USE AMONG ADOLESCENTS AND YOUNG ADULTS WITH CANCER OR CHRONIC HEMATOLOGIC DISORDERS

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Background: Internet use among adolescents and young adults (AYAs) has become ubiquitous. When diagnosed with cancer or chronic hematologic diseases, AYAs encounter new information needs, such as learning about their conditions and understanding treatment options. It is unknown how AYAs with cancer or hematologic diseases use the Internet and the factors that influence their health-related Internet use (HRIU).
Objectives: The purpose of this study was to describe AYAs' HRIU and their perceived benefits and risks associated with HRIU.
Design/Method: We conducted a cross-sectional study at the Tomorrow Fund Clinic at Hasbro Children's Hospital in Providence, Rhode Island. Structured surveys were designed to collect information regarding demographics, emotional adjustment to illness, and characteristics of HRIU using Likert scales and open responses. Quantitative analysis was conducted using SPSS and qualitative data was reviewed to draw thematic conclusions.
Results: Fifty AYA patients with cancer or chronic hematologic diseases participated in the study. All participants reported using the Internet; 93% participants reported using the Internet frequently or that the Internet is easy to access, and 93% reported using e-mail, shopping online, searching for news, or social communication. Only 37% participants, however, reported using the Internet frequently to learn more about their health or additional treatments, 9% to find others with similar illness, and 19% to communicate with family, friends, and healthcare workers regarding their health. Although almost half of the participants felt they could not trust the Internet, only 27% wished they had not searched the Internet for information about their health.
Conclusion: Although AYA patients with cancer and chronic hematologic diseases use the Internet to search for information, communication, and socialization, they use the Internet less frequently when it pertains to their illness. Of those with HRIU, most reported using the Internet for seeking information rather than to communicate their personal health information or to socialize with other patients with similar conditions. Although patients preferred to have the Internet as a source of information, most patients did not trust the information they found. Future studies can investigate ways to support AYAs' HRIU, specifically to guide information seeking to trustworthy sites and improve Internet health literacy.

Poster # 755

IDENTIFICATION OF KEY DRIVERS OF PATIENT EXPERIENCE IN A MID-SIZE PEDIATRIC HEMATOLOGY-ONCOLOGY CLINIC

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Background: Patient experience-based research is a rapidly growing and important area within healthcare. High patient experience levels are associated with better doctor-patient communication, improved patient compliance, reduced likelihood of malpractice, and greater physician job satisfaction. In addition, physician reimbursement and pay-for-performance measures are linked to patient experience metrics. Currently little data exists related to improving

patient satisfaction, and no reports have identified key drivers of patient experience in populations served by pediatric hematology-oncology (PHO) outpatient clinics.
Objectives: To determine Key Drivers of Top-Box scores for "Rate This Provider" and "Likelihood of Your Recommending This Practice to Others".
Design/Method: Patient experience was measured using Consumer Assessment of Healthcare Providers and Systems (CAHPS®) surveys returned during 2014 through 2016 (n=209) at a regional children's hospital PHO outpatient clinic. The instrument included 25 items scored on a 5-point Likert scale in addition to a "Rate This Provider" 10-point scale. The primary study outcomes were to determine predictors of a Top-Box score for "Rate This Provider" (defined as 9 or 10) and "Likelihood of Your Recommending This Practice to Others" (defined as 5, "Very Good"). Predictor selection was conducted using least absolute shrinkage and selection operator based multiple logistic regression.
Results: A Top-Box score for "Rate This Provider" was achieved on 189 (90.4%) surveys and a Top-Box Score for "Likelihood of Your Recommending This Practice to Others" was reported on 181 (86.6%) surveys. The most predictive items of a Top-Box score for "Rate This Provider" were high scores related to "Your confidence in this care provider" (OR 10.3; 95% CI: 1.8, 58.8) and "Explanations the care provider gave you about your problem or condition" (OR 6.8; 95% CI: 1.2, 38.5). The most predictive items of a Top-Box score for "Likelihood of Your Recommending This Practice to Others" were high scores related to "How well staff worked together to care for you" (OR 142.6; 95% CI: 27.6, 735.8) and "Friendliness/courtesy of the nurse/assistant" (OR 8.7; 95% CI: 1.5, 49.6).
Conclusion: With regards to provider rating in a mid-size PHO clinic, Key Drivers of patient experience were patient-reported confidence in the provider and providers' explanations of the patient's problem or condition. Key Drivers of recommendations of the practice were perceived teamwork of the staff and friendliness/courtesy of nursing/assistants. These results will be used for future goal setting and PDSA (Plan-Do-Study-Act) patient experience improvement initiatives.

Poster # 757

IMPROVEMENT RATE OF TEN AM DISCHARGES ON THE PEDIATRIC HEMATOLOGY ONCOLOGY INPATIENT SERVICE AT THE MEDICAL UNIVERSITY OF SOUTH CAROLINA

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Background: A hospital's inpatient teams' timely and efficient discharge process has shown improvement in several desirable outcomes including patient satisfaction, improved use of hospital resources and increased efficiency of daily rounds.
Objectives: In an attempt to improve patient flow and patient satisfaction, the impatient Pediatric Hematology/Oncology service at the Medical University of South Carolina attempted to complete 50% of patients' discharge orders by 10 am.
Design/Method: We reviewed our data from all discharges from 8/1/15-9/17/15 to examine the reason for discharges occurring after 10 am. We found a significant number were due to completion of therapy, rule out sepsis evaluations or other medical interventions. A significant

amount of delays were simply due to lack of awareness of potential for discharge and thus, failure to coordinate discharge plans in time for the 10 am deadline. On admission the PHO fellow completed data sheets for each patient, detailing the admission. Information regarding prescriptions was also recorded. Transfusion goals were discussed in advance. Discharge planning was prioritized during morning, and afternoon rounds and 24 hours in advance of the anticipated discharge date and actual times of discharge orders and occurrence were recorded. We collected data using our data collection form.
Results: Goals were met for all three months of the quarter when <48 hour admissions were eliminated. Our results were the following: October 2015:28/52 = 54%, November 2015:36/58 = 62%, December 2015: 24/46 = 56%. Data from the Quality Measures Dashboard was compared and is 61.2%, 65.3%, and 62.5% respectively for the months of October, November and December 2015.
Conclusion: Our timely and efficient discharge process has shown improvement in several desirable outcomes including improved patient satisfaction scores, improved use of hospital resources and increased efficiency of our inpatient team. We learned that a focus on pre-planning and better team communication allowed us to identify potential barriers and successfully achieve our goal.

Poster # 759

AMOTOSALEN AND UVA IS MORE EFFECTIVE IN THE INACTIVATION OF T CELLS THAN GAMMA IRRADIATION WHEN ASSESSED BY A LIMITING DILUTION ASSAY (LDA)

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Background: Viable T cells in blood components cause Transfusion Associated Graft vs. Host Disease (TA-GvHD) with high mortality. Gamma irradiation (GIRR) (2500 cGy) of platelet components (PC) is used to mitigate this risk. Photochemical treatment (PCT) of PC with a psoralen (amotosalen) and UVA light (INTERCEPTTM Blood System) has replaced GIRR in Europe for >10 years and is authorized by AABB to reduce the risk of TA-GvHD.
Objectives: T cell inactivation by PCT and GIRR was compared using a sensitive limiting dilution assay (LDA).
Design/Method: An LDA assay with culture of 10^7 peripheral blood mononuclear cells (PBMCs) in a single well and detection of proliferating T cells was validated by comparison of T cell proliferation in culture media, plasma, and plasma containing 10^7 inactivated T cells. PBMCs harvested by leukapheresis from individual donors were spiked (10^6/mL) into identical units of human plasma and inactivated using either PCT or GIRR, or left untreated. PCT and GIRR cells were incubated (10^7/mL) for 14 days with pooled allostimulator PBMCs from 10 unrelated donors (5x10^6 treated with 7500 cGy) and growth stimulating factors (PHA, IL-2). T cell inactivation by PCT (10^7 PBMCs/well) was compared to that by GIRR (10^5, or 10^6 PBMCs/well). Proliferation was assessed by 3H-thymidine (3H-Thy) (6.7 Ci/mmol) incorporation into PBMCs. Wells were inspected microscopically and scored for clonal growth. T cell precursor frequency for each donor was measured by incubation of untreated PBMCs (50,

25, 13, 6.5, 3, and 1/well) in the presence of 10^7 inactivated PBMCs. Twelve wells were used for each dilution and the protocol was conducted in 6 replicates.
Results: No T cell growth for PCT PBMCs was detected by 3H-Thy incorporation above the cut-off for viable PBMCs with 10^7 cells/well cultured. However, 3H-Thy incorporation above the cut-off was observed when 10^6 GIRR PBMCs/well were cultured. No incorporation was observed when 10^5 GIRR PBMCs/well were cultured. Proliferating T cell colonies were observed in 4/6 replicates with 10^6 GIRR PBMCs/well, and in none of the cultures with 10^5 GIRR or PCT PBMCs/well.
Conclusion: T cell inactivation with PCT (amotosalen/UVA treatment) is more robust (>6.2 log10) than with 2500 cGy GIRR (>4.2log10 - <5.2 log10).This study was supported by Cerus Corporation.

Poster # 761

THE COMPLEXITY OF CONTINUITY: PATIENT AND PROVIDER ENCOUNTERS OVER A TRAJECTORY OF CARE

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Background: Children with complex medical illness such as childhood cancer and their caregivers experience substantial health care interactions over the course of an illness. Treatment regimens last from several months to several years and involve both inpatient and outpatient care. Parents often experience frustration and confusion when they encounter multiple new providers and are given information that is conflictual with communication from prior providers. Continuity of care is recognized as a necessary component of safe and effective care, however actualization of the concept is often lacking due to the complexity of health care systems.
Objectives: This project aimed to identify the total number of distinct health care encounters with a patient and family that were documented in the medical record.
Design/Method: Retrospective chart review of the medical record of a single child with cancer from diagnosis to death. All health care providers who documented during a day of care were identified and recorded on a spread sheet for each day of care. Health care provider is defined as medical, nursing, therapy, and psychosocial professionals. Continuity is defined as > or equal to 3 continuous encounters by two or more health care providers in either the inpatient or outpatient settings. Data was analyzed using social networking methods.
Results: Time from diagnosis to death was 221 calendar days with 107 distinct days of documented medical care, of which 85 days (80%) involved inpatient care. Total number of health care providers who documented in the EMR from diagnosis to death were 269 distinct individuals. During 5 admissions that totaled 85 days of service, families experienced 688 encounters with health care providers (range 63-341) of which 328 (range 47-113 – 48%) were single encounters with a given provider. The longest period of continuity over the course of care was 4 consecutive days with 4 providers. Greatest continuity was seen in Oncology and Critical Care MDs, least continuity was seen in nursing and subspecialty services.
Conclusion: The findings of this study demonstrate that while continuity of care is a prevalent concept in health care delivery, the nature of staffing of health care providers leads to significant discontinuity in care. Our current data is limited by the review of a single patient and only those

providers who documented a note in the EMR. It is likely that the numbers of individuals who interact with the patient and family are significantly greater.

Poster # 763

UTILIZATION OF PALLIATIVE CARE IN PEDIATRIC ONCOLOGY: AN INTERPROFESSIONAL EVALUATION OF KNOWLEDGE, BELIEFS, PERCEIVED BARRIERS, AND INVOLVEMENT OF SERVICES

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Background: The care of pediatric patients with cancer and their families is complex and evolving. Despite significant advances in outcomes, symptoms of disease and complications of therapy continue to cause pain and other symptoms that could be improved with the involvement of pediatric palliative care (PPC) services. The American Academy of Pediatrics (AAP)1 and Institute of Medicine (IOM)2 have published statements and recommendations in support of collaboration with PPC services for all children with serious life-threatening and life-limiting illnesses. Additionally, PPC is recommended as a standard of care in pediatric oncology in addressing the psychosocial needs of children and adolescents with cancer and their families3.
Objectives: The overall purpose of this study was to evaluate the knowledge and beliefs of pediatric oncology healthcare providers (HCPs) regarding involvement of PPC and to assess potential barriers that may interfere with its utilization. Additionally, this study evaluated the current involvement of PPC services in pediatric oncology programs that belonged to a statewide hematology alliance in a large Midwestern state.
Design/Method: A cross sectional, descriptive survey design guided data collection and analysis. A survey consisting of 30 questions evaluated demographic factors, institutional resources, beliefs, perceived barriers, and current utilization practices. The Qualtrics survey was distributed via email. Data were collected from 156 HCPs (nurses, advanced practice professionals, and physicians). Analysis was completed using IBM SPSS version 24.
Results: Significant variability was noted in perspectives regarding PPC and utilization when comparing respondents from various professional roles, practice environments, and among those with different education and professional experience. Over 99% of respondents stated that involving PPC benefits children, however 56% reported PPC was involved “never” or “rarely” in the care of oncology patients. The leading indications for PPC involvement were consistent with advanced disease, occurring late in the trajectory, rather than upon diagnosis as recommended. The influence of practice environments was identified in this study, with free-standing children’s hospitals reporting fewer barriers and increased involvement of PPC services.
Conclusion: Although progress has been made, care delivered is still not congruent with the recommendations of the AAP and IOM. Knowledge gained from this study emphasizes the important role for all HCPs in advocating for support of PPC programs, education of the public, and commitment to the involvement of PPC services while caring for pediatric oncology patients. 1. AAP Section on Hospice and Palliative Medicine, Pediatrics, 20132. IOM, Dying in America, 20143. Weaver, et al., Pediatr Blood and Cancer, 2015

Poster # 765

AFFORDING OPPORTUNITIES TO DISCUSS DETERIORATION IN PAEDIATRIC PALLIATIVE CARE CONSULTATIONS: A CONVERSATION ANALYTIC STUDY

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Background: Communication is fundamental for delivering quality care to children who have life-limiting conditions (such as cancer) and their families. There are few direct observational studies investigating how healthcare professionals communicate with patients and families in palliative care settings, and whichcommunicative practices facilitate optimal outcomes.
Objectives: Discussing the potential deterioration of a child who has an advanced illness such as cancer has recognised benefits for future care, but can be challenging in a clinical context where uncertain illness trajectories are common. Existing research is restricted to indirect forms of evidence such as self-report data from clinicians and families. This study directly explores how discussions about deterioration are managed within actual paediatric palliative care consultations.
Design/Method: Nine consultations were video recorded in an Australian paediatric palliative care service. Each consultation involved the same paediatric palliative care specialist. Conversation analysis was used to identify and explore recurrent ways in which discussions about deterioration came to be realised.
Results: The study identified two communicative practices used by a paediatric palliative care specialist that afforded opportunities to discuss deterioration: 1) soliciting the family's agenda for the consultation; 2) initiating and maintaining topics where discussing deterioration is a relevant possibility. Across these different practices, a common feature was indirect initiation of discussions about deterioration. This approach made such discussions possible, but without mandating or even suggesting that such discussion must occur.
Conclusion: Identifying the importance of discussing deterioration to plan for and enhance future care was made possible through direct observational analysis of actual paediatric palliative care consultations. These communicative practices balance the benefit of discussing deterioration against a recognised importance of allowing discussions to be directed by a child's family. This was achieved by creating opportunities for discussing deterioration, without making such discussions necessary.

Poster # 767

TEAM MEMBERS ARE FAMILY: EXAMINATION OF THE RELATIONSHIPS BETWEEN ONCOLOGY STAFF AND BEREAVED PARENTS AND THE IMPACT ON PARENTAL GRIEF

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Background: Following the death of a child, many parents cope with their grief via making meaning. Meaning making is a social construct, occurring within relationships. Given the prolonged nature of pediatric cancer treatment and the difficult decisions it entails, relationships between parents and care team members are fostered over time and through extensive collaboration. These relationships have the potential to be sources of support for parents during the child's treatment and conduits for making meaning of the child's life and treatment journey after their death. However, the extent to which relationships with care team members influence parents' ability to make sense of and successfully cope with their loss has not been examined.
Objectives: The purpose of this study was to examine how interactions with their deceased child's pediatric oncology care team impact parents' grief.
Design/Method: This study employed a convergent parallel mixed methods design. Data was collected from 30 bereaved parents whose children died from progressive cancer or cancer-directed treatment 1-3 years prior to participation. The quantitative component included standardized depression and grief-related symptom questionnaires and a meaning making questionnaire. The qualitative component included a semi-structured interview protocol. Spearman's correlation was utilized to measure the associations between questionnaire scores and parent and child treatment demographics.
Results: Statistically significant correlations were found among depression, grief, and meaning making, with higher levels of depression correlated with higher levels of grief, and both grief and depression correlated with lower levels of meaning making. The duration of treatment, amount of time passed since the child's death, whether the parent had any other children, and all other demographic variables did not correlate significantly with parents' level of depression or grief. A thematic analysis of the interviews identified the following overarching themes: parents' necessity to assimilate throughout and beyond the cancer journey; the importance of functioning as a good parent during treatment and after the child dies; parents' viewing the care team "like family" during treatment; and the care team's ability to aid parents' sense making, benefit finding, and identity reconstruction after the child dies. Parents endorsing severe depressive and grief symptoms did not describe forming close relationships with any particular care team members. However, those parents who did describe forming close relationships with team members endorsed high meaning making levels.
Conclusion: Results from this study may form a foundation from which to further assess the care team's impact on parental bereavement as well as future considerations for clinical interventions.

Poster # 769

HOW DO CHILDREN WITH CANCER DIE: A RETROSPECTIVE CHART REVIEW AT A PEDIATRIC CANCER CENTER

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Background: Although there has been significant improvement in the overall survival rates of childhood cancer, almost 2,000 children will die annually in the United States as a direct result of cancer or complications from treatment. These children are more likely to receive high-intensity medical care in the end of their lives than children with other complex medical conditions. While

it is important to continue research to improve survival and minimize treatment side effects, consideration must be given to improving care for dying children.
Objectives: To improve care, we first need a better understanding of the dying patient population. The purpose of this study is to describe and analyze the inpatient deaths of children with cancer at a pediatric hospital.
Design/Method: This study is a retrospective chart review of patients with cancer who died between January 18, 2011 and March 30, 2015 and were treated at Texas Children's Cancer Center. The diagnosis was considered or 'curative intent' if the patient 1) had not yet experienced a relapse of their disease, or 2) had acute lymphoblastic leukemia and only relapsed once. Date of Do-nNot-Resuscitate (DNR) was the earliest date documentation in the medical record.
Results: We identified 281 patients who died during this time frame, 140 (50%) died in the cancer center hospital while 8% (23 patients) died in inpatient hospice. The average age was 9.3 years (range 0 -22 years); 52% were male and 50% were Hispanic. Most patients (47%) had leukemia or lymphoma, 17% had brain tumors, 21% had solid tumors, and 15% had other diagnoses. Thirteen patients (12%) had a second malignancy, two of these patients had a third malignancy. Approximately one quarter of patients died without evidence of active disease and 42% were receiving curative treatment. Most patients, 84%, had a DNR order prior to death. DNR was signed <1 week before death in 66%, and 1-4 weeks before deathin 33%.
Conclusion: Nearly half of children with cancer who died in the hospital were on a curative treatment trajectory. DNR occured close to the time of death for the majority of these patients. Analysis and improvement of end of life treatment must include consideration of the patients' trajectory towards death.

Poster # 771

QUALITY OF CARE COLLABORATIVE FOR PAEDIATRIC PALLIATIVE CARE IN AUSTRALIA (QuoCCA)

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Background: Geography and population distribution present challenges to the care of children with life-limiting conditions (LLC) within Australia. Children and young people have unique needs in relation to the provision of palliative care within Australia.
Objectives: This project aims to improving the quality of care provided to children in close proximity to their home through educational initiatives. This is primarily delivered through "pop-up" education. 'Pop-up' education usually occurs (face-face or telehealth) when a specialist service is building capacity within a child and family's local community and creating a paediatric network. The education provided can be specific to symptom management, end of life care, physical aspects of patient care according to their individualised need and diagnosis and psychosocial needs. The setting is usually in a non-metropolitan location, and the education is provided in a timely manner in relation to the patient's needs.

Design/Method: The project is a collaboration of the specialist paediatric palliative care services in each state of Australia. The project is being evaluated using pre and post intervention questionnaires completed by participants in the 'pop-up' educational initiatives. Evaluation will consider factors such as knowledge, confidence and efficacy around providing care for children with LLC.
Results: Forty-six "pop-up" education sessions had been delivered between June 2015 and November 2016. This has included each state and territory of Australia. There have been 507 participants in pop-up education sessions (92 hours of education). Nurses represented the largest group of attendees. Medical and allied health staff also attended demonstrating the need for education to applicable to an inter-disciplinary audience.To date there has been an improvement in the knowledge and confidence of participants to:• manage symptoms (pain, nausea, dyspnoea, seizures, and anxiety), • manage a new referral, • be aware of available resources• be confident in how to help a family prepare for a child's death• confidence in the provision of medications to children's receiving palliative care (including subcutaneous delivery)
Conclusion: A collaboration of paediatric palliative care services providing education in a planned and co-ordinated way shows promise in increasing capacity for paediatric palliative care within Australia, and should assist achieving goals of the National Palliative Care Strategy 2010.

Poster # 773

TRAINING PEDIATRIC FELLOWS IN PALLIATIVE CARE: A COMPARISON OF SIMULATION-BASED TRAINING AND DIDACTIC EDUCATION

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Background: Although palliative care (PC) communication skills can be learned through trial and error, pediatric fellows have few opportunities to practice communication, and learning by doing may be harmful for families. Despite these issues and recommendations from professional societies, most fellowship programs either lack formal training or provide only lecture-based PC education. Simulation-based training has been successful in other high-stakes communication encounters, and has the potential to change PC education.
Objectives: In this pilot study, we assessed: (1) the relative effectiveness of simulation-based vs didactic education, (2) communication skill retention, and (3) effect on PC consultation rates.
Design/Method: Thirty-five pediatric fellows in hematology/oncology, cardiology, critical care, and neonatology at two institutions enrolled: 17 in the simulation-based group (single institution) and 18 in the didactic education group (second institution). Simulation-based subjects participated in a 2-day program over 3 months (three simulations and videotaped PC panel) where scenarios focused on: introducing PC, discussing goals of care and resuscitation preferences, and mediating disagreement between the family and medical team. Didactic-education subjects received written education designed to be similar in content and time. (1) Fellow self-assessments in PC comfort, knowledge, and adequacy of medical education, were measured at baseline, post-intervention and three months; mean between-group differences for each outcome measure were assessed. (2) Two blinded external reviewers rated each simulation-group fellow's encounters on nine communication domains. Within-group changes over time were assessed. (3) The simulation-based site's PC consultation rate was compared in the six

months pre- and post-intervention.
Results: Compared to the didactic group, subjects in the simulation-based group improved in PC comfort/ self-efficacy (16.4 vs 6.1, Δ10.3, p=0.003) and perceived adequacy of medical education (7.4 vs 0.4, Δ7.1, p<0.001). Both groups had improved PC knowledge; this was not different between groups (1.1 vs 1.8, Δ-0.7, p=0.20). Reviewers noted non-sustained improvement in four domains: relationship building (p=0.01), opening discussion (p=0.03), gathering information (p=0.01), and communicating accurate information (p=0.04). PC consultation rate increased 64%, an improvement when normalized to average daily census (p=0.04). Simulation-group fellows more strongly agreed that they would use the education in practice (p=0.04), and recommended that educational methodology (p=0.004).
Conclusion: Well-trained physicians are necessary to providing high quality PC. This simulation-based curriculum is an effective method for improving PC comfort, education, and consults, although it does not lead to sustained improvements in communication competence or knowledge. More frequent, deliberate practice is likely needed to lead to sustained improvements in communication competence.

Poster # 775

PEDIATRIC PALLIATIVE CARE (PPC) ACCESS IN CHILE: PRIVATE PRACTICE HEALTH INSURANCE LAW IMPLEMENTATION

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Background: There are 600 new pediatric cancer cases in Chile in a year, with an overall survival of 70% and there are two systems that guarantee the access for patients to health providers: The public system, or national health fund (FONASA), and the private one, supported by insurance health institutions (ISAPRES), both financed by employees or contributors. Today in Chile the distribution of the population between both systems is 75% and 25% respectively. In 2004, in Chile, was enacted the law number 19.966 of explicit health guarantees (GES), that forces health systems to provide contributors the access, along with many other pathologies, to palliative care and pain relief for oncologic patients, despite the age. PPC is well developed and provided in the public system, but no precedents have being settled in the private area.
Objectives: To show the results of the first PPC team focused on the private practice in Chile.
Design/Method: According to data published by Chilean ministry of health pain relief and palliative care program, extrapolating the patient distribution in the private practice area, and assuming a similar overall survival, the estimated number of patients that could be beneficiated by this program should be between 20 and 25 per yeaer. We count on an interdisciplinary team (nurses, kinesiologist, psychologist and physicians) able to offer care according to each patient needs: Home visit, outpatient consultation, telephone assistance, treating teams counseling, supplies provision, etc. Demographics and charateristics of our group are presented.
Results: In the first 13 months of functioning, 21 cases have been evaluated (including 2 non oncologic patients) and 14 of them have been admitted to the program. Aveerage age of 8.6 years old. 8 female. Time from admission to program of 5 months (range 0.2-20) central nervous system tumors and relapsed leukemias are the main diagnoses.

Conclusion: Chilean law guarantees a benefit to patients but their access is not properly assured. The mission of our team is to provide integral care to this patients and to become a reference team for the health insurance institions and their affiliated.

Poster # 802

EVALUATION OF SERUM PROCALCITONIN, SERUM INTERLEUKIN-8 AND INTERLEUKIN-6 TO PREDICT RISK GROUPS IN CHILDREN WITH FEBRILE NEUTROPENIA AND CANCER - UTILITY IN A DEVELOPING COUNTRY

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Background: Early diagnosis of sepsis in children with febrile neutropenia remains difficult due to non-specific clinical and laboratory signs of infection. There is a need to assess the utility of inflammatory markers in clinical risk assessment for their ability to discriminate between low-risk and high-risk neutropenic patients since presently there is an insufficient data to recommend their routine use.
Objectives: To evaluate the utility of serum procalcitonin (PCT) serum interleukin-6 and interleukin-8 to predict the risk of bacteremia in febrile neutropenia with cancer.
Design/Method: This is a prospective study of children on therapy admitted with febrile neutropenia between 2015-2016 and sampled for markers at admission. The intravenous antibiotics are administered as per the hospital antimicrobial policies. The febrile neutropenia episodes were categorized into two groups - Group I: no focus of infection and Group II: clinically/microbiologically documented infection. Statistical analysis for comparison were performed using z-test and Receiver operating curves at various cut off levels.
Results: A total of 46 episodes of febrile neutropenia were analysed. 76% were categorized as group I and 24% as group II. The mean value of PCT in group II was higher (28.07 ng/ml) as compared to group I (1.03ng/ml) though there was no significant statistical difference. At a cut off level of 2 ng/ml for PCT, sensitivity of 63%, specificity of 91%, PPV of 70%, NPV of 88% were observed. There was no significant difference in the IL-6 and IL-8 levels between both the groups. But at an optimal cut off value of 50 pg/ml, IL-6 had a NPV of 80% and at a cut off level of 130 pg/ml, IL-8 had a NPV of 73%, however with low sensitivity and specificity. The mean number of days of hospitalization was 5.89 days. The cost of intravenous antibiotics and hospitalization for a day is approximately INR 3000 and the cost of antibiotics as outpatient for a day costs approximately INR 500.
Conclusion: IL-6,IL-8 and PCT can be utilized to define a group of patients with a low risk of sepsis in view of their favorable NPV. The utility of these biomarkers together can facilitate early discharge from the hospital, and the use of oral antimicrobial therapy in turn reducing the cost of therapy especially in a developing country.

Poster # 804

CHANGE IN BODY MASS INDEX AMONG SURVIVORS OF CHILDHOOD CANCER: A RETROSPECTIVE CHART REVIEW FROM AN URBAN PUBLIC HOSPITAL

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Background: More than 80% of pediatric cancer patients survive. About 40% of pediatric cancer survivors are obese after treatment. Hispanic race/ethnicity and low socioeconomic status (SES) have been associated with an increased risk of obesity among the general population. Understanding changes in body mass index (BMI) among this understudied population is of importance given their propensity to be obese.
Objectives: To determine changes in BMI z-score 3 years after diagnosis of cancer among pediatric patients and describe differences based on gender and type of malignancy.
Design/Method: A retrospective chart review of patients who were diagnosed and treated in an urban public hospital was performed. Data was collected on age, gender, type of malignancy, height, and weight, at the following time points: time of diagnosis, 0.5, 1, 2 and 3 years post diagnosis. BMI was calculated, then age-standardized and sex-standardized BMI z-scores were determined for each patient using height, weight, sex and age data based on the Centers for Disease Control and Prevention National Center for Health statistics growth curves. Differences in BMI z-scores between diagnosis and 3 years after diagnosis were analyzed by paired t-tests.
Results: Thirty-nine patients, diagnosed between 1993-2009, aged 2-16 years at time of diagnosis were identified. 21 had leukemia and 18 had other malignancy. The cohort was predominantly Hispanic and with public health insurance. In the overall cohort, 33% were overweight or obese at diagnosis compared to 86% at the 3-year interval (mean z-score of 1.6 vs.1.8). BMI z scores increased significantly over the years ($\Delta = 0.76$, $p<0.01$). Gender had little effect on the difference in mean z-scores. Analysis by gender demonstrated that at diagnosis, 33% of females were overweight or obese, 56% at 3 years, with males exhibiting a similar distribution. The diagnosis of leukemia had a difference in mean z-scores of 0.97, however not significant.
Conclusion: This sample of predominantly Hispanic patients demonstrated a significant increase in BMI z-score over a 3-year interval, with a similar gender distribution. A higher percentage of individuals with BMI's $\geq$ 85th at baseline and at the three-year interval was seen in this cohort than what was previously reported in the general pediatric cancer population. Based on this early data, proper weight management and interventions need to be tailored targeting this patient subset. Further analysis of biomolecular correlates such as leptin, blood glucose, liver function tests, and lipid panels is ongoing.

Poster # 806

PREDICTIVE GENOMIC SEQUENCING: THE IMPACT OF A STRUCTURED INFORMED CONSENT MODEL ON PARENTAL UNDERSTANDING

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Background: Next generation sequencing (NGS) tests are revolutionizing analysis of individual genomes for variants predicted to impact health; consequently clinical research initiatives are seeking to rapidly integrate NGS into clinical practice. Although NGS tests have many benefits, they have the potential to identify variants of uncertain clinical utility, pathogenic variants associated with adult-onset conditions, and other incidental findings. Given the impact of this information on families, it should be articulated prior to testing; however the best methods to adequately communicate the risks and benefits of testing are unknown. Previous research on informed consent conversations (ICC), in the context of therapeutic pediatric trials, has demonstrated poor communication and a lack of parental understanding around study purpose and basic scientific concepts. Members of our study team have proposed a two-step approach to ICCs with the use of a simplified informational coversheet in the highly complex arena of pediatric phase I clinical trials. Given the additional complexities associated with NGS tests and the increasing expectations placed on precision-based medicine, it is imperative to develop effective methods for communicating, including improving ICCs, with families offered predictive genomic sequencing.
Objectives: To assess the impact of a structured informed consent process on parental understanding and satisfaction when predictive cancer germline sequencing is offered to their child.
Design/Method: Within the context of a prospective study evaluating the feasibility of clinical NGS in children with newly diagnosed or relapsed cancer we sought to evaluate the impact of an ICC approach involving a two-visit, structured communication process with informational coversheet. Mixed methods approaches were used to measure parental and adolescent knowledge, attitudes, and beliefs around study purpose, predictive sequencing, and informed consent process. All families approached for the parent study were eligible, regardless of their decision around sequencing.
Results: To date 271 participants have enrolled on study (85%, n =317) and of those eligible for surveys and interviews (n = 241), 80% have agreed to participate. Some families have declined study participation in favor of clinical testing for the specific mutation(s) associated with the child's cancer type. The majority of those enrolled (96%, n = 261) are electing to learn predictive germline results for cancer predisposition. Preliminary review of the study data indicates that the majority of participants have low decisional conflict around sequencing decision and understand study purpose, including the risks and benefits of participation.
Conclusion: Use of a structured communication model can facilitate quality ICC in parents offered predictive NGS.

Poster # 808

PREVENTION OF WOUND COMPLICATIONS AFTER CHEMO-PORT PLACEMENT IN CHILDREN

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Background: Wound dehiscence after chemo-port placement is a rare but significant complication. It often necessitates a return to the operating room and delay in initiation of therapy. The subcuticular skin closure technique is common in pediatrics due to the excellent cosmetic result. However, at our institution we felt that the technique left the wound more vulnerable to complications. This lead to a system wide change in practice in which the running simple "baseball" stitch was used for chemo-ports. We sought to review our results and investigate if the patients had experienced a reduction in wound dehiscence and overall wound complications.
Objectives: To review the outcomes at our institution for the past 4 years in regards to wound related complications after chemo-port placement. We hypothesized that by using a simple running skin closure technique during chemo-port placement the rate of wound dehiscence and overall wound complication could be significantly decreased.
Design/Method: IRB approval was obtained and patients < 18 years who received a tunneled central line with port from June 2012 to April 2016 were analyzed. Data collected on patients included patient demographics, skin closure type, and wound complications within 30 days. Chi-square was performed to examine the univariate association with skin closure technique and wound dehiscence. Logistic regression was performed examine the multivariable association between skin closure type and wound dehiscence and to compute odds ratios.
Results: There were 259 ports placed in this cohort: 125 used running simple skin closure technique, and 134 used the subcuticular skin closure. Patients were found to not have any difference in rate of dehiscence or overall wound complications based on gender, age, location of port, or use of steroids or chemotherapy within 1 week of port placement. When compared, only 1 case (0.80%) in the running simple group vs 10 cases (7.46%) in the subcuticular group experienced a wound dehiscence [unadjusted OR=14.07 (1.69, 116.99) p = 0.0144]. When comparing overall wound complications the running simple group had 3 (2.4%) versus 12 (8.96%) in the subcuticular group [unadjusted OR=4.78 (1.27, 17.94) p = 0.0203]. When adjusting for port number both dehiscence and overall wound complications remained statistically significant.
Conclusion: We conclude that the running simple skin closure for chemo-port placement has superior outcomes in regards to prevention of dehiscence and overall wound related complications when compared to the subcuticular technique.

Poster # 810

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY IN PEDIATRIC PATIENTS: RISK FACTORS IDENTIFIED BY RESTROSPECTIVE REVIEW

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common complication among pediatric cancer patients and survivors. The incidence of CIPN can be 35 – 50% in patients with acute lymphoblastic leukemia. Limited understanding of risk factors and effective means to identify and evaluate CIPN within pediatric patients results in under diagnosis and under treatment.

Objectives: We sought to characterize the onset, severity and course of motor and sensory CIPN associated with several commonly used chemotherapy drugs to identify risk factors. We hypothesized that key influences would include the therapy design as well as intrinsic characteristics of the host.
Design/Method: A retrospective chart review involving all newly diagnosed pediatric (ages 2-21) cancer patients at the Maine Children's Cancer Program from 1997-2012 was undertaken. Key variables collected from each patient included: age, sex, height, weight, diagnosis (type and stage), chemotherapy regimen, and the onset and duration of motor and/or sensory neuropathy. The severity of motor and sensory neuropathies were assessed using the Modified Balis Score(MBS) and the Common Terminology Criteria of Adverse Effects(CTCAE) at 3 month intervals from the beginning of the chemotherapy to one year post treatment completion.
Results: Three hundred and forty patients (178 males, 162 females) were eligible for analysis. Of those, 95 individuals were between 2-5 years old, 83 between 6-10 years old, 114 between 11-15 years old, and 48 between 16-21 years old. We found that the presence and duration of motor neuropathy was significantly correlated with patient age ($p = 0.0018$) and chemotherapy drug classes ($p = 0.0194$). Particularly, age less than 15 years and the combined use of vinca alkoid (VA) and platinum based chemotherapeutic agents were positively associated with earlier onset and increased prevalence of motor neuropathies but not sensory neuropathies. The total number of CIPN drugs was found to be a significant predictor of the severity score for sensory neuropathy at 3 ($p = 0.001$) and 6 ($p = 0.039$) months and for motor neuropathy at 3 ($p < 0.001$), 6 ($p = 0.000$), and 12 ($p < 0.001$) months of treatment. CIPN drug class (VA and platinum agents) significantly correlated with only the severity of motor neuropathy ($p < 0.001$). In addition, patients' age and gender are significantly associated with CIPN severity ($p < 0.05$).
Conclusion: Our data suggest significant predictive values of patients' age, gender, drug classes and number of CIPN drugs used regarding the development and severity of CIPN, particularly chemotherapy-induced motor neuropathy.

Poster # 812

CLINICAL AND LABORATORY PARAMETERS ASSOCIATED WITH SEVERE RSV INFECTION IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH UNDERLYING MALIGNANCY

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Background: Progression of respiratory syncytial virus (RSV) infection from upper (URTI) to lower respiratory tract infection (LRTI) causes significant morbidity and mortality in oncology patients and hematopoietic cell transplant (HCT) recipients. Few studies have defined the clinical and laboratory factors associated with LRTI progression and use of RSV-directed therapies like aerosolized ribavirin and palivizumab in this population.
Objectives: Primary objective was to identify clinical and laboratory variables associated with RSV progression from upper to lower RTI. Secondary objectives included evaluating: (a) the influence of RSV infection on therapy-related complications, including delays in chemotherapy; and (b) viral-associated end organ dysfunction and morbidity in RSV+ patients.
Design/Method: Single-center, retrospective cohort study of oncology and HCT patients with

laboratory-confirmed RSV infection (+RSV antigen or PCR detection from nasopharyngeal, NP, or bronchoalveolar lavage, BAL, specimens) between 1/1/10 -12/31/15. Clinical, diagnostic, treatment, and outcome data were collected. Statistical analyses were performed using non-parametric methods.
Results: RSV infection occurred in 62 patients (54 Oncology, 8 HCT) at a median age 5.1 years (0.4-22.7 years). Patients were mainly hospitalized (40%) males (38, 61%) with acute leukemia (37, 60%). RSV detected by PCR (N=7, 11%; median cycle time at RSV diagnosis 22.7, 18.1-27.2) or antigen (55, 89%) from all NP and BAL specimens. At the time of RSV infection, 51 (82%) patients presented with URTI and had median ANC 1980 (0-19,680) and median ALC 569 (0-12,138). Of the 11 (18%) patients whom progressed to LRTI, 5 required ICU care (4 mechanical ventilation, 1 ECMO). Patients with LRTI were significantly younger than patients with URTI [median age 2.6 (1.35-7.87) vs 5.5 (0.38-22.67) years, p=0.025]. Median ANC or ALC, including profound lymphopenia (ALC<300), were similar between the patient groups. Twenty (33%) RSV+ patients had additional co-infections (16 respiratory viruses, 3 bacteremia, 3 invasive fungal, 4 other), and 11 patients had concomitant RSV and rhinovirus 8 (47%) or adenovirus 3 (18%). Of 41 RSV+ oncology patients scheduled for chemotherapy, 16 (39%) experienced chemotherapy delay due to neutropenia. Profound lymphopenia was similar in patients with and without therapy delay (p=0.148). No co-morbid effects or end-organ dysfunction noted after 30 days post-infection. Both palivizumab and ribavirin were administered to 9 (15%) RSV+ patients, and only one (2%) patient received ribavirin. Aerosolized ribavirin and palivizumab did not prevent progression to LRTI.
Conclusion: Patients with LRTI were younger than those with URTI in this immunocompromised pediatric population. No clinical or laboratory data predicted progression from upper to lower RTI.

Poster # 814

SAFE TRANSFUSION PRACTICES FOR CHILDREN UNDERGOING THORACO-ABDOMINAL RESECTION FOR ADVANCED NEUROBLASTOMA

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Background: Though large randomized, controlled studies have documented the safety of restrictive hemoglobin thresholds (hemoglobin < 7g/dL) in critically ill children, the thresholds at which critically ill children are transfused continues to vary. Children following prolonged surgical procedures may be at risk of hemodynamic instability post-operatively that leads providers to transfuse red blood cells more liberally.
Objectives: To determine if a restrictive pre-transfusion hemoglobin threshold compared to a liberal transfusion threshold changes outcomes in children with advanced neuroblastoma undergoing thoraco-abdominal resection.
Design/Method: Retrospective chart review of 200 patients admitted to the New York Presbyterian-Weill Cornell pediatric intensive care unit following thoraco-abdominal resection for neuroblastoma between 2007-2014. Pre-operative variables and intra-operative variables were collected to control for disease severity and surgical complications. Primary post-operative

outcomes were length of intensive care unit stay, length of mechanical ventilation, and length of vasoactive medication use.
Results: Of the 200 patients, 80 were transfused post-operatively. Of those patients, 21 were transfused for hemoglobin < 7 g/dL and 59 were transfused for hemoglobin > 7 g/dL. There were no significant differences in the disease severity or surgical complications of these two groups of patients, indicated by the pre-operative or intra-operative characteristics. There was no significant difference in post-operative length of intensive care unit stay ($p = 0.45$), length of mechanical ventilation ($p = 0.5$), or length of vasoactive medication use ($p = 0.27$) in patients in the restrictive transfusion category. There were no mortalities in either group.
Conclusion: Blood transfusions in critically ill children following thoraco-abdominal resection for neuroblastoma can be undertaken at a restrictive hemoglobin threshold (< 7 g/dL) without significantly worse outcomes in the intensive care unit.

Poster # 816

THE MOONSHOT INITIATIVE AND ITS IMPACT FOR PEDIATRIC ONCOLOGY

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Background: During the 2016 State of the Union Address, United States President Barack Obama announced the establishment of a "Cancer Moonshot" to advance cancer research. As part of this initiative, there is an increased focus on improving the efficacy of clinical research. One such measure of improving clinical research is the application of the Pragmatic–Explanatory Continuum Indicator Summary (PRECIS-2) tool to distinguish explanatory versus pragmatic clinical trials across 9 different domains. In pediatric oncology, the Children's Oncology Group (COG) exists as the world's largest, collaborative children's cancer research entity that encompasses many of these domains. We analyzed all 152 phase III clinical trials in the COG database by utilizing the PRECIS-2 tool to determine the number of COG trials that were consistent with pragmatic clinical trials.
Objectives: To determine the number of COG phase III clinical trials that met the PRECIS-2 criteria for pragmatic clinical research.
Design/Method: Utilizing the COG database, we identified 152 phase III clinical trials. The protocols for each of the trials were reviewed according to the following domains: eligibility, recruitment, setting, organization, flexibility in delivery, flexibility in adherence, follow-up, primary outcome, and primary analysis. Each of the criterion was scored on a yes-or-no scale to determine if a trial met the criterion identified in the domain.
Results: Out of 152 phase III clinical trials identified on the COG website, we found that 149 clinical trials (98%) met all 9 of the criteria as outlined by PRECIS-2 for pragmatic clinical trials. We found that the 3 clinical trials which did not meet all the PRECIS-2 criteria did not meet the primary outcome criterion in being directly relevant to trial participants.
Conclusion: Nearly all of the COG phase III clinical trials meet the criteria for pragmatic clinical research. The clinical trials that did not meet the standard of pragmatic research had primary outcomes that were reflective of supportive care and not considered part of standard care. In the United States, 90% of children with cancer are seen at COG institutions. Current treatment paradigms are derived from therapy identified in prior trials that serves as the standard

arm of subsequent phase-III trials. The COG has merged evidence-based care that is accessible to all patients with well-designed clinical research to deliver optimum therapy and serve as a model for pragmatic clinical trials.

Poster # 818

PATIENT AND FAMILY PERSPECTIVES ON THE WILLINGNESS AND REASONS FOR PARTICIPATION IN PEDIATRIC CANCER RESEARCH

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Background: Advances in pediatric cancer treatment have been possible in part due to increasing understanding of the molecular biology of these diseases at diagnosis. Historically, clinicians were reluctant to include children in research studies that require serial attainment of biological specimens. Recent studies suggest adolescent patients and their parents are willing to participate in biological research studies, with or without direct benefit, yet no studies examined this for younger children. Understanding patient and family perspectives regarding participation in studies utilizing invasive procedures during therapy will better guide future study design.
Objectives: Evaluate the willingness of patients and patient caregivers to participate in research studies that require attaining additional biological specimens, and how that willingness is associated with the invasiveness of testing or with direct patient benefit. 2) Collate patient and caregiver views on medical research, and on reasons for or against participation in invasive research studies.
Design/Method: Single institution survey assessing 1) English-speaking pediatric cancer patients treated at NCH, aged ≥ years and 2) caregivers of such patients of any age. The survey was designed to study willingness to participate in biological studies of increasing invasiveness, with potential direct patient benefit or for research study only. Surveys completed via REDcap and facilitated by study member onsite. Psychologist and educational specialists reviewed surveys for ease of understanding and content. Data analysis is primarily descriptive. Differences in responses between patient and their caregiver was explored using non-parametric statistics.
Results: Caregivers tend to be more willing to have their child participate in medical research and felt being part of research was no different than seeing their regular doctor. Majority of families responded that they would be willing to donate peripheral blood samples, including isolation of circulating cells. Caregivers stated they would not be willing to obtain additional biopsies of tumor. Preliminary results suggest families would be less willing to donate tumor samples without direct benefit to their child.
Conclusion: Patients and caregivers expressed a willingness to participate in research studies involving biological specimen acquisition, with some variation based upon invasiveness of procedures and severity of disease. With this data, families less likely to biopsy tumor sites would at least be willing to donate blood to isolate circulating tumor cells, however more education for families on limited risks of minimally invasive techniques to obtain specimens may be warranted. Additional studies and research are needed to further evaluate patient and family willingness to participate in pediatric cancer research.

Poster # 820

PREFERENCES FOR RECEIVING TEST RESULTS AND PATIENT PORTAL USE IN PEDIATRIC ONCOLOGY CARE: A QUALITATIVE EXPLORATION

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Background: Management of pediatric cancer requires frequent laboratory and radiology testing to monitor treatment response and disease status. Caregivers of pediatric oncology patients rely heavily upon this information and anxiously await results. Online patient portals provide caregivers with direct, unlimited access to their child's medical records including test results. Test results may appear in the portal before review by a physician. Little is known about how caregivers of children with cancer prefer to learn about test results and what influence patient portals may have.
Objectives: To assess preferred methods for result acquisition and use of patient portals among caregivers of children with cancer.
Design/Method: Qualitative, semi-structured, one-on-one interviews were conducted with 15 caregivers of children with cancer (8 solid tumors; 5 leukemia/lymphoma; 2 brain tumors) currently on treatment (diagnosed 0.25 to 5 years prior). Open-ended questions explored preferences for test result acquisition and knowledge/use of portals. Interviews were digitally recorded, transcribed, and analyzed by two researchers using a modified grounded theory approach until saturation of themes was achieved.
Results: Result acquisition: Universally, caregivers wanted to learn results "as soon as possible" to decrease "worry" or "anxiety". Accepted methods of delivery included "in person", phone, email, or portal. Caregivers sometimes had different preferences (i.e. in person versus telephone) based on the kind of test and anticipated outcome (i.e. stable versus progressive disease). All caregivers wanted their physician to have reviewed the results. Many wanted a printed copy "to have as a record", "read themselves", or facilitate family communication, though some found the printed copy too "complicated" to read.Use of portal: All participants had internet access. Ten used the portal "often"/"sometimes" for checking test results. Perceived advantages included getting results "fast", visualizing trends, and "keeping a record". Disadvantages included misunderstanding results with nine endorsing that electronic results are "confusing" and at times cause distress. Many use Google in attempting to understand terminology. Six reported viewing results via the portal prior to being informed by the care team, sometimes creating concern.
Conclusion: Caregivers wanted test results as soon as possible and recognized the portal as a potential mechanism. Many utilized the portal regularly with some viewing results prior to care team disclosure. Misunderstanding the language used in reports sometimes created unnecessary distress. This study provides insight into the urgency of understanding patient portal use and its effect on clinical care and outcomes especially as patient portals become more ubiquitous.

Poster # 822

ESTIMATING POPULATION LEVEL FAMILY COSTS OF AN OUTPATIENT ENCOUNTER

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Background: Despite evidence of the financial burden of childhood complex diseases on families, practical consideration of this burden is difficult. Understanding the relationship between repeated encounters with the medical system needed for treatment for cancer or hematologic diseases and family travel costs, lost wages, and medical co-pays is necessary. We hypothesize that costs of any single encounter will be similar across a population, affected by socio-demographic factors, and independent of diagnosis.
Objectives: Assess the variation of family costs associated with an outpatient encounter at a single hematology/oncology clinic.
Design/Method: We performed a cross-sectional survey of one caregiver for each patient checking into Texas Children's Cancer and Hematology Center outpatient clinic for one week (Monday-Friday). The survey consisted of 28 multiple choice and open ended questions designed to elicit family burden for that day's encounter around co-pays, food, travel, and time. Co-pays and food costs were self-reported. To estimate travel costs, families were asked for home address, mode of transportation, and if they were paying for parking. Distance from home to clinic was derived using Googlemap. A cost-per-mile of $0.53 was applied for car travel, $2.50 per person for public transportation. To estimate lost wages, the median earnings for the respondent's census tract, gender, race, and employment status were applied to all time in travel and clinic.
Results: A total of 278 surveys were completed (72% response rate), mostly (76.9%) by mothers. Nearly 50% were Hispanic and 25% preferred the Spanish survey. Cancer diagnoses were more common (60.8%) than hematologic. Only 19.4% had a co-pay with that visit, median of $42.50 (range $5 to $500). Caregivers expected to pay a median of $20 ($0 to $100) for food. The median cost of travel associated with each encounter was $33.03 ($5 to $1,782.52). The median indirect cost of lost wages was $49.97 ($6.05 to $543.86). Across the population, the median cost of an outpatient encounter was $127.03 ($25.20 to $1811.05). For the 23% of families living >40 miles from clinic, the median encounter cost was $237.12. Total encounter cost was not significantly associated with diagnosis, race/ethnicity, or insurance.
Conclusion: Family-related costs of a single medical encounter were measurable across a population at a single clinic. The primary driver of cost was distance from home to clinic. Investigations of inpatient costs and survey generalizability are needed. Population-based estimates of medical encounter costs may increase inclusion of the family's perspective into medical decisions.

Poster # 824

LONGITUDINAL SUBSPECIALTY CLINIC FOR PEDIATRIC RESIDENTS: ENHANCING PREPAREDNESS FOR FELLOWSHIP THROUGH CONTINUITY AND MENTORSHIP

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Background: Recent changes in graduate medical education prompted the Council of Pediatric Subspecialties (CoPS) to address the preparedness of residents entering fellowship. Based on a widely distributed survey, they found that 54% of fellowship program directors believed residents were not prepared for fellowship. CoPS recommended experiences to enhance fellowship preparedness such as longitudinal subspecialty clinic, increasing patient exposure, and faculty role-modeling. Likewise, the Accreditation Council for Graduate Medical Education (ACGME) requires that a subset of resident experiences be individualized based on career plans and allows for a subspecialty continuity clinic in the third year of residency. To address the recommendations above, we developed a curriculum for residents to participate in a subspecialty continuity clinic in their final year of training.
Objectives: To evaluate the impact of a subspecialty continuity clinic experience for pediatric residents through a descriptive analysis of the learners' and preceptors' experiences.
Design/Method: Residents that expressed interest were required to be deemed competent by their primary care clinic preceptors. Subspecialty clinics were held half day a week throughout the final year of residency. Since 2013, twelve residents participated, with seven in hematology/oncology. Evaluative methods are ongoing and will include surveys and interviews of the residents and preceptors. Interview topics include strengths/ weaknesses of the curriculum, meaningfulness of the experience, ability to maintain continuity, and impact on career decisions. Probing questions will address themes such as autonomy, continuity, and the mentoring relationship. Transcripts of the interviews will be coded in an iterative process and themes identified.
Results: Preliminary qualitative survey results revealed positive themes such as continuity of care, clinical decision making, and mentorship. Residents felt that they established continuity and had in depth exposure to the disease process over time. They valued observing how experienced physicians approach clinical decision making, especially in unclear situations. They appreciated the mentoring relationship formed with their attending.
Conclusion: The preparedness for pediatric residents to enter fellowship has been questioned in light of recent changes to graduate medical education. Many clinical experiences in residency are focused on inpatient and acute care experience with a striking lack of continuity, even in the primary care continuity clinic. Longitudinal subspecialty clinics provide improved patient continuity, enhanced mentorship, and allow for a greater understanding of the evolution of the disease process. This is a useful framework in which to consider programmatic and curricular changes to address gaps in training and preparedness for fellowship training.

Poster # 826

CISPLATIN OTOTOXICITY IN PATIENTS WITH OSTEOSARCOMA TREATED WITH AND WITHOUT THE ORGANIC CATION TRANSPORTER 2 INHIBITOR PANTOPRAZOLE

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Background: Standard treatment regimens for osteosarcoma (OS) include cisplatin, which causes a cumulative high-frequency hearing loss by damaging cochlear hair cells. Cisplatin cellular uptake is mediated by membrane transporters including the organic cation transporter, OCT2, which is expressed on cochlear hair cells but not on OS tumor cells. The proton pump inhibitor, pantoprazole, inhibits OCT2 and selectively blocks cisplatin uptake in cochlear hair cells in animal models.
Objectives: To assess the impact of intravenous pantoprazole on cisplatin-induced high frequency hearing loss in patients with OS and compare hearing loss to a historical control population.
Design/Method: Patients with OS treated with cisplatin (60 mg/m2 on days 1&2 of cycles 1-4) plus doxorubicin and methotrexate received pantoprazole with cisplatin on cycles 1&2 or 3&4. The primary endpoint is high-frequency hearing threshold (HFHT) derived by averaging hearing thresholds (dB) at 4, 6 and 8 kHz in each ear at baseline (BL), prior to Cycle 3 (preC3), and end of therapy (EOT). A historical control group was selected from 124 patients with OS treated from 2000-2016 with audiogram data at BL, preC3 and EOT. Wilcoxon Rank Sum test was used to compare groups. In the prospective cohort, patient reported outcome (tinnitus and hearing loss) was assessed prior to each cycle.
Results: Complete data sets (BL, preC3, EOT) were analyzed for historical control (n=20, median age of 14.3 years) and pantoprazole treated (n=7, median age of 12.9 years) patients. In control patients, the median(range) HFHT in dB was 3.3(0-15) at BL, 5(0-77) preC3, and 16(0-75) at EOT. For pantoprazole treated patients, HFHT was 4.2(1.7-10) at BL, 5.8(0-52) preC3, and 32(10-58) at EOT. Change in HFHT (dB) from BL to preC3 in 3 patients who received pantoprazole during C1&2 was 40, 0.8, and 0 dB. In 4 patients who received pantoprazole during C3&4, change in HFHT from preC3 to EOT was 11, 1.7, 2.5 and 3.3 dB. At EOT, there was no difference in HFHT in patients who received pantoprazole compared to historical controls (p=0.43). All patients reported tinnitus and hearing loss at least rarely after one cycle of cisplatin and often/almost daily at EOT.
Conclusion: HFHT is an objective, continuous measure of cisplatin-induced hearing loss. In a small prospective study, pantoprazole did not prevent hearing loss in children with OS receiving cisplatin 60 mg/m2/dose x 2 days (median cumulative dose 720 mg/m2). By EOT, all patients reported tinnitus and hearing loss often/almost daily.

Poster # 828

BONE MINERAL DEFICIENCY IN THE IPSILATERAL HIP OF SURVIVORS OF CHILDHOOD LOWER EXTREMITY SARCOMAS

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Background: Childhood cancer survivors (CCS) are prevalent and experience a high burden of morbidity. Low bone mineral density (BMD) has been well-documented in this population. Among CCS, survivors of lower limb sarcomas may be at particular risk for reduced BMD due to exposure to multiple therapies that impact bone development, as well as prolonged immobilization. Low BMD has been previously described in survivors of childhood sarcomas.

We anecdotally noted a discrepancy between the BMD in the ipsilateral and contralateral hips of survivors of lower extremity sarcomas and hypothesized that the ipsilateral hip of survivors of childhood lower extremity sarcomas is at increased risk for low BMD relative to the contralateral hip and lumbar spine.
Objectives: To compare the BMD in the ipsilateral hip of survivors of lower limb sarcomas to the lumbar spine and contralateral hip.
Design/Method: This was a single center, retrospective chart review. Survivors of childhood lower limb sarcoma seen in our survivorship program between 12/2010-12/2016 and had a Dual-energy X-ray Absorptiometry(DXA) scan were eligible. Survivors' age at diagnosis, sarcoma type, chemotherapy received, type of surgery, radiation exposures and DXA Z-scores were obtained. The non-parametric Wilcoxon Signed Rank test was utilized for paired analysis for Z-scores. The mean differences between Z-scores were calculated as ipsilateral minus contralateral, ipsilateral minus spine and contralateral minus spine.
Results: Of 17 childhood lower limb sarcoma survivors, 10 (58.8%) had Osteosarcoma and 7 (41.2%) Ewing's Sarcoma. The mean age at diagnosis was 13.8 [5.6-19.1] years, and 11 (64.7%) were male. All survivors were treated with chemotherapy, 9 (52.9%) received high dose methotrexate, 15 (88.2%) underwent tumor resection with limb salvage surgery, 2 (11.8%) had transfemoral amputation and 4 (23.4%) received local radiation therapy. Fourteen survivors had Z-score measurements for the ipsilateral hip and spine. The Z-scores for ipsilateral hip were significantly lower than those for the spine (mean difference = -0.85, $p < 0.0236$). Ten survivors had Z-score measurements for the ipsilateral and contralateral hip. The Z-scores for the ipsilateral hip were lower than for the contralateral hip (mean difference = -0.69), but did not meet clinical significance ($p < 0.1133$). Twelve patients had Z-score measurements for the contralateral hip and spine. The mean Z-scores for the contralateral hip were not different from the spine ($p < 0.5571$).
Conclusion: Survivors of lower extremity sarcomas had significantly lower BMD in the ipsilateral hip relative to the lumbar spine. The fracture risk of the ipsilateral hip needs further study.

Poster # 830

VITAMIN D STATUS IN NEWLY DIAGNOSED PEDIATRIC CANCER PATIENTS: EFFECTS OF DEMOGRAPHICS, TUMOR TYPE AND SUPPLEMENTATION

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Background: Vitamin D deficiency negatively affects bone health in children. It may cause more severe sequelae in patients with cancer who are already at risk for osteopenia, vertebral fractures and avascular necrosis due to disease treatment. Previous investigations of the prevalence of vitamin D status in this patient population have given widely varying estimates. Furthermore, there are gaps in knowledge about how to improve Vitamin D status and bone health in pediatric cancer patients.
Objectives: To investigate vitamin D status in a cohort of newly diagnosed pediatric oncology

patients, examine associated demographic risk factors and assess the effect of vitamin D supplementation on Vitamin D levels.
Design/Method: We conducted a retrospective cohort study of 163 children with newly diagnosed cancer at Rady Children's Hospital from August 1, 2012 to April 30, 2015. Socio-demographics, vitamin D levels, and vitamin D supplementation data, if applicable, were obtained from the medical record. Univariate, multivariate and longitudinal models were used to determine predictors of vitamin D status at diagnosis and to follow patients' vitamin D levels over time. Vitamin D status was defined according to the Endocrine Society Clinical Practice Guideline (deficient <=20ng/mL, insufficient 21-29ng/mL, sufficient >=30ng/mL).
Results: Sixty-four percent (N=104) of patients in our cohort were either vitamin D deficient (32%;N=52) or insufficient (32%;N=52)) at diagnosis, with a mean vitamin D level of 27.5 ±12 ng/mL. Younger age (p=0.019), Non-Hispanic ethnicity (p=0.002) and female gender (p=0.008) were significant predictors of higher vitamin D levels at diagnosis in the multivariate analysis. In the longitudinal model, supplementation showed significant increase in Vitamin D levels (p<0.001). Additional longitudinal analysis showed that Hispanics had significantly lower vitamin D levels than Non-Hispanic children after supplementation (p=0.001), as did patients who were older than 10 years (p=0.024). Children with solid tumors (p=0.021) also had lower Vitamin D levels during chemotherapy treatment.
Conclusion: Vitamin D deficiency and insufficiency were common in our cohort of pediatric cancer patients. We identified several populations at high risk of vitamin D deficiency/insufficiency, particularly Hispanics, as well as males and older children. Patients with solid tumors had lower Vitamin D levels only while undergoing treatment. We hypothesize that chemotherapy regimens for solid tumors may interfere with vitamin D absorption. Our results showed that supplementation improves vitamin D levels over time. These findings should spur further research, such as prospective trials of the impact vitamin D supplementation on bone health outcomes in newly diagnosed patients, particularly in high risk populations.

Poster # 832

FOUNDATION ONE GENOMIC PROFILING AND THERAPEUTIC IMPACT

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Background: Genomic profiling of cancer may reveal complex and actionable genetic markers with potential for therapeutic intervention. Foundation One utilizes comprehensive detection protocols sensitive to base pair substitutions, insertions and deletions, copy number alterations and select gene rearrangements in 343 cancer genes and a broad range of gene fusions. Foundation One provides a streamlined tool for genomic interrogation of cancers and produces a concise, personalized set of actionable information relevant to individual patients based on their cancer's unique profile. We aim to review our institution's experience using Foundation One services to document the prevalence of actionable mutations and therapeutic impact.
Objectives: Evaluate change in health care management based on the results returned from Foundation OneEvaluate frequency of gene changes in Nicklaus Children's Hospital cancer patient population using genetic screening data completed by Foundation One
Design/Method: 27 pediatric patients age range 1.6 years to 24 years, median age of 11 years

with mode of 3 years, representing 11 unique pediatric cancer types were profiled using Foundation One 343 gene panel. 12 patients were in their primary cancer presentation at the time of profiling, while 15 were in relapse.
Results: The total number of Foundation One genomic alterations(FGAs) present in the cohort was 100, per patient alterations ranged from 0 to 30(average of 3.7). FGAs were present without therapeutic target in 8(29.6%), present with actionable therapeutic target in 15(55.5%), not present in 4(14.8%). Genes with the highest frequency of alteration TP53 (25.9%) and CDKN2 (14.8%). 3 (20%) patients were chosen for new targeted therapy. Patient 1 with primary GBM was to start crizotinib for MET amplification but did not due to insurance issues. Patient 2 with relapsed GBM received everolimus, while patient 3 with relapsed PNET received hydroxyurea, both without benefit. In a 4th patient FGAs of H3F3A K28M forced an upgrade in tumor type to GBM from ganglioglioma. 12 (80%) patients with actionable therapeutic targets did not get new therapies based on the results. Overall, just 11.1% of our total patient population had a change in management due to Foundation One profiling.
Conclusion: Foundation One genomic profiling identified many actionable targets in our patient population; however, a clinical benefit was not achieved. It may not be clinically relevant to continue using this gene panel routinely for our patients, though it is of increasingly more value as the bank of actionable alterations expands and may be helpful in refining a diagnosis and for research purposes.

Poster # 834

USE OF AN ANIMATED VISUAL NARRATIVE TO IMPROVE PATIENT CARE AND HEALTH LITERACY REGARDING FERTILITY PRESERVATION SERVICES IN A CANCER AND BLOOD DISEASES INSTITUTE

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Background: Patients with a new oncology diagnosis receive an overwhelming amount of information. They are introduced to multiple new services over a short, stressful period of time. Large volumes of new information can be intimidating and lead to low retention of information, and low utilization rates with ancillary services.
Objectives: Assess the utility and acceptance of an animated visual narrative to introduce fertility preservation services for new patients in the Cancer and Blood Diseases Institute (CBDI) at Cincinnati Children’s Hospital Medical Center (CCHMC).
Design/Method: New CBDI patients (and their parents/caregivers) who received a fertility consult were given an introduction to the service via an animated video containing introductory information about the need for fertility preservation consultation. Patients/caregivers completed a questionnaire using a Social Validity framework. The Social Validity Measure (SVM) and Social Validity Measure – Patient Version (SVM-PV) were designed uniquely for this project, based on adaptations of established Social Validity measures in the field. Patients then received the complete fertility consultation as per institutional standard of care. Clinical measures included satisfaction of service introduction method, time spent for consultation, and rate of utilization of

services. The data was analyzed using descriptive statistics (quantitative results from social validity measures; time spent introducing services; utilization of services, duration of consultation, and number of subsequent visits before decision was made about intervention).
Results: We administered the standardized introductions to 7 patients (4 female, 3 male). Social validity measures (SVM) and data were recorded for all 3 patients (> 13 yrs old) and SVM for 11 caregivers. Social validity data collected suggested participants understood the information well and were able to answer questions about it.
Conclusion: Our primary objective was to assess the acceptability of a standardized animated introduction to fertility consultation services for new patients receiving care in the CBDI at CCHMC. We found that the use of an animated visual narrative with an empathetic patient centered approach can be valuable and beneficial to patients and families. The data suggests that this approach is both acceptable to patients and families and demonstrates favorable social validity. These results will be used to standardize the introduction of fertility services with maximal social validity.

Poster # 836

IMPACT OF IgG MONITORING AND IVIG SUPPLEMENTATION ON THE FREQUENCY OF FEBRILE ILLNESSES IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS

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Background: Pediatric acute lymphoblastic leukemia (ALL) patients are immunosuppressed due to their disease and therapy and are thus at risk for infections. Some have suggested that monitoring IgG levels and giving intravenous immunoglobulin (IVIG) infusions to those with low levels may help to prevent infections. However, there have not been rigorous evaluations to determine outcomes of supplementation.
Objectives: To assess the benefit of IgG monitoring/supplementation in preventing febrile illness in pediatric ALL patients.
Design/Method: We identified all pediatric ALL patients diagnosed between 2006-2011 at Vanderbilt Children's Hospital (N=151) and assessed if they were receiving IgG monitoring/supplementation. All febrile events were captured from start of ALL consolidation through the end of 2012 and subjects were censored at time of end of therapy, death, lost to follow-up, 30 days pre-stem cell transplant or end of study period. A subject was considered standardly monitored for 30 days after an IgG level was checked and was over 500 mg/dl or supplemented with IVIG for a IgG <500 mg/dl and non-standardly monitored if not given IVIG for a IgG <500 mg/dl. Periods of monitoring and not monitoring were assessed for all subjects and outcomes are expressed as episodes per 1000 subject days and comparisons made through Poisson test.
Results: Seventy three subjects were never monitored for a median of 792 days (51,014 days total) and 78 subjects were monitored during some of their therapy (median of 1032 days, 75,329 days total). Of these, 19,447 days were monitored (16597 standardly and 2850 not-standardly) and 55,882 days were not. IgG <500 mg/dl was detected in 50 subjects on 263 occasions and

67% of the time was supplemented with IVIG. IVIG was also given 72 times for level >500 mg/dl. Total febrile illness was higher in those (6.8/1000 days) who received some monitoring versus no monitoring (5.1/1000 days) ($p<0.001$). However, in the monitored group febrile illness was 6.9/1000 days when not monitored, 6.1/1000 days when standardly monitored and 7.4/1000 days when non-standardly monitored. Febrile upper respiratory infection, culture positive blood stream infection and need for intensive care unit admission were rarer events and were not different between groups. IVIG was given 247 times to 43 subjects with a complication rate of 4.9% (2 fever, 2 nausea, 6 headaches, 1 allergy, 1 nausea/fever).
Conclusion: This data suggests that monitoring and supplementing IVIG for low IgG may have a modest reduction on febrile illness but further study is needed.

Poster # 838

BISPHOSPHONATE AS MAINTENANCE IN VERY HIGH RISK OSTEOSARCOMA

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Background: OST is the most common primary bone tumor affecting children and young adults. Patients with localized, completely resected, and a good response to induction chemotherapy have a >80% 3-year survival. However, patients with OST with a poor initial response have a 60% 3-year survival and those with metastasis at diagnosis, non-isolated lung relapse or are unresectable have a 3-year survival of 0-30%. There is currently no standard of care for such patients.Bisphosphonates are indicated for some primary bone diseases, cancer-induced bone pain, and bone metastasis. Zoledronic Acid (ZA) has been shown to reduce bone pain and bone tumor burden in several cancer subtypes including OST and has shown promise in animal models of OST and a 2008 COG feasibility study showed the safety of monthly ZA given concurrently with chemotherapy for children with OST (Goldsby, Eur J Cancer, 2013). Over the last 12 years patients with poor prognosis OST treated by us were offered a bisphosphonate as a "maintenance" drug after completion of standard therapies. In a literature review we found no studies of ZA used as maintenance for OST.
Objectives: We report our experience using bisphosphonates as maintenance in patients with poor prognosis osteosarcoma (OST).
Design/Method: We defined "High Risk OST (HRO)" as: Poor Response to Induction Chemotherapy (Group A), First Relapse Resected (Group B) – excluding late isolated resected lung nodule, and Primary Metastatic, Multiple Relapses or Unresectable Disease (Group C). We identified all patients defined as HRO from 01/01/05 to 01/01/2017 who received at least 4 bisphosphonate doses.
Results: During this period 16 of the 23 patients with HRO received at least 4 bisphosphonate doses (15-ZA, 1-aldronate), 5 were female, with a median age of 17 (7-29). The ZA dose was 2.3mg/m2 (4mg max) as in the COG safety study. The aldronate dose was 70mg weekly. Group A (n=6) received a median of 6 doses of ZA (4-7), Group B (n=5) a median of 8.5 (5-24), and Group C (n=5) median 15 (5-27). The ZA dosing interval for Groups A,B and C was 1.1,3.1, and 3.2 months respectively.Three Group C patients got concurrent bevacizumab. One patient stopped ZA because of rising creatinine. Three-year overall/progression-free survival for ALL

patients, Group A, B and C are: [0.5/0.3,0.5/0.17,0.8/0.6,0.2/0.2] respectively.
Conclusion: Our single institution, retrospective preliminary study suggests that bisphosphonates may benefit some high risk patients with OST. We are planning on opening a prospective pilot study to explore this hypothesis.

Poster # 840

ASSESSING THE ROLE OF PARENTAL HEALTH LITERACY IN PEDIATRIC ONCOLOGY

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Background: Poor parental health literacy is associated with decreased treatment adherence and poorer child health outcomes in diabetes and asthma, but this association in other pediatric diseases such as cancer remains unknown. This is particularly salient given the demanding health management responsibilities placed on parents of children with cancer, which affect treatment adherence.
Objectives: Determine the association between parental health literacy and measures of cancer care knowledge, medication understanding, and medication adherence.
Design/Method: In a cross-sectional study of parents of children with cancer receiving chemotherapy in Vanderbilt's pediatric oncology program, we evaluated health literacy and its effect on cancer knowledge, medication understanding and adherence. Among English-speaking primary caregivers of children 17 years and younger, we administered the Newest Vital Sign (NVS), Parental Health Literacy Activities Test (PHLAT), Pediatric Oncology Parent Knowledge Assessment Tool (POPKAT), Medication understanding questionnaire (MUQ), and 4-item Moriskey Medication Adherence Scale (MMAS-4). The NVS and PHLAT are validated measures of health literacy. The POPKAT is a 12-item questionnaire regarding pediatric cancer care knowledge, such as when to call for a fever or chills. The MUQ and MMAS-4 are validated measures of medication understanding and adherence. For each literacy score (NVS and PHLAT), we fit simple regression models with POPKAT score as the response variable and parental education and time since diagnosis as additional covariates. Likelihood ratio test was conducted to determine if interaction between health literacy and education was necessary. The analysis was repeated treating both the medication understanding and medication adherence scores as response variables.
Results: Among 97 parents (98% participation rate), median time since diagnosis was 243 days. Most participants were mothers (80%). Over 50% were privately insured. Ninety-four percent reported completion of high-school-level education. NVS was associated with cancer knowledge as measured by the POPKAT; with every 1-point increment in NVS, the POPKAT score increased by 0.31 (95% CI: 0.03, 0.59; p-value=0.030). Neither parental education nor time since diagnosis improved the model fit. Neither literacy score was associated with medication understanding or adherence. The PHLAT was not associated with cancer knowledge.
Conclusion: These findings suggest an association between poor parental health literacy and cancer care knowledge, independent of education and time since diagnosis. Additional studies are necessary to further explore this association, and to inform literacy-targeted interventions for at-risk families.

Poster # 842

TREATMENT RELATED HYPOTHYROIDISM IN CHILDHOOD MEDULLOBLASTOMA: IS THIS PREVENTABLE?

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Background: Hypothyroidism is a well-recognized, post-radiation complication in children > 3 years old (yo) treated for medulloblastoma (MB). Despite decreased neuroaxis radiation in standard risk (SR) patients, permitted by chemotherapy, photon radiation-related hypothyroidism is unimproved at 55-70%. While thyroid stimulating hormone (TSH) suppression during radiation may prevent treatment-related hypothyroidism, supportive data are scarce.
Objectives: To determine if TSH suppression by prophylactic levothyroxine administration during radiation reduces subsequent treatment-related hypothyroidism in children with MB.
Design/Method: Retrospective review of MB patients >3 yo, serially diagnosed and treated at this institution between 2004-2015 was conducted comparing hypothyroidism in children treated with prophylactic levothyroxine during radiation (Treatment) (Harriet Lane Handbook) versus those not treated (Control). Most controls were diagnosed before cases-though uniformity of all other treatment considerations likely allows unbiased comparison. Using Children's Oncology Group guidelines, cumulative radiation doses were 54-55.8 Gy-tumor bed, and 23.4Gy and 36 Gy-neuroaxis in standard (SR) and high risk (HR) patients, respectively. Serial serum free thyroxine and thyroid stimulating hormone measurements were obtained prior to and following treatment completion. Kaplan-Meier estimation and Cox proportional hazards modeling were performed in SAS ver. 9.4. Only patients treated with photon radiation, and without genetic syndromes, relapse, central hypothyroidism, or early death from disease were analyzed.
Results: Seven patients diagnosed after 2014 (5 SR, 2 HR) and treated with prophylactic levothyroxine were compared for hypothyroidism-free survival to 17 control patients (15 SR, 2 HR). Of the SR patients at 22 months follow-up (maximum treatment group follow-up time, ages 3- 14 yrs), 3/5 (60%) of levothyroxine-treated patients developed hypothyroidism compared to 7/15 (47%) not having such treatment. Of HR patients, 50% (1/2) in both the Treatment and Control groups had developed hypothyroidism at this same timepoint. Median time to hypothyroidism onset after radiotherapy was 1.75 yrs (95% CI 1.00-1.83 yrs) and 1.92 yrs (95% CI 1.33-inf. yrs) in treatment and control SR groups, respectively. Cox proportional hazards modeling of the 20 SR patients found neither age nor gender to be significant covariates-inclusion did not alter finding of no significant difference between time to hypothyroidism in treated and control patients (p=0.20)
Conclusion: No evidence of decreased treatment-related primary hypothyroidism in SR patients was observed following levothyroxine administration during radiation in children with MB in this limited-size institutional study. These findings differ from previously published data. Prospective randomized trials investigating levothyroxine administration during radiation on subsequent development of treatment-related hypothyroidism are warranted.

Poster # 844

FACTORS INFLUENCING THE LENGTH OF STAY IN FEBRILE PEDIATRIC ONCOLOGY PATIENTS

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Background: Prolonged Length Of Stay (LOS) predisposes oncology patients to multidrug-resistant infections thereby delaying their chemotherapy and compromising health outcomes (1). Moreover, it adds significant economic burden and adversely affects the health care resources (2).Understanding the factors affecting prolonged LOS is crucial for enhancing quality of care (3).
Objectives: To delineate the factors that impacts the LOS in febrile Pediatric Oncology patients.
Design/Method: This is a retrospective analysis of febrile oncology patients admitted between Jan 2015 and Nov 2016 to a tertiary healthcare center. Data for each admission was collected from the hospital EMR and analyzed for the impact on LOS. Multiple logistic regression analysis was used to find predictors for prolonged LOS (more than 72 hours), after adjusting for potential confounders. Values are reported as Odds Ratio (OR) and 95% Confidence Intervals (CI). All analysis was performed using SAS 9.4.
Results: Admissions were divided into two groups based on their LOS. Forty-two out of seventy four total admissions had prolonged LOS. Study groups had equally distributed baseline characteristics including age, gender, diagnosis, ANC and prophylactic G-CSF. Univariate analysis showed positive blood cultures and antifungal administration were statistically significant for prolonged LOS. ($p=0.01$ and $p=0.02$) Multivariate analysis showed odds of having prolonged LOS were six times higher if blood cultures were positive (OR=6.43, CI 1.29-32.12, $p=0.02$) and three times higher with antifungal medication administration (OR=3.06, CI 1.08-32.23, $p=0.04$). Prolonged LOS group had more positive cultures from other sites like throat, urine, wound or ear swabs, though not statistically significant. This group also had elevated CRP, low bicarbonate, low albumin and Clostridium difficile colitis without reaching statistical significance.
Conclusion: Having positive blood cultures or requiring treatment with antifungal medications can be used as predictors for prolonged LOS among Pediatric Oncology patients admitted with fever.References: 1.Sutter DE, Infect Control Hosp Epidemiol, 2011 2.Schilling MB, Exp Ther Med, 20113.Rosa, PLoS ONE, 2014

Poster # 846

ANALYSIS OF COMPLICATIONS AND FAILURE MODE OF PEDIATRIC CENTRAL VENOUS CATHETERS

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Background: Placement of a central venous catheter (CVC) is a common procedure in children.When CVCs cause complications, it magnifies the complexity of their already difficultcourse.
Objectives: The goal of this study is to compare the usage of different types of CVCs -internal jugular (IJ) vs. subclavian (SC) - in pediatric patients to find which has theleast rate of mechanical, infectious, or thrombotic complication rates.
Design/Method: This is a single center retrospective chart review of patients 0-18 years, who received CVC placement as part of routine clinical care between January 2010 and September 2015. Clinical, procedural and complications data were collected on CVC line placement at our institution. The radiology information systems database and surgery department procedures database were searched to find all procedures for CVC placement.
Results: Eighty-five subjects had a total of 143 CVC placements at our institution during a five-year time frame were included in our analysis. More than half of the subjects were male (n=43, 57.3%) and the average age was 6.9 (± 6.2). Majority of CVC were placed for chemotherapy (n=70, 49%) and 17 (11.9%) for chronic infusions. IJ vein was accessed in 87 (60.8%) of the cases and 56 (39.1%) used the SC vein. All subjects had documented removal of CVC line with majority 61 (42.6%) removed for complication (SC group n=32, 57.1%, IJ group n=29, 33.3%) during the course of treatment. A multivariable modified Poisson regression with robust error variance was performed and SC was associated with higher risk of complication removals (RR 1.71; 95% CI 1.12 - 2.61, p = 0.013) and remained significantly higher after adjusting for patient age, number of lines placed, and chronic infusions (RR 1.99; 95% CI 1.34 - 2.96, p = 0.001).
Conclusion: While the initial complication rates for CVC placement are low, the majority are eventually removed for complications. Our data suggests that IJ access for CVC placement has a lower complication rate than SC, which may affect chronically ill pediatric patients and their ability to receive necessary interventions in their future.

Poster # 848

VALIDATION OF A NAUSEA ASSESSMENT SCALE IN PEDIATRIC ONCOLOGY PATIENTS

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Background: Chemotherapy induced nausea and vomiting (CINV) is a well-known adverse effect of most chemotherapy treatment protocols, and can negatively impact a patient’s quality of life during therapy. Despite the extensive body of literature on antiemetic therapies, there exist few validated tools to objectively assess nausea, and even fewer so in the pediatric population. One such tool is the Baxter Retching Faces (BARF) scale developed by Dr. Amy Baxter and colleagues, but this scale has not yet been validated in the pediatric oncology population.
Objectives: The primary objective of this study is the validation of the BARF scale in pediatric oncology patients actively receiving chemotherapy. The secondary objective is to conduct a subgroup analysis of the BARF scale in pediatric oncology patients evaluating levels of chemotherapy emetogenicity, diagnosis, age, and gender.
Design/Method: Pediatric patient’s age 4 to 18 years receiving active treatment for a malignancy at Nationwide Children's Hospital (NCH) are eligible for inclusion. Patients for

whom English is not the primary language, or those otherwise unable to communicate nausea or pain severity, are excluded from the study. To assess the primary objective and provide convergent and discriminant validity, patients are presented with two visual analog scales (VAS) and two faces scales (BARF for nausea and Wong-Baker for pain) along with a brief script explaining the exercise. Patients are asked to first identify their nausea and pain on a VAS scale and then identify the corresponding face on the BARF and Wong-Baker scale, respectively. Spearman ρ correlation coefficients will then be calculated for each pair. We anticipate a strong correlation within the two nausea scales (VAS and BARF) and two pain scales (VAS and Wong-Baker), but weak correlations within the two VAS scales (VAS-nausea and VAS-pain) and two faces scales (BARF and Wong-Baker).
Results: In progress
Conclusion: An overarching goal of the validation of the BARF scale in pediatric oncology patients is to support the implementation of an objective nausea assessment tool in this vulnerable population. With the adoption of a uniform nausea assessment, nurses and clinicians will be better informed to make antiemetic treatment decisions in the clinical arena and patients will hopefully receive better nausea control. If validated, we plan to use this tool at our institution to prospectively evaluate the performance of a standardized institution based antiemetic guideline.

Poster # 850

RISK FACTORS AND INCIDENCE OF INFECTION DURING INDUCTION CHEMOTHERAPY FOR HIGH RISK NEUROBLASTOMA

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Background: High-risk neuroblastoma is an aggressive disease with high recurrence rates and overall poor outcomes. Treatment begins with an induction phase comprised of intense multi-agent chemotherapy with the goal of maximally reducing tumor bulk at primary and metastatic sites. Given the high intensity of chemotherapy required in induction, neutropenic fever and infectious complications are common.
Objectives: To describe the incidence, types of infections, and risk factors for infection in high-risk neuroblastoma induction chemotherapy.
Design/Method: We performed a retrospective review of infection related complications in 76 children treated for high-risk neuroblastoma at Texas Children's Hospital between January 1, 2002 and January 1, 2015. The electronic medical record was reviewed for demographic information, diagnostic information, presence of febrile neutropenia (FN), and presence and type of bacterial and fungal infections in each induction chemotherapy cycle. Additional potential risk factors for infection including type of venous access and need for total parenteral nutrition (TPN) were also recorded.
Results: There were 72 episodes of serious bacterial or fungal infection in 76 patients who underwent a total of 365 cycles of induction chemotherapy. All chemotherapy was followed by prophylactic myeloid growth factor. Fifty-eight percent of patients developed one or more serious bacterial or fungal infections during induction chemotherapy, and 25% of patients had two or more infections. Each cycle, approximately 20% of patients had an infection. The most

common infection was bacteremia, with gram-positive organisms (69%) being more common than gram-negative. The rate of fever and neutropenia was high with 75% of patients having at least one admission for FN over 5 cycles, and 30% of patients developing FN each cycle. Female patients were more likely to acquire an infection during induction chemotherapy (RR 1.4 p=0.009), as were patients under age three years at diagnosis (RR 1.4, p=0.007). When limited to blood stream infections only, patients with an external central venous catheter were 2.13 times more likely to develop infection compared to those with a totally implantable venous access device (p=0.007). Finally, need for TPN was associated with slightly higher risk of blood stream infection (p=0.045).
Conclusion: The incidence of serious bacterial and fungal infections during induction chemotherapy for high-risk neuroblastoma is high, with more than half of patients hospitalized for at least one infection during this time period. However, mortality from these infections is low. Female patients, children under 3 years at diagnosis and those with external central venous catheters were at highest risk of developing infections.

Poster # 852

DEVELOPMENT OF THE DAY 100 TALK: CURRENT PROVIDER COMMUNICATION PRACTICES AND REACTIONS TO A CONVERSATION GUIDE

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Background: The initial months of childhood cancer treatment may be a critical communication window to ensure family-centered cancer care. We proposed the "Day 100 Talk," (D100) a novel communication intervention consisting of a nine-question conversation guide, with two primary goals: to enhance family illness understanding, and to enhance the oncologist's understanding of family context, thereby facilitating parent adaptation and engagement. However, oncology provider communication strategies utilized during the first 3-6 months of childhood cancer care may or may not align with the use of a conversation guide.
Objectives: To explore 1) oncology providers' communication strategies with continuity patients during the first 3-6 months of childhood cancer care and 2) provider reaction to D100 concept and the nine-question conversation guide.
Design/Method: We conducted in-depth interviews and a focus group with oncology providers at a large pediatric cancer center to explore 1) current communication strategies during the first 3-6 months of childhood cancer care and 2) provider reactions to D100 concept and conversation guide format.
Results: Eleven providers (4 fellows/first-year instructors, 4 attending physicians, and 3 nurse practitioners) participated in in-depth interviews and/or a focus group. Oncology providers reported several communication strategies, including: 1) repeating illness information, 2) "listening for" families' cancer-related beliefs and values rather than directly probing, 3) exercising professional judgment to anticipate families' communication needs, and 4) focusing communication on perceived areas of expertise (e.g. chemotherapy side-effects) rather than those of relative inexpertise (e.g. emotional coping, spirituality). Oncology providers reported that D100 had the potential to augment their current practices by enhancing their understanding of family context. Only one of the 11 providers interviewed objected to the conversation guide

format. However, providers noted that they worried about the possibility of "Opening Pandora's Box" by exploring family context. Providers reported greater comfort with exploring family context in the context of an interdisciplinary cancer care team.
Conclusion: Based on oncology provider feedback, D100 was re-conceptualized as an interdisciplinary conversation between the family, oncology provider, and a psychosocial clinician, to ensure complementary expertise and optimally meet families' potential communication needs. A feasibility pilot study of D100 is currently underway. The novel 3-part D100 IOT tool and pragmatic training program are intended to be scalable nationally, and have high potential to promote family adaptation and engagement in cancer care.

Poster # 854

SAFETY OF DISCHARGE FOR CHILDREN WITH CANCER AND FEBRILE NEUTROPENIA USING ABSOLUTE NEUTROPHIL COUNT THRESHOLD VALUES AS A SURROGATE MARKER FOR ADEQUATE BONE MARROW RECORVERY

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Background: While there is consensus that pediatric cancer patients with fever and neutropenia (F&N) require inpatient hospitalization and broad-spectrum parenteral antibiotics while evaluating for invasive bacterial disease, there is less clarity regarding parameters whereby such patients can be safely discharged off antibiotics. The most recent pediatric-specific guidelines in 2012 suggest a post-nadir absolute neutrophil count (ANC) greater than 100/uL as a reasonable value.
Objectives: To identify risk of recurrent infection based on discharge ANC following hospitalization for F&N to establish an appropriate threshold for safe discontinuation of empiric antibiotics and discharge to home.
Design/Method: We performed a retrospective review of 350 episodes of F&N in 178 pediatric cancer patients admitted to Vanderbilt Children's Hospital between 2007 and 2012. Inclusion criteria included presence of a central venous line, no empiric antibiotics within seven days preceding the F&N episode, afebrile for > 24 hours at discharge and no identified bacterial or fungal infection. We assessed outcomes at seven days post-discharge in the cohort, divided into subgroups based on ANC at discharge with subgroups of ANC < 100/uL (n = 14), ANC = 100-199/uL (n = 51), ANC = 200-499/uL (n = 125), ANC >= 500/uL (n = 160).
Results: Overall seven-day readmission rates were low (n = 17, 4.6%). Patients with discharge ANC of 100-199/uL (n = 2, 3.9%), 200-499/uL (n = 5, 4.0%), and >=500/uL (n = 8, 5.0%) had similar rates. The occurrence of new fever and the need to restart empiric antibiotics were also not different between these subgroups. Notably, patients with a discharge ANC < 100/uL (n = 2, 14.3%) had higher readmission rate than the other groups, but this difference did not reach statistical significance due to the lower number of patients in this subgroup. One patient in each ANC subgroup was found to have a new bacterial bloodstream infection upon readmission, with the exception of the ANC 100-199/uL subgroup. In the subset of 217 patients with a post-nadir ANC>=100/uL and without further indication for ongoing hospitalization apart from neutropenia, 94 (43.3%) patients remained hospitalized while awaiting further ANC increase, resulting in 126 additional days of hospitalization.

Conclusion: Our results provide further evidence that a post-nadir ANC > 100/uL is a safe recommendation as the threshold value for evidence of bone marrow recovery, empiric antibiotic discontinuation, and discharge home. Adherence to this threshold could eliminate unnecessary hospital days and potentially reduce nosocomial morbidity.

Poster # 856

UTILITY OF PROCALCITONIN CONCENTRATION IN THE EVALUATION OF PEDIATRIC ONCOLOGY PATIENTS HOSPITALIZED WITH FEVER

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Background: In pediatric oncology patients hospitalized for fever, blood cultures do not always yield positive results making it difficult to discriminate between infectious etiology, inflammatory response and other causes. The presence of fever with or without neutropenia is often a trigger to initiate antibiotic therapy which continues well after investigations yield negative results for infection and as long as fever persists. Few studies have examined the utility of serum procalcitonin (PCT) as a discriminatory marker of bacteremia/sepsis in pediatric oncology patients.
Objectives: Evaluate PCT levels as a discriminatory marker of bacteremia/sepsis in pediatric oncology patients admitted with fever.
Design/Method: A chart review was performed for seventy–nine children with a known malignancy, actively receiving chemotherapy and hospitalized for fever over a 5 year period (1/1/2011 – 11/30/2016). Of these, 14 hospitalizations of 12 children met our inclusion criteria which were: 1) patients 0 - 18 years of age with onset of fever with or without neutropenia, 2) hospitalized at St. Joseph's Hospital, Marshfield with 3) PCT levels obtained within the first 24-48 hours of hospitalization and 4) blood cultures drawn prior to initiation of antibiotics and monitored for 5 days for bacterial growth. PCT levels were considered to be elevated if > 0.5 ng/mL.
Results: All patients with bacteremia had elevated PCT levels. 7/14 (50%) of patient hospitalizations were consistent with positive bacterial blood cultures. Of these, 5 were positive for gram negative bacteria. An additional 3 patient hospitalizations were consistent with proven viral infections. 7/14 (50%) patients were neutropenic at the time of fever onset.4/4 of patients with normal PCT levels had negative blood cultures. PCT levels were elevated in 3/7 patients with negative blood cultures, of which 2 met the criteria for sepsis while the third would have been considered to be in sepsis days prior to the PCT level. Mean and median PCT levels were higher in children hospitalized with positive blood cultures (59 and 10.9 respectively) versus negative blood cultures (9.5 and 0.47 respectively).
Conclusion: Elevated PCT appears to be a useful tool in predicting bacteremia and ongoing infectious/inflammatory conditions in pediatric oncology patients hospitalized with fever. However, therapy for these patients was guided by their clinical picture and culture results. PCT levels did not impact duration or course of therapy.

Poster # 858

MOOD AND DISTRESS MONITORING IN AYA CANCER, A PILOT STUDY

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Background: Mood and distress issues are common in adolescent and young adult (AYA) patients with cancer, but the issues are not easily evaluated. Few tools exist for this population.
Objectives: We developed a concise, unique survey to capture mood and distress. We sought to test its acceptance and feasibility in a pilot study.
Design/Method: The survey incorporated the established PHQ-9 instrument. Eleven original distress questions were added to explore a patient's concerns about family, social and internet interactions, sexual and medical concerns, etc. Administered during clinic visits, a physician discussed the answers privately with the subject, to take action if necessary for issues raised. A post-study assessment was administered to subjects, parents and staff.
Results: Six subjects were enrolled in this pilot, five adolescents from ages 13-17, and one young adult, 19. Surveys were administered in 4-6 week intervals, three per subject. Data was made anonymous and tabulated. Several mood symptoms, including one suggesting self-harm, were detected. Distress issues were also identified, ranging from problems with schoolwork to friends and appearance. No referrals were deemed necessary. Practical barriers were identified. The post-study assessment found the survey acceptable and feasible. Questions were revised.
Conclusion: The AYA cancer population is at risk for mood and distress issues that can be identified by this tool. It was deemed acceptable and feasible by patients and staff. The tool acted as a "conversation starter" for patients, giving permission to discuss issues. Improvements and refinements of the tool are planned. New MB Mood and Distress Questions (revised after pilot):Please rate your level of concern, 0 / 1 / 2 / 3 / about how your parent/guardian/caregiver is doing?about your safety or bullying, at home or at school?about your friends, or ability to keep or make friends?about your schoolwork, or job, or future career?about your reproductive health and sexual matters?about your use of the internet and social media?about your worship practices or religious practices?about your ability to cope with how people treat you?about your ability to cope with your own thoughts and feelings?about your appearance and social life?copyright pending MB Foundation 2016, permission for free useResearch reported in this publication was supported by a grant from the MultiCare Institute for Research & Innovation. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of MultiCare Health System.

Poster # 860

PARENT PERSPECTIVES ON THE ROLE OF LATE EFFECTS IN INITIAL TREATMENT DECISION-MAKING

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Background: More than 80% of children with cancer become long-term survivors, but most survivors experience late effects of cancer treatment. Pediatric oncologists evaluate treatment options and develop clinical trials with dual goals of increasing rates of cure and decreasing late effects. However, we know little about which late effects are most worrisome to parents, nor how they weigh late effects when making treatment decisions.
Objectives: To explore how parents of children with cancer think about late effects of cancer therapy during active cancer treatment, including the role of late effects in initial treatment decision-making.
Design/Method: Semi-structured interviews were conducted with 12 parents of children with cancer who were actively receiving cancer therapy at the Dana-Farber/Boston Children's Cancer and Blood Disorders Center (Boston, MA, USA) and within a year of diagnosis. Interviews were audio recorded, transcribed verbatim, and qualitatively analyzed by 2 coders using thematic analysis.
Results: Ten of the twelve parents interviewed reported that they had decided between two or more treatment options for their child's cancer. Of those, 50% (5/10) reported that late effects were an important factor in their decision-making process. The majority of parents interviewed wanted early and detailed information about their child's risk of late effects; some wanted this information in order to make treatment decisions for their child, and some wanted information in order to feel prepared for what may lie ahead after treatment completion. However, some parents felt they had little choice but to accept late effects in return for a better disease outcome, and other parents felt too overwhelmed by their child's illness and immediate treatment concerns to focus on late effects at the time of diagnosis. As a result, some parents considered late effect discussions less important at diagnosis and wished to return to these issues during or after treatment. While many recalled reviewing specific late effects during the informed consent discussion for treatment, some parents felt these issues were only addressed perfunctorily, with most of the conversation focused on treatment and acute side effects.
Conclusion: Parents desire detailed information about their child's risk of late effects to make informed treatment decisions, and to feel prepared for life after cancer treatment. However, despite the role of late effects in treatment decision-making, many parents feel that late effects are either inadequately addressed or too overwhelming to process at diagnosis. Parents may benefit from assessment of their information needs and a return to these issues over time.

Poster # 862

FAMILY-CENTERED ADVANCE CARE PLANNING FOR TEENS WITH CANCER (FACE-TC): A DEMONSTRATION OF KEY COMPONENTS OF THE FACE INTERVENTION/RESPECTING CHOICES INTERVIEW FOR AYA CANCER PATIENTS

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Background: Studies have consistently demonstrated that teens with life-limiting illnesses would like to have a voice in their own future medical care, and that their families would like help breaking the ice to have these conversations. The FAmily CEntered ACP for Teens with

Cancer (FACE-TC) is an empirically guided intervention aimed at improving pediatric palliative care and end-of-life care by facilitating Advance Care Planning (ACP) among adolescent and young adult (AYA) patients and their families. The FACE study aims to empower AYAs with cancer and works to overcome the barriers surrounding advance care planning in this population. The FACE-TC intervention: (1) promotes an active, patient-centered, family engaged informed decision-making process for ACP;(2) is the first structured and individualized ACP intervention for AYAs with cancer; (3) integrates the evidence-based Respecting Choices® Next Steps ACP intervention; (4) utilizes a structured curriculum delivered by certified facilitators; (5) focuses on promoting QOL for both AYAs and their families; (6) improves upon advance directive documentation by having a healthcare worker facilitate patient and family conversations about treatment preferences, then share them with the health care team, thereby ensuring ACP actions are taken; (7) preserves the integrity of the parent-child relationship; (8) respects individual differences, involving patients/families in treatment decisions at the level they prefer; and (9) gives adolescents a voice. Our findings have the potential to become standard-of-care evidence-based practice, which can overcome critical barriers to progress in AYA oncology ACP.
Objectives: The study aims to elucidate what choices AYAs with cancer make, whether the choices stay the same over time, whether religious experiences and beliefs influence their choices and if choices across racial groups are different or the same
Design/Method: Single-blinded, longitudinal, randomized controlled clinical trial.
Results: N/A
Conclusion: During this presentation, key aspects of the FACE-TC intervention, specifically exemplar video clips from the Respecting Choices Next Steps interview will be demonstrated through and an interim update of the study benchmarks will be provided.

Poster # 864

LATE EFFECTS IN HIGH RISK NEUROBLASTOMA SURVIVORS TREATED WITH HIGH DOSE CHEMOTHERAPY AND STEM CELL RESCUE

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Background: The tremendous success in high risk neuroblastoma (HRNB) therapy over the past 2-3 decades has seen 5-year survival rates improve from 15% to >50% and, consequently, there has been a growing population of HRNB survivors. Therefore, understanding the late effects of multimodal HRNB treatment that includes high dose chemotherapy and autologous stem cell rescue (ASCR) is becoming increasingly relevant.
Objectives: This single center study aims to describe overall survival, prevalence and risk factors for late effects and quality of life in HRNB survivors.
Design/Method: Retrospective review of clinical data and yearly quality of life questionnaires (QOL) pertinent to survivors of HRNB who were relapse free at least 1 year after receiving high dose chemotherapy and a single ASCR between 2000-2015 at Fred Hutchinson Cancer Research Center, Seattle, WA.
Results: Among 83 patients, 61 survivors (30 males) were eligible for inclusion. Median age at time of transplant was 3 years (range 0.9- 27 years) and median follow-up after transplant was 5.4 years (1.67-16.33 years). Overall survival at 5 and 10 years was 66.4% (± 6.7%) and 60% (±

7.4%) respectively. Forty (65.6%) patients developed ≥1 late effects. Occurrence and number of late effects were both significantly related to the time elapsed from transplant (P<0.001, P<0.001 respectively) but not to gender or age at transplant. A requirement for hearing aids was the most common late effect (n=23, 37.7%). A variety of dental late effects were seen among 17 patients (27.9%) and occurred more frequently in children <2 years at transplant (P= 0.008). Other late effect categories included: endocrine (21.3%), orthopedic (14.8 %), renal (13.1%) melanotic nevi (8.2%), neurologic impairments (8.2%) subsequent malignancies (4.9%), restrictive lung disease (4.9%), cardiac (3.3%), and focal nodular liver hyperplasia (3.3%). Linear growth was significantly impaired at 9 years post-transplant relative to time of transplant, with median height Z-scores changing from -0.01 (range -2.8 to 3.02) to -1.08 (range -2.89 to -0.13, P<0.001). Body weight was impaired at the same time-point with median weight Z-scores changing from -0.14 (range -2.23 to 2.62) to -0.78 (range -2.86 to 0.4, P=0.005). Four patients received growth hormone and showed improved growth. Overall, despite a high frequency of reported late effects, among 37 patients who completed QOL questionnaires, 97% reported good, very good, or excellent QOL.
Conclusion: The increasing proportion of HRNB survivors after aggressive multimodal therapy experiencing high incidence of late effects highlights the necessity for pro-active monitoring and management of late effects

Poster # 866

RACIAL DIFFERENCES IN SURVIVAL OF PEDIATRIC PATIENTS WITH BRAIN AND CENTRAL NERVOUS SYSTEM CANCER, UNITED STATES, 2001-2012

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Background: Brain and central nervous system (CNS) cancer is the second most common childhood cancer and is the leading cause of cancer death among children and adolescents. Despite improvements in survival during the past 40 years, some data suggest a racial disparity for survival.
Objectives: Our study describes survival by race by using national data to better understand the effects of demographic and clinical factors.
Design/Method: Data from the National Program of Cancer Registries were used to evaluate relative survival (RS) (cancer survival in the absence of other causes of death) among children and adolescents aged 0-19 years diagnosed with brain and CNS cancer during 2001-2012. Data were from 29 states and covered 66% of the US population. Overall and specific to black and white races, RS was stratified by sex, age, cancer stage, anatomic site, histology, US Census region, and county economic status.
Results: We identified 16,675 primary brain and CNS cancer cases during 2001-2012, with a 5-year RS of 75.5% (95% confidence interval [CI]: 75.0-76.5). White patients had a significantly higher 5-year RS (76.5%; 95% CI: 75.7-77.3) than black patients (70.8%; 95% CI: 68.6-72.9). The racial difference remained significant at 1 and 3-year RS, for both sexes, among children and adolescents, and in the South Census region. Cancer stage, primary anatomic site, histology, and economic status also affected racial differences for survival.

Conclusion: This study highlights brain and CNS cancer survival differences between black and white pediatric patients and identifies potential contributing sociodemographic and clinical factors. Future investigation of access to care, socioeconomic status, and host genetic factors may explain why race is a marker for survival and could help guide public health planning.

Poster # 868

IMPACT OF ROUTINE SURVEILLANCE ON SURVIVAL IN PEDIATRIC CANCER

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Background: Pediatric cancer treatment guidelines recommend examinations and testing after treatment but are often based on the assumption that earlier detection of relapse improves survival. However, routine surveillance is time consuming, often involves radiation exposure, and is potentially futile given many relapses/progressions are detected due to symptomatic presentation. It has been shown that scheduled follow-up programs have failed to detect relapse in about 50% of cases.
Objectives: To evaluate the method of detection for disease progression and/or relapse in children with cancer and assess if differences exist in survival based on method of detection.
Design/Method: A retrospective cohort study at the University of Michigan (Ann Arbor, Michigan, United States) was performed between June 2005 and September 2014 on children who experienced a first progression and/or relapse of cancer and were followed through April 2016. Only patients with follow-up at the institution were included in the study. Disease categories included: leukemia/lymphoma or solid tumors. It was determined if first relapse/progression was detected on routine surveillance or symptom evaluation. Overall survival (OS) from diagnosis was evaluated based on type of cancer and method of detection of first progression/relapse. Differences were evaluated using chi-square analysis.
Results: There were 311 patients out of a total 338 patients with relapse/progression analyzed (leukemia/lymphoma 77 and solid tumors 234). There were 199 patients with progressive disease and 112 patients with relapsed disease. Of those with leukemia/lymphoma, 57% had first relapse/progression detected by routine surveillance. Of those with solid tumors, 70% had first relapse/progression detected by routine surveillance. Patients with relapsed/progressive leukemia/lymphoma had median OS of 63 months from diagnosis; detection by symptom evaluation had median OS of 121 months from diagnosis compared with routine surveillance median OS of 43 months from diagnosis (p-value 0.319). Patients with relapsed/progressive solid tumors had median OS of 57 months from diagnosis; detection by symptom evaluation had median OS of 32 months from diagnosis compared with routine surveillance median OS of 73 months from diagnosis (p-value 0.006).
Conclusion: Routine surveillance detected higher rates of relapse/progression in patients with solid tumors (70%) versus leukemia/lymphomas (57%). The OS was significantly longer for patients with solid tumors whose relapse/progression was detected through routine surveillance compared with symptom evaluation. However, there was no statistically significant difference in OS for patients with leukemia/lymphoma based on method of detection.

Poster # 870

CONFIDENCE IN SURVIVORSHIP CARE IN PARENTS OF YOUNG CANCER SURVIVORS: DOES HEALTH LITERACY MATTER?

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Background: Health literacy is the degree to which an individual can process health information to navigate the healthcare system. Adequate health literacy is crucial when undergoing care for complex diseases such as cancer. With over 450,000 childhood cancer survivors in the US, survivors' families must understand past and current management, as well as possible sequelae. However, this understanding may be affected by health literacy level, which is significantly lower among underserved populations.
Objectives: To assess health literacy levels in parents/guardians of young cancer survivors and determine whether levels were correlated with confidence in long-term survivorship care.
Design/Method: Parents/guardians (n=95) of childhood cancer survivors aged 2-24 years were recruited from Rady Children's Hospital's survivorship clinic. Participants completed surveys assessing health literacy (NVS and TOFHLA instruments), confidence in survivorship care, and acculturation level if Hispanic. Health literacy and survivorship care confidence outcomes were analyzed by socio-demographics, cancer subtype, time since completion of therapy, and acculturation level.Statistical analyses were performed with t-test, ANOVA, Pearson correlations, Fisher's exact test and logistic regression.
Results: Ninety-five parents/guardians were surveyed, including Hispanics (44.2%) and Spanish-speakers (25.4%). Hispanics had lower education levels overall compared to Non-Hispanic Whites ($p<0.001$). Health literacy assessments used were strongly correlated ($r=0.649$, $p<0.001$). Ninety-four percent of subjects possessed adequate health literacy as measured by TOFHLA and 68% did as measured by NVS. Overall, those with a high school education or less had lower heath literacy ($p=0.001$). There was no significant difference in health literacy between Hispanics and Non-Hispanics but Spanish-speakers had lower health literacy (NVS: $p=0.009$, TOFHLA: $p=0.026$). Among Hispanics, those with higher acculturation levels had higher health literacy ($r=0.554$, $p=0.002$). Confidence in survivorship care was not significantly impacted by gender, ethnicity, education, language, health literacy level, or receipt of a survivorship care plan. Parents/guardians whose provider explained concepts in a comprehendible manner reported greater confidence in survivorship care ($p<0.05$).
Conclusion: Our results show that Hispanics with lower acculturation and limited English proficiency and caregivers with lower education, independent of ethnicity, have lower health literacy. Education level, acculturation, and primary language of caregivers should be assessed as part of survivorship care. Effective patient-provider communication is critical in order for caregivers to understand and have confidence in survivorship care. Hispanic caregivers with low acculturation and limited English proficiency may benefit from delivery of care adapted to their language, culture, and health literacy level to optimize understanding and confidence in care and ultimately reduce disparities in outcomes.

Poster # 872

ANXIETY RELATED OUTCOMES IN CHILDHOOD CANCER SURVIVORS

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Background: The population of childhood cancer survivors is quickly growing as curative treatments improve survival for childhood cancers. These survivors require lifelong medical care due to potential long term side effects of treatment, both physical and psychological. There is minimal data regarding psychological outcomes, particularly those focused on age at the time of cancer diagnosis and how those outcomes relate to ongoing health care issues in survivors of pediatric cancer.
Objectives: To describe anxiety related outcomes related to ongoing heath care needs for childhood cancer survivors, and compare these results when stratified based on age at the time of cancer diagnosis.
Design/Method: A questionnaire was distributed to childhood cancer survivors during follow up oncology clinic appointments. The questionnaire addressed different aspects of anxiety and depression, both in general and as they relate to the survivor's prior diagnosis, ongoing health care status, and follow up appointments. A chart review was completed to ascertain details regarding diagnosis and treatment. Once the survey results and chart review information were collected, the participants were divided into groups based on age at diagnosis for analysis.
Results: PROMIS tools used to assess generalized anxiety and depressive symptoms revealed no significant results. Survey sections that focused on different anxiety outcomes based on prior diagnosis were evaluated with the Pearson product-moment correlation coefficient and Spearman's rank correlation coefficient comparing each section of the survey with age at diagnosis, along with the following secondary variables: age at time of study, duration of treatment, and time since last treatment. The survey section that addressed general questions related to feelings about ongoing healthcare needs due to prior diagnosis demonstrated a statistically significant result. Older age at diagnosis (ages 15-18) was correlated with a higher level of anxiety outcomes in this section; Pearson's R 0.41. The results from other sections of the survey were not found to be statistically significant.
Conclusion: Despite the lack of statistically significant results between a majority of the variables and the anxiety related outcomes, the results highlight important aspects of ongoing care for this patient population. For each anxiety related outcome, there were some participants who identified high levels of ongoing anxiety. This highlights the importance of the health care providers addressing these issues during long term follow up, as anxiety and other related mental health long term effects may be just as prominent for many patients as the physical effects of their diagnosis.

Poster # 874

IDENTIFYING PATIENT AND FAMILY CENTERED OUTCOMES RELEVANT TO INPATIENT VERSUS AT-HOME MANAGEMENT OF NEUTROPENIA IN CHILDREN WITH ACUTE MYELOID LEUKEMIA

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Background: Little data exist on the comparative effectiveness of inpatient versus at-home monitoring of children with AML and neutropenia. While it is important to assess the comparative effectiveness of these two approaches relative to clinician derived outcomes, it is also necessary to identify and compare outcomes meaningful to patients and their families.
Objectives: To identify outcomes related to inpatient versus at-home management of post-chemotherapy neutropenia that are important to children with AML and their families that may be examined in future comparative effectiveness studies.
Design/Method: An in-depth qualitative study was conducted to better understand the experience of patients and their families during periods of neutropenia after AML chemotherapy. Semi-structured interviews were conducted with parent-patient dyads for patient's ≥ 8 years of age. Parent only interviews were conducted for patients < 8 years of age. Interviews were performed either within 6-12 months of completion of the second course of chemotherapy or up to 3 years after completion of all frontline AML chemotherapy. Participants were purposefully sampled to include a combination of patients whose neutropenia was managed in the hospital and others managed at home. Interviews were audio recorded, transcribed and analyzed for repeated themes using a modified grounded theory approach.
Results: Interviews were conducted from November 2015 to December 2016 with 72 respondents (46 parents and 26 children) recruited from 7 children's hospitals across the United States (3 early discharge sites). We identified 3 main themes repeated across respondents: (1) children and parents described substantial distress about the impact of prolonged hospitalizations on siblings, (2) parents felt safer and less anxious in the hospital as they trusted hospital staff to be well equipped to identify and manage neutropenia complications and (3) patients experienced sleep disturbances during therapy that were worse in the hospital. Parents were universally concerned about their child acquiring an infection during neutropenia, while child concern about infection varied by age with teenagers expressing greater concern. Neither parents nor children were concerned about chemotherapy course delays.
Conclusion: A systematic qualitative investigation of the experiences of children with AML and their families consistently identified stress on siblings, parent anxiety over neutropenia complications, patient sleep disturbance and concerns of infection as important patient-centered outcomes. These themes are being used to develop a structured questionnaire to enable a quantitative comparison between children with AML and neutropenia managed in the hospital versus at home in a prospective multi-institutional trial.

Poster # 876

PREVALENCE OF HEMOGLOBINOPATHIES AMONG ONTARIO CHILDREN AFTER THE IMPLEMENTATION OF UNIVERSAL HEMOGLOBINOPATHY SCREENING

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Background: In Ontario, since universal hemoglobinopathy screening was implemented, approximately 60-80 affected infants have been identified each year. All Ontario children with pathological hemoglobinopathies are referred to one of five pediatric centres. When considering ethnic populations that are most affected by hemoglobinopathies, the proportions of Chinese, South Asian, Middle Eastern, Black and Filipino populations are expected to reach 21%, 28%, 11%, 12% and 6.8%, respectively based on projections from Statistics Canada. Newborn screening does not account for the large number of affected children who immigrate to Ontario each year and the incidence and prevalence of hemoglobinopathies in Ontario remains unknown.
Objectives: To estimate the prevalence of hemoglobinopathies among Ontario children after the implementation of universal hemoglobinopathy screening on November 24, 2006.
Design/Method: Clinical databases from five pediatric tertiary care health centres (Ottawa, Hamilton, Kingston, London, Toronto) were used to identify children who were born with a hemoglobinopathy between November 24, 2006 and March 31, 2013. De-identified patient data for hemoglobinopathy diagnoses and diagnosis dates were entered into a REDCap database. We used 2011 national census data to calculate the crude prevalence rate for hemoglobinopathies in Ontario. In 2011, there were 1,417,015 Ontario children between 0-9 years of age.
Results: During the study period, there were 527 confirmed hemoglobinopathy cases, corresponding to a prevalence of 1 in 2689 Ontario children. 508 (96%) of these patients had a β-hemoglobinopathy. Sickle cell disease (SCD) comprised 81% of β-hemoglobinopathies while β-thalassemia and other β-hemoglobinopathies made up 12% and 7%, respectively. The majority of affected children were followed in Toronto (78%) followed by Hamilton (9%), Ottawa (9%), London (4%) and Kingston (<1%). HbSS was the most common SCD genotype (58%) followed by HbSC (27%). 27% of the children with β-hemoglobinopathies also had α-thalassemia deletions. 25% of children with α-thalassemia deletions had 2 or more α-globin abnormalities, including 6% with HbH disease and 3% with Hb Bart syndrome. α-thalassemia deletions are not identified with current newborn screening techniques.
Conclusion: The number of hemoglobinopathy cases that were identified in this study is approximately 25% higher than the expected 360-480 cases predicted to be identified through Ontario newborn screening over the study period. This supports the hypothesis that newborn screening alone is not enough to identify a large number of children who are affected by hemoglobinopathies. In the next phase of this project, we will identify immigrant and Ontario-born children with hemoglobinopathies using health administrative data and determine population-based incidence and prevalence.

Poster # 878

UTILIZATION AND COST OF INTRAVENOUS IRON THERAPY: A SINGLE INSTITUTION EXPERIENCE

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Background: Intravenous (IV) iron is utilized by various subspecialists for a variety of indications, yet beyond its use for managing anemia in end-stage renal disease (ESRD), there are limited data regarding its appropriate role in pediatrics. It is often considered an unsafe medication, largely due to historical reports describing anaphylaxis with older and higher molecular weight IV iron preparations. Recent data demonstrate that IV iron is effective and safe, even in pediatrics, allowing for the uneventful infusion of up to 1000 mg with a single dose of certain formulations.
Objectives: In this retrospective study, we aimed to examine the frequency, costs and risks associated with IV iron use at a large pediatric medical center in order to inform and optimize its use in the pediatric and young adult population.
Design/Method: A comprehensive review of electronic medical records was undertaken for all patients who received IV iron at Cincinnati Children's Hospital Medical Center from January 1, 2010 through October 31, 2016. Data included demographics, underlying medical conditions, order details, premedications used, relevant laboratory results, cost per dose and infusion-associated adverse events.
Results: In total, 357 patients received a combined 3820 doses during the study period. Three iron preparations were used: iron sucrose (IS, 59.4%), ferric gluconate (FG, 40.2%) and low molecular weight iron dextran (LMWID, 0.4%). Nephrology (65.9%), Gastroenterology (15.2%), and Hematology (10.5%) were the most common ordering providers. The most frequent indications included dialysis-dependent ESRD (26% of patients), inflammatory bowel disease, iron deficiency anemia and epidermolysis bullosa. The median number of doses per patient was 4 (range 1 to 240). Ninety-one patients (25.5%) received a single dose, while 19 (5.3%) received greater than 50 doses. Doses ranged from 1.3 to 1030 mg (mean 83.5±58.3 mg). The most common dose for FG was 125 mg and for IS was 100 mg, while LMWID allowed for single dose infusions as high as 1030 mg per dose. The average wholesale cost per dose was $61, $42 and $57 for FG, IS and LMWID, respectively. One minor adverse reaction (mild swelling with FG) was documented over this time period.
Conclusion: IV iron is used commonly across disciplines with significant variability and seemingly no standardization for dosing or therapeutic response monitoring. Despite widespread safety concerns with IV iron administration, very few adverse events were noted, reinforcing this therapy as safe. Future directions include the creation of IV iron standardization protocols and encouraging better cost-effective use of multiple pediatric formulations.

Poster # 880

A RETROSPECTIVE STUDY EVALUATING THE UTILITY OF OFF-THERAPY SURVEILLANCE IMAGING OF NON-CNS SOLID TUMORS WITH A FOCUS ON RHABDOMYOSARCOMA

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Background: Surveillance imaging plays a prominent role in monitoring pediatric patients diagnosed with a solid tumor who have completed therapy. Historically surveillance imaging is recommended at routine intervals based on limited evidence. Data is sparse regarding usefulness of scheduled surveillance imaging of solid tumors. Surveillance imaging includes: ultrasound

(US), computed tomography (CT), magnetic resonance imaging (MRI), nuclear medicine (NM), and X-rays. Many of these modalities expose patients to contrast, radiation, and/or require sedation subjecting patients to general anesthetics; all of which are associated with additional health risks. Furthermore in the era of value driven care financial burden of surveillance imaging should be examined.
Objectives: To demonstrate the utility or lack thereof for surveillance imaging in monitoring patients with a history of a non-CNS solid tumor now off therapy.
Design/Method: Retrospective review of patient medical records in Intermountain Healthcare's electronic medical record system and financial data warehouse. A census was generated of solid tumor patients diagnosed with Rhabdomyosarcoma, Neuroblastoma, Wilms tumor, Hepatoblastoma, and Ewing sacrcoma between January,1 2005 and December 31, 2012 at Primary Children's Hospital in Salt Lake City, Utah. Patients had either a minimum off-therapy follow-up of 2 years, or relapsed within 2 years of completing therapy. Off-therapy imaging was analyzed with incorporation of cost data. Imaging was divided into two categories; routine surveillance, defined as imaging done in accordance with a scheduled monitoring plan; and unscheduled, designated as imaging performed due to history or physical exam findings.
Results: Two-hundred-ninety-two unique patients with eligible diagnoses were identified who underwent a total of 7,490 images. Of the 292 eligible patients, 57 relapsed. Of the 57 relapses, 29 (51%) were found on routine surveillance imaging and 28 (49%) were found with unscheduled imaging. There was no difference in overall survival between these two groups. Of the 40 Rhabdomyosarcoma cases, 12 relapsed and only 2 (17%) of these were discovered with routine imaging. Overall Rhabdomyosarcoma imaging surveillance cost was $345,579.79, of which $223,248.59 (65%) was incurred through surveillance of patients who never relapsed.
Conclusion: Off-therapy surveillance did not affect outcomes in our relapsed solid tumor patients. Surveillance imaging in Rhabdomyosarcoma patients is ineffective at detecting asymptomatic relapse. In caring for Rhabdomyosarcoma patients providers should be mindful of off-therapy surveillance imaging's decreased utility, the financial burden it carries, and the potential associated medical complications.

Poster # 901

INCREASED RISK OF THROMBOEMBOLIC EVENTS IN CHILDREN WITH PELVIC OSTEOSARCOMA

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Background: Pelvic osteosarcoma is a rare entity with challenging management and poor outcome, comprising < 10% of osteosarcoma diagnoses in the United States. While there are a few previous reports associating pediatric pelvic osteosarcoma with tumoral vascular extension and subsequent thromboembolism, none specifically addresses the potential higher rates of non-tumoral thrombotic events. Moreover, there are no specific guidelines about prophylactic anticoagulation in this group of patients.
Objectives: Our objective is to recognize thromboembolic events as one of the common complications in patients with pelvic osteosarcoma and to initiate the discussion in the scientific community about the role of thromboprophylaxis in patients with this type of tumor.

Design/Method: Retrospective chart review of 7 patients with pelvic osteosarcoma who were treated at Texas Children's Hospital between 2007 and 2016. We described the clinical characteristics, presentation and treatment of thromboembolic events in this group of patients.
Results: Four of our patients developed thrombotic events; patient 1 had a left middle cerebral artery stroke after 24 weeks of adjuvant chemotherapy, while intubated for respiratory failure during a diagnostic bronchoscopy done as a part of infection work up; patient 2 presented with fever and right leg swelling, then was found to have an extensive thrombosis of the right lower extremity proximal deep veins, 2 weeks after cycle 1 of induction chemotherapy; patient 3 relapsed 15 months off therapy presenting with a right lower extremity proximal deep vein thrombosis and patient 4 was incidentally found to have a left iliac vein thrombosis while being evaluated for disease progression. None of the patients with thrombotic events had evidence of hereditary thrombophilia and none of the thromboses were catheter related; all 4 patients died from disease progression. Patients 5, 6 and 7 received thromboprophylaxis with enoxaparin and had no thromboembolic issues reported. Patient 5 passed away from disease progression, while patients 6 and 7 are still alive and off therapy without evidence of recurrence to the date of this abstract.
Conclusion: Patients with pelvic osteosarcoma appear to have a higher incidence of thromboembolic events, probably related to vascular compression by tumor, patient immobility, extensive orthopedic surgery, chemotherapy or tumor-related factors. Prophylactic anticoagulation seems to favorably affect the development of thromboembolic episodes. Larger studies are needed to confirm the findings of this case series.

Poster # 902

SUSTAINED REMISSION IN A PATIENT WITH MALIGNANT HISTIOCYTOSIS USING TARGETED THERAPY AGAINST BRAF-V600E MUTATION

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Background: Malignant neoplasm of histiocytes is a rare malignancy in children. Its estimated incidence is 0.05 per 100,000 people in Europe and is rarely seen in children. Without treatment, such neoplasms are fatal. No strategy has been agreed upon as standard therapy. The BRAF-V600E mutation is a common genetic phenomenon in histiocytic disorders.
Objectives: We describe the successful utilization of targeted therapy with combined BRAF and MEK inhibition in a patient with BRAF V600E mutation positive malignant histiocytosis after failure of other treatment strategies
Design/Method: We performed a case review for our patient and reviewed the literature for similar cases.
Results: Our patient is a 14 year old Caucasian male with a history of Oppositional Defiant Disorder and Pervasive Developmental disorder. He presented with a month-long history of right-sided neck swelling and was treated for lymphadenitis. Despite treatment, the mass grew and was biopsied. Biopsy revealed 30% atypical cells, CD4+/dim partial CD(2, 3, 5, 7)/CD14+/CD8-/CD30-, consistent with Peripheral T-cell Lymphoma-NOS. He received standard four drug induction (Daunorubicin, dexamethasone, methotrexate, and vincristine). End of induction Positron Emission Tomography (PET) scans showed less than 50% reduction in

tumor burden. He received re-induction with methotrexate, cyclophosphamide, cytarabine, mercaptopurine, vincristine, and pegaspargase. Subsequent PET-CT was unchanged, and so his treatment was intensified to ifosfamide, carboplatin and etoposide for two cycles. He experienced significant toxicity, including thrombosis, pancytopenia, acute kidney injury and repeated episodes of sepsis. Repeat PET-CT scan showed partial response with new lymph node involvement. His original biopsy specimen was analyzed at Foundation One Medicine for genomic profiling, which revealed a BRAF-600E mutation. Biopsy from the new lesion was positive for CD163, PU1, and POU2F2, while lacking CD1a, S100, CD23, PAX5, and CD21. When taken with the original results, this is consistent with malignant histiocytosis. Combination therapy targeting the RAF-MEK-ERK pathway with dabrafenib and trametinib delays the emergence of resistance to BRAF inhibition alone and improved the rate of progression free survival in melanoma patients. Our patient received FDA approved doses for malignant melanoma as targeted therapy and tolerated therapy well. Repeat PET-CT at 57 days showed complete metabolic response.
Conclusion: Cancer exome sequencing and targeted treatment should be considered in children with rare tumors. Review of the literature suggests that BRAF gene mutations are common in disorders of histiocyte origin. Combined BRAF and MEK inhibition is a promising treatment for children with BRAF-V600E mutation harboring malignancies and should be evaluated in a larger study.

Poster # 903

ANAPLASTIC ASTROCYTOMA IN A CHILD WITH COFFIN-SIRIS SYNDROME AND GERMLINE SMARCE1 MUTATION: A NOVEL CASE

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Background: Coffin-Siris syndrome (CSS) is a phenotypically heterogeneous, congenital malformation disorder caused by germline mutations in the chromatin remodeling SWI/SNF complex genes. SMARCE1 missense mutations engender the rarest known SWI/SNF variants in CSS, with 6 published cases to date. Loss-of-function mutations in SMARCE1 have been implicated in the development of clear cell meningiomas and multiple spinal meningiomas in non-syndromic patients. Interestingly, only 3 cases of malignancy have been previously described in CSS patients, one involving the central nervous system. The oncogenic potential of missense SMARCE1 variants in CSS is unknown, and the risk of cancer predisposition in CSS remains to be elucidated.
Objectives: Report a case of anaplastic astrocytoma (WHO grade III) in a child with CSS and a de novo germline missense SMARCE1 mutation.
Design/Method: Case report with germline whole exome sequencing.
Results: An 18-month old girl with a complex medical history significant for psychomotor delay, congenital heart disease, feeding difficulties and scoliosis underwent a brain and spinal MRI as part of investigative work up of her clinical condition. Imaging demonstrated an asymptomatic right parietal cortex mass. A presumptive diagnosis of a low grade glioma was made. Close clinical and radiographic surveillance showed a doubling in the lesion’s size over

the subsequent 6 months, prompting surgical resection of the lesion. Pathology revealed an anaplastic astrocytoma, negative for H3.3 K27M and ATRX mutation. Formal genetics evaluation highlighted soft dysmorphic facial features, bilateral over-folded ear helices, dysplastic 5th toenails and bilateral horizontal nystagmus. She was enrolled on the St. Jude institutional trial for infants with high grade glioma and treated with 6 cycles of systemic chemotherapy. Whole exome sequencing of peripheral blood lymphocytes revealed a de novo heterozygous germline SMARCE1 mutation denoted as NM_003079.4:c.277A>G (p.Tyr111Cys)c, supporting the diagnosis of CSS. She remains disease free at 18 months from her tumor resection and continues to receive rehabilitative services for the associated anomalies.
Conclusion: This is to our knowledge, the first formally documented report of a malignant brain tumor in a child with CSS and germline SMARCE1 mutation. Current evidence implicates other components of the SWI/SNF complex, including SMARCB1 and SMARCA4, as tumor suppressor genes; however, our case report emphasizes the need to investigate the role of missense SMARCE1 mutations in tumor predisposition, presumed to be through a gain of function mechanism, to better inform genetic counselling for children with CSS.

Poster # 904

LANGERHANS CELL HISTIOCYTOSIS PRESENTING AS POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

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Background: Post-transplant lymphoproliferative disorder (PTLD) presents after solid organ or allogeneic hematopoietic stem cell transplantation (HSCT). A majority of cases are associated with EBV infection. The histology of the monomorphic type PTLD is similar to non-Hodgkin lymphoma, with diffuse large B cell lymphoma being the most common(1). Langerhans cell histiocytosis (LCH) is a disease caused by lesions containing CD1a+/CD207+ dendritic cells that varies in clinical presentation from self-limited to severe, disseminated disease(3). We report a case of a three year old female who required a liver, small bowel, and pancreas transplant at two years of age for microvillus inclusion disease and subsequent intestinal failure associated liver disease. Two years post-transplant, she was noted to have fever and extensive lymphadenopathy. PET CT showed multiple sites of lymphadenopathy, and biopsy was consistent with LCH. She was successfully treated with LCH III therapy, although she had multiple complications during treatment, including sepsis.
Objectives: To discuss a rare type of PTLD and its possible associations, and to describe effective treatment.
Design/Method: Literature review and chart review was done to identify prior cases and to investigate the inciting factors for LCH development in this case.
Results: We identified one case report of a prior patient who developed LCH-type PTLD after liver transplantation for fulminant liver failure of unknown etiology. This patient achieved remission of PTLD, but unfortunately passed away from liver failure(2).
Conclusion: LCH has been associated with PTLD in the context of patients who had a liver transplant as a result of liver failure caused by LCH and subsequently developed PTLD with typical histology(4). There has been one case report of a patient developing LCH-type PTLD

after liver transplantation(2). In this case, it was noted the patient had a recent EBV-reactivation prior to diagnosis. EBV was not detected after remission of LCH. Unfortunately, this patient died of transplant rejection. We describe a case of LCH-type PTLD after multi-organ transplant, who also presented after EBV-reactivation. Our patient was successfully treated as per LCH III and remains in remission over 4 years later and EBV remains negative. EBV has been identified in patient samples of LCH and suggested as a possible etiology(5). This case suggests EBV may be associated with the development of LCH-type PTLD as it is with PTLD of more common types.1. Allen, Pediatr Clin North Am, 2015.2. Honda, Liver Transpl, 2005.3. Allen, Blood, 2015.4. Newell, J Pediatr, 1997.5. Shimakage, Hum Pathol, 2004.

Poster # 905

METASTATIC ANGIOMATOID FIBROUS HISTIOCYTOMA WITH EWSR1-CREB1 FUSION WITH THERAPEUTIC RESPONSE TO INTERLEUKIN-6 RECEPTOR ANTIBODY TOCILIZUMAB

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Background: Angiomatoid fibrous histiocytoma is a rare soft tissue tumor with intermediate malignant potential. Metastasis to regional lymph nodes and/or lung is described in less than 5% of patients. Complete surgical resection of primary and metastatic sites is essential for cure. Angiomatoid fibrous histiocytoma has been associated with three characteristic gene fusions, EWSR1-CREB1, EWSR1-ATF1, and FUS-ATF1. Interleukin-6 (IL-6) secretion has been described in tumors with EWSR1-CREB1 fusion, and may promote tumor growth due to autocrine stimulation. Tocilizumab is an IL-6 receptor antibody that has potential benefit as a targeted therapy in refractory neoplasms with IL-6 secretion.
Objectives: To report a case of metastatic angiomatoid fibrous histiocytoma with EWSR1-CREB1 fusion treated with IL-6 inhibitor.
Design/Method: Case report
Results: A 3 year-old male with DiGeorge syndrome presented with microcytic anemia, intermittent fever and a left posterior calf mass that had been present for approximately 1 year. MRI showed a 5.6 cm infiltrative mass with a multiloculated cystic appearance. The lesion was biopsied, and EWSR1-CREB1 fusion was detected consistent with angiomatoid fibrous histiocytoma. Further imaging found inguinal and pelvic lymph node spread as well as multifocal pulmonary metastasis. Due to extensive systemic involvement, chemotherapy was initiated with vincristine, dactinomycin, and cyclophosphamide with initial improvement and resolution of pulmonary nodules; however, a PET scan performed after 5 cycles showed active disease in the left calf, as well as in the inguinal, pelvic, iliac, and retroperitoneal lymph nodes. Serum inflammatory cytokines testing revealed elevated IL-6 level. In addition, the patient had increased ESR, CRP and ferritin. Treatment was initiated with 10 mg/kg tocilizumab every 4 weeks. Two weeks after treatment initiation, ESR and CRP normalized and anemia improved. After 5 cycles of tocilizumab, PET showed decreased FDG uptake in the lower extremity mass as well as in the inguinal lymph nodes, with no new areas of metastatic disease. Serum IL-6 was further elevated indicating blockage of the IL-6 receptor by the antibody. Currently, the patient is

doing well on tocilizumab every three weeks without any adverse events.
Conclusion: We present the first report of a child with metastatic angiomatoid fibrous histiocytoma with EWSR1-CREB1 fusion and elevated serum IL-6 whose disease progressed during treatment with traditional chemotherapeutic agents, but showed improvement after targeted therapy with tocilizumab, an interleukin-6 receptor antibody. For pediatric patients with metastatic angiomatoid fibrous histiocytoma and elevated IL-6 levels, treatment with tocilizumab may be considered as a salvage regimen.

Poster # 906

GRISCELLI TYPE II SYNDROME AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: SISTERS WITH THE SAME MUTATION BUT DIFFERENT PRESENTATIONS

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Background: Griscelli syndrome (GS) is an autosomal recessive condition, with three subtypes. Type 1 (GS1) is known to have neurological abnormalities, particularly seizures and oculocutaneous albinism and Type 2 (GS2) is known to have immunological compromise, hemophagocytic lymphohistiocytosis (HLH), and oculocutaneous albinism. Unlike GS1, GS2 has a distinct lack of seizures and neurological abnormalities. The primary gene associated with GS2 and HLH is RAB27A, which affects a GTPase that anchors melanosomes in melanocytes and releases cytolytic granules from T cells and NK cells. HLH, a known complication of having GS2, is a familial or acquired life-threatening syndrome of immune over-activation. HLH is clinically characterized by fever, pancytopenia, hepatosplenomegaly, high ferritin, hypertriglyceridemia, hypofibrinogenemia, and hemophagocytosis. This genetic mutation causing GS2 and HLH is rare and now known to be familial but has rarely been described in two relatives.
Objectives: Exploration of a previously unreported phenomenon of siblings with vastly different presentations of GS2 and HLH having the same previously unreported genetic frameshift mutation in the RAB27A gene.
Design/Method: Retrospective chart review.
Results: Patient 1 was a 5-year-old Hispanic female who presented with oculocutaneous albinism and status epilepticus secondary to left-sided encephalitis. After initial presentation, her seizure proved difficult to control. Whole blood genetic workup revealed an RAB27A frameshift mutation with other downstream nonsense mutations associated with GS2. The diagnosis of GS2 was confirmed via skin biopsy. She developed splenomegaly, pancytopenia, hypofibrinogenemia, hypertriglyceridemia, pancytopenia, and was diagnosed with HLH. She died before allogeneic stem cell transplant (SCT) could be performed. Patient 2 is a 4-month-old Hispanic female who presented with oculocutaneous albinism, high fever, hypofibrinogenemia, hypertriglyceridemia, and pancytopenia. She is the younger sister of patient 1. Her workup demonstrated elevated interleukin-2-receptor, ferritin, and marked hemophagocytosis on bone marrow biopsy. She fulfilled the diagnostic criteria for HLH and was treated with etoposide and dexamethasone with normalization of inflammatory markers after 4 weeks of therapy. Whole blood genetics assay revealed homozygosity for RAB27A frameshift mutation. Patient 2

received an allogeneic SCT.
Conclusion: We have demonstrated a case of two sisters with GS2 and HLH with the same RAB27A frameshift gene, which is previously unreported. Patient 1 presented like GS1 but ultimately was diagnosed with GS2 and HLH. Patient 2 presented with HLH and was diagnosed with GS2. Both girls were found to have a frameshift mutation in the RAB27A gene despite the varying presentation of GS2.

Poster # 907

EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES: THE MD ANDERSON CANCER CENTER EXPERIENCE

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Background: Embryonal Tumor with Multilayered Rosettes (ETMR) is a relatively rare tumor of the central nervous system (CNS) with poor prognosis, which includes ependymoblastoma, medulloepithelioma, and embryonal tumor with abundant neuropil and true rosettes (ETANTR). Despite recent publications, to-date no defined robust treatment strategy or advanced brain tumor imaging (ABTI) have been described for these malignancies.
Objectives: We evaluate our institutional experience with these tumors, including imaging characteristics which could better define anatomic/metabolic profile of these tumors.
Design/Method: We performed a retrospective analysis of six pathology-proven ETMR cases from 2010-2016 treated at our institution and review of the literature.
Results: Six patients were identified, ranging from 2.7 to 12.8 years of age at diagnosis. Tumors were located in the brainstem, spine, and frontal lobe in three, two, and one patient, respectively. Presenting signs varied depending on tumor location, which ranged from cranial nerve and cerebellar dysfunction, cord compression, and proptosis. Patients received a combination of surgery, chemotherapy, and radiation. Pre-operative neuroimaging including ABTI was performed. This showed mild heterogeneous enhancement with minimal or no perilesional edema and restricted diffusion on brain magnetic resonance imaging (MRI). We evaluated the brainstem lesions using magnetic resonance spectroscopy (MRS) which showed choline/creatinine ratio greater than 2, depressed N-acetyl aspartate (NAA), low myo-inositiol (in intermediate echo) and lipid/lactate peaks, typical for high grade neoplasm. Diffuse tensor imaging (DTI) revealed deviated corticospinal tracts with no evidence for tumor infiltration. The only preoperative CT scan performed on the frontal lobe lesion showed spotty calcification, not commonly seen in high grade neoplasms. One spinal lesion showed multinodular T2 dark mass at L2-L5 with a less than 1 cm leptomeningeal nodule at T10. The other well defined spinal mass at L2-S3 revealed mild enhancement.
Conclusion: Improved methods of early diagnosis of ETMR are evolving most notably the LIN28A immunostaining and 19q13.42 amplification. Though pre-operative MRI scans have been performed, advanced brain tumor imaging including MRS and DTI, have not been reported in the literature for ETMR. We describe for the first time ABTI characteristics for these tumors. This could enable better tissue characterization based on metabolic profile increasing the anatomic MRI specificity, improved outline of fiber-tracts aiding precision-guided biopsy and

tumor planning, and treatment response by following the choline-creatinine ratio. Prospective studies for these biologically elusive, rare tumors should include in addition to molecular characterization, neuroimaging with ABTI which could help in diagnosis, surgical planning and follow-up of treatment response.

Poster # 908

RECURRENT ATYPICAL HEMOLYTIC UREMIC SYNDROME IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA UNDERGOING MAINTENANCE CHEMOTHERAPY: A ROLE FOR 6-MERCAPTOPURINE?

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Background: Patients with diarrhea and/or shiga toxin-negative hemolytic uremic syndrome (HUS) are categorized as atypical HUS (aHUS). Cases of aHUS have also been linked to infections, chemotherapeutic agents, cancer and mutations in complement or its regulatory protein genes or acquired complement factor H (CFH) antibodies. Very few cases associated with acute lymphoblastic leukemia (ALL) have occurred while on chemotherapy.
Objectives: To report two children with B-lineage ALL (B-ALL) undergoing maintenance chemotherapy that developed aHUS with recurrence upon restarting chemotherapy including 6-mercaptomurine (6-MP).
Design/Method: Clinical course and laboratory studies in the two cases were reviewed retrospectively. Previously reported cases of HUS associated with ALL are summarized.
Results: A 7-year-old girl (patient 1) and a 3-year-old boy (patient 2) with B-ALL undergoing a maintenance chemotherapy consisting of 6-MP, vincristine and methotrexate were diagnosed with aHUS after presenting with hematuria and found to have microangiopathic hemolysis, renal dysfunction, pancytopenia and hypocomplementemia. Chemotherapy regimens were held. Patient 2 also tested positive for influenza A in respiratory secretions and was treated with oseltamivir. Hemolysis resolved and their kidney function and complement levels normalized following peritoneal dialysis, plasmapheresis and packed red blood cell (pRBC) transfusions. After discharge, both patients resumed maintenance chemotherapy, including 6-MP. However, soon after, they once again developed microangiopathic hemolysis, acute renal failure, pancytopenia and hypocomplementemia consistent with recurrent aHUS. Chemotherapy regimens were held. Patient 1 required chronic peritoneal dialysis and developed seizure episodes due to posterior reversible encephalopathy syndrome. She was given vincristine, pulse methylprednisone and fresh frozen plasma (FFP) infusion for the treatment of aHUS with improvement. Patient 2 in addition tested positive for parainfluenza type 2 at the time. He received FFP and pRBC transfusions with complete recovery. For patient 1, 6-MP was replaced by oral cyclophosphamide without recurrence of aHUS. She evolved into chronic kidney disease over years. She tested negative for any causative mutations in the complement regulatory proteins or for anti-CFH antibodies. Patient 2 did not receive any more chemotherapy, as he completed his total planned treatment time. His kidney function has remained normal.
Conclusion: 6-mercaptopurine has not been implicated in aHUS. The cases of recurrent aHUS

upon exposure to 6-MP, along with potential other triggers reported here raise the possibility of a role for 6-MP in aHUS pathogenesis in ALL. Atypical HUS should be considered in the differential diagnosis of acutely developing anemia, thrombocytopenia and renal disease in patients receiving 6-MP.

Poster # 909

RESOLUTION OF LEPTOMENINGEAL ENHANCEMENT AFTER SURGICAL RESECTION OF PRIMARY ATYPICAL CHOROID PLEXUS PAPILLOMA

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Background: Choroid plexus tumors (CPT) are uncommon brain tumors that most often occur in young children. The clinical aggressiveness of CPTs follows a spectrum which is divided into 3 groups with atypical choroid plexus papillomas (APPs) falling in the middle as WHO grade II entities. APPs are differentiated from typical choroid plexus papillomas based on increased mitotic activity. We share an unusual case of a 12 month-old female with a large APP whose apparent metastatic disease, noted by leptomeningeal enhancement, resolved after surgical resection of the primary tumor.
Objectives: Describe the resolution of leptomeningeal enhancement after the resection of the primary atypical choroid plexus papilloma.
Design/Method: Case report.
Results: A 12 month-old female presented with one month of vomiting, weight loss, decreased appetite and irritability. Initial CT scan showed a right lateral ventricular tumor with communicating hydrocephalus, prompting placement of an external ventricular drain. Subsequent MRI brain and spine showed a large, heterogenous, enhancing mass located in the atrium of the right lateral ventricle. There was also extensive abnormal thick leptomeningeal enhancement along the brainstem, superior aspect of the cerebellum, basal cisterns, perisylvian cortical sulci, spinal cord and cauda equina consistent with metastatic disease. Angiogram showed the tumor was supplied by multiple small caliber vessels, making embolization impractical.After a multidisciplinary conference, a ventriculoperitoneal shunt was placed and chemotherapy was started in hopes of decreasing tumor vascularity and minimizing bleeding risk associated with surgery. The patient was discharged home after receiving carboplatin (8mg/kg on 2 consecutive days) and etoposide (3mg/kg on 3 consecutive days).The patient re-presented one week after discharge with increased irritability and worsening nausea and vomiting. Repeat MRI showed increased primary tumor size and worsening peritumoral edema with midline shift. Gross total resection of the primary tumor ensued without major complications. A 2 week post-op lumbar puncture for CSF cytology demonstrated no tumor cells. No post-operative chemotherapy has been given and imaging has shown progressive resolution of leptomeningeal enhancement at 1 day, 2 weeks and 2 months after surgery. Patient is now 3 months status post-surgical resection and is clinically thriving with minimal left-sided weakness. Formal neurocognitive evaluation revealed appropriate development in all areas.
Conclusion: Leptomeningeal enhancement in the setting of an APP may spontaneously regress

after surgical resection of the primary tumor. This case raises questions about the nature of leptomeningeal enhancement in those with APPs and requires further exploration.

Poster # 910

PHILADELPHIA CHROMOSOME POSITIVE AML: A RARE PEDIATRIC ENTITY

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Background: Acute myeloid leukemia (AML) comprises 15-20% of childhood leukemia and is associated with multiple cytogenetic anomalies. The Philadelphia chromosome, t(9;22), is generally associated with chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL). Prior studies demonstrate that only 0.5-3% of pediatric patients with AML have the Philadelphia chromosome (Ph+) and have poorer outcomes. Due to its rarity there is currently no standard treatment approach for Ph+ AML. Treatment modalities have included chemotherapy with or without tyrosine kinase inhibitors (TKIs) and hematopoetic stem cell transplant (HSCT). Data is limited but outcomes have been dismal without stem cell transplant.
Objectives: To describe a case of pediatric Ph+ AML and our rationale for treatment approach.
Design/Method: Clinical, histologic, immunophenotypic and molecular details of the case are provided. We compared our case to the clinical outcomes of other reported cases of Ph+ AML.
Results: A 15 year-old Caucasian female was diagnosed with AML after several weeks of fever and fatigue. She started Induction 1 therapy per the Children's Oncology Group (COG) protocol AAML 1031. Cytogenetics revealed t(9;22). Pathology, history and the presence of the minor Ph+ transcript favored diagnosis of Ph+ AML over CML in acute blast crisis. Imatinib was initiated on day 7 of Induction 1 using dosing from prior COG Ph+ ALL protocols. Patient was switched to Dasatinib on day 11 due to substantial nausea and vomiting. Patient had no minimal residual disease (MRD) after Induction 1. She received an additional cycle of Induction chemotherapy per the high-risk arm of AAML 1031 before proceeding with 10/10 matched unrelated donor HSCT. TKI was held 30 days pre-transplant to minimize risk of veno-occlusive disease. TKI was restarted 7 weeks post-transplant and continued for 1 year. Day 100 bone marrow was MRD negative with undetectable BCR/ABL by quantitative PCR.The patient tolerated HSCT well overall with the exception of acute skin graft versus host disease (GVHD) that developed 137 days post transplant. GVHD is being managed with sirolimus, phototherapy and topical medications. She is currently 14 months post transplant and doing well.
Conclusion: Pediatric Ph+ AML is rare and not addressed by COG protocols and without an established standard treatment approach. This patient has done well after treatment as high risk with TKI followed by HSCT with continued use of TKI. With such a low incidence of pediatric Ph+ AML it is important to analyze treatment regimens of patients to help establish a standard of care.

Poster # 911

A NOVEL MAP3K8-GNG2 FUSION PREDICTED TO ACTIVATE THE MAPK PATHWAY IN AN ADOLESCENT WITH MELANOMA RESPONDING TO MEK INHIBITION

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Background: MAP3K8 is a MAP3K Serine/Threonine protein kinase that has a key role in the activation of ERK1/2 via MEK and in melanoma, drives resistance to BRAF inhibition by activating ERK primarily through MEK-dependent mechanisms. The kinase activity of MAP3K8 is regulated by the C-terminal domain and truncated MAP3K8 exhibits increased kinase activity and enhanced cell transformation compared to wild-type.
Objectives: We present an adolescent with melanoma with a previously unreported MAP3K8-GNG2 gene fusion that was only evident through the use of integrated comprehensive genomic analysis. The novel fusion is predicted to activate the MAPK pathway and led to targeted therapy with a MEK inhibitor resulting in a clinical response.
Design/Method: A 10 year-old male was diagnosed with a spitzoid melanoma of the right ankle with regional lymphatic spread and treated with complete lymph node dissection. Approximately one year later, the patient developed locally recurrent disease that quickly progressed with in transit and satellite metastases involving the right lower extremity. Immunostaining for BRAF V600 and BRAF break-apart FISH were negative. The patient was referred to our center and over the course of 15 months received multiple therapies due to disease progression including Ipilimumumab, Pembrolizumab, hyperthermic limb perfusion, and Talimogene Laherparaepvec. The patient was enrolled on the St. Jude Genomes for Kids (G4K) study and whole genome, exome and transcriptome sequencing were performed on a tumor and paired normal sample.
Results: Genomic analysis revealed an expressed and in frame MAP3K8-GNG2 fusion gene caused by a complex, but balanced, translocation between chromosomes 10 and 14 that preserved the MAP3K8 kinase domain, confirmed by RNASeq. The final 44 amino acids of MAP3K8 were replaced with the G protein gamma subunit-like domain of GNG2. The novel fusion was predicted to activate the MAPK pathway, indicating a potential role for MEK inhibitor therapy. Trametinib is a selective, small-molecule inhibitor of MEK1/2 that is FDA-approved for treatment of BRAF V600E/K-mutant metastatic melanoma. In vitro data also suggests a role for Trametinib in in BRAF/NRAS wild-type mela¬noma and activity of MEK inhibition for NRAS-mutated melanoma was recently shown in a phase II study. The patient was started on daily oral Trametinib and had marked improvement on physical exam and PET imaging after 4 months, despite treatment delays and dose-reductions due to asymptomatic decrease in cardiac function.
Conclusion: Our case highlights the importance of integrated tumor sequencing in identifying potentially druggable novel lesions such as the MAP3K8-GNG2 fusion described here.

Poster # 912

INFLIXIMAB INDUCED POLYMORPHIC LYMPHOPROLIFERATIVE DISORDER IN A PEDIATRIC PATIENT WITH CROHN'S DISEASE

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Background: The treatment of autoimmune diseases has been revolutionized in recent years secondary to immunomodulator agents. However, as with all therapy there can be side effects and complications. There has been an increased incidence of lymphoproliferative disorders, infections, and vascular disorders with anti-tumor necrosis factor alpha agents, such as infliximab. There has been limited experience with treatment of these disorders in pediatrics.
Objectives: To discuss management of polyclonal lymphoproliferative disorder in a pediatric patient with Chron's disease treated with infliximab.
Design/Method: We describe the case and the treatment of a patient with polyclonal lymphoproliferative disorder.
Results: A 14 year old male with a history of moderate to severe Crohn's disease had been treated with methotrexate and pentasa. However, this was discontinued secondary to pericarditis, and he was then managed on infliximab for 16 months. He presented with enlarging right groin lymph nodes at month 15. Initially, was treated with antibiotics. However, node continued to remain enlarged and grew in size. An ultrasound was done which showed enlarged right sided inguinal lymph nodes measuring largest 3 x 4.5 x 3 cm. He reported low grade fevers for several days, highest to 101.3 resolved with Tylenol. He denied any other symptoms or pain. He had an excisional biopsy and pathology was consistent with polyclonal lymphoproliferative disorder, EBV negative. Initial PET/CT was positive for inguinal lymph node and intense metabolically active enlarged right paratracheal and subcarinal lymph nodes and moderately metabolically active right inguinal lymph node. At this time infliximab was stopped and no additional therapy was given. One month after diagnosis, patient started to complain of severe pain in legs. He was unable to walk or do daily activities. A second follow up PET/CT was done six weeks later which showed Interval mild decrease in size and metabolic activity of metabolically active right paratracheal, subcarinal and right inguinal lymph node and also stable moderately diffuse increased skeletal activity. Laboratory data showed increased WBC to 23, no blasts, CRP 36, ESR 41. A bone marrow was done and was negative. Patient was then started on steroids with resolving pain and inflammation.
Conclusion: This case highlights the need for more studies of these disorders in pediatrics. Studies should also look at how these immunomodulator therapies interact with an underlying abnormal immune system to enhance the development of lymphoma and lymphoid proliferations. Providers should also be aware that stopping long term infliximab may cause a release of inflammatory cytokines.

Poster # 913

CLINICAL AND SURGICAL MANAGEMENT OF PIGMENTED EPITHELIOID MELANOCYTOMA OF THE HEAD AND NECK

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Background: Pigmented epithelioid melanocytoma (PEM) is a rare, generally low-grade, melanocytic tumor that can spread to regional lymph nodes. Management of these tumors involves removal of the primary skin lesion as well as sentinel lymph node biopsy. Further management of patients with sentinel lymph node metastasis is unclear as patients with PEM

have excellent prognosis compared with melanoma. Here we present two pediatric patients with PEM of the head and neck and their management strategies.
Objectives: To highlight the clinical and surgical management of pediatric PEM of the head and neck.
Design/Method: Retrospective review of medical records of two patients with PEM treated at Texas Children's Cancer Center in Houston, Texas.
Results: Case 1. A 7-year-old female presented with a 2-month history of a painful mole above the right clavicle. Excisional biopsy demonstrated a Breslow thickness 0.6 mm dome- and wedge-shaped lesion of sharply circumscribed melanocytic proliferation consistent with PEM. Right supraclavicular sentinel lymph node biopsy was negative for metastatic melanocytoma. The patient was followed clinically for recurrence for 20 months post-operatively before discharge from the oncology clinic. Case 2. A 10-year-old male presented with a 17-month history of a pigmented mole on the tip of the nose. Biopsy of the lesion demonstrated a densely pigmented proliferation of spindled and epithelioid melancoytes with Breslow depth 0.5 mm consistent with PEM. Due to the unique anatomical location, sentinel lymph node mapping showed drainage to both the left submandibular region and right supraclavicular region. Sentinel lymph node biopsies demonstrated microscopic metastatic disease in both sentinel lymph nodes. PET/CT was subsequently performed to evaluate for distant metastasis and did not identify any other areas of concern. Due to the morbidity of performing an extensive bilateral neck lymph node dissection and the generally indolent nature of PEM, we opted for conservative management with close clinical observation. The patient has been followed now for 6 months with no clinical signs of recurrence.
Conclusion: PEM of the head and neck in pediatric patients can present unique surgical challenges depending on location. Given the generally indolent nature of PEM and favorable prognosis, it may be feasible to clinically observe some patients after excision of the primary lesion and sentinel lymph node biopsy to avoid potentially morbid surgery and medical therapy.

Poster # 914

PHOTOTOXIC DERMATOSES IN CHILDREN UNDERGOING TREATMENT FOR ACUTE LEUKEMIA

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Background: Voriconazole is increasingly used for mold prophylaxis in children with acute leukemia and those undergoing transplantation; it is phototoxic and its adverse effects may be exacerbated by concomitant use of other photosensitizing agents.
Objectives: Describe 4 cases of phototoxic dermatoses in patients receiving voriconazole while undergoing treatment for leukemia.
Design/Method: Case series
Results: Case 1: A 4-year-old male treated for T-cell acute lymphoblastic leukemia (ALL) started voriconazole three months after diagnosis. Two weeks later, he received high-dose methotrexate (HDMTX), after which he was noted to have fragile skin that tore easily. Following the second cycle of HDMTX, he developed redness of his forearms/cheeks/neck/ears. Three days after his third cycle, his arms became erythematous with blistering, with a sharp line of

demarcation where his sleeves ended. He was treated with topical corticosteroids. Voriconazole was discontinued and his skin improved over 48 hours.Case 2: A 6-year-old male with Pre-B ALL and nodular pulmonary infection was treated with voriconazole. He developed a mild sunburn on his arms/face/neck/scalp prior to his second cycle of HDMTX and the rash worsened after HDMTX, but then improved with emollients. After the third cycle of HDMTX, the erythema returned and worsened to 2nd degree burns. His fourth cycle of HDMTX was delayed by one week and the dose of MTX was decreased by 25%; the rash recurred but was less intense. After discontinuing voriconazole, the rash improved but continued to flare with any sun exposure throughout the remainder of his therapy.Case 3: A 16-month-old female with acute myeloid leukemia (AML) and on voriconazole mold prophylaxis was admitted to receive cytarabine/etoposide. On day 3, she developed an erythematous eruption of the scalp in the distribution of a sunburn sustained the week prior. Over the next several days, erythema worsened and blistered. She was treated with 2.5% hydrocortisone ointment and petroleum to the scalp, and the rash resolved over 72 hours.Case 4: A 12-year-old male with relapsed ALL was on voriconazole mold prophylaxis; three months later he received total body radiation for transplant conditioning. Two weeks later, he developed confluent erythema over sun-exposed areas of his face/neck/wrists/forearms bilaterally. He was treated with topical corticosteroids and absorbent soft silicone foam dressings and skin lesions healed.
Conclusion: Concomitant use of voriconazole and methotrexate appears to be synergistically phototoxic, and substitution of voriconazole should be considered for patients with skin eruptions. Strict sun-protection measures should be implemented in all patients receiving photosensitizing agents.

Poster # 915

RESPONSE TO TYROSINE KINASE INHIBITOR LENVATINIB IN A CHILD WITH REFRACTORY PAPILLARY THYROID CARCINOMA

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Background: Lenvatinib is an oral multi-targeted tyrosine kinase inhibitor that is approved by the Food and Drug Administration for the treatment of adults with radioiodine refractory well differentiated thyroid carcinoma. The effect of lenvatinib in children with thyroid carcinoma has not been published.
Objectives: To present a child with refractory papillary thyroid carcinoma whose disease responded to lenvatinib.
Design/Method: Case report.
Results: A 14-year-old female with a previous history of asthma presented with respiratory distress and neck swelling. One month prior, she had been treated for miliary tuberculosis in Mexico. On presentation, she required 10 liters of supplemental oxygen and initial computed tomography (CT) scan of the neck showed massive bilateral cervical lymphadenopathy and complete replacement of the thyroid gland with tumor. Papillary thyroid carcinoma was diagnosed based on fine needle aspiration cytology. Qualitative BRAF p.V600E mutation was negative. CT scan of the chest revealed numerous bilateral pulmonary nodules, and radioactive

iodine was not a feasible option given extensive lung disease. The patient was also not deemed a surgical candidate, and was started on the oral kinase inhibitor sorafenib at 200 mg/m2 twice a day. Despite a favorable clinical and radiographic response within two weeks, she presented with respiratory distress and an oxygen requirement four months after starting sorafenib. The patient was subsequently enrolled on a phase 1 study with oral lenvatinib at 14 mg/m2/day. She had a dramatic clinical improvement and the tumor showed partial response after four cycles. Total thyroidectomy and lymph node dissection was attempted after five cycles; however only partial debulking was possible due to the adherent and infiltrative nature of the tumor. She had tumor progression in the lungs while the lenvatinib was held in the perioperative period. She was taken off protocol and continued on lenvatinib off study. The patient experienced multiple episodes of grade 3 proteinuria that required dose interruptions and adjustments. Twelve months after starting lenvatinib, she is receiving 7.5 mg/m2 of lenvatinib on alternate days with stable disease and good quality of life.
Conclusion: Lenvatinib may be an option for children with advanced papillary thyroid carcinoma that is refractory or not amenable to radioactive iodine treatment. The phase 2 study of lenvatinib in children with refractory thyroid carcinoma (NCT02432274) is currently ongoing.

Poster # 916

EXTRAMEDULLARY MASS WITH IMMUNOPHENOTYPE DISTINCT FROM BONE MARROW AS INITIAL PRESENTATION OF MLL REARRANGED B-ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Extramedullary soft tissue masses may be the first presentation of a pediatric hematopoietic malignancy, of which the most common are B cell leukemia/lymphoma. The treatment regimens for precursor B-cell vs. mature B cell malignancies are very different in intensity and duration. To make the correct diagnosis we rely on morphology, immunophenotyping and cytogenetic analysis.
Objectives: We describe a unique case of B lymphoblastic leukemia presenting with unilateral maxillary mass and upon bone marrow evaluation, found to have conflicting immunophenotyping results between the primary mass and bone marrow.
Design/Method: Our patient presented with a facial mass, biopsy of the mass was performed, with initial pathology consistent with small round blue cell tumor. Given location and appearance differential diagnosis included rhabdomyosarcoma and neuroblastoma. However immunohistochemical staining was consistent with a hematologic malignancy, flow cytometry of the biopsy was done, and bone marrow biopsy/aspiration was obtained as part of the work-up. Flow cytometry results could not be reconciled and forced us to obtain a separate bone marrow specimen for testing at an outside laboratory, which finally allowed us to make a unifying diagnosis.
Results: Flow cytometry of the facial mass demonstrated features of B-cell lymphoblastic lymphoma with +CD19, CD38 and dim TdT, and negative CD20, CD10 and CD34. Flow cytometry from the first bone marrow aspiration demonstrated markers of both precursor (negative CD20) and mature B lymphocytes (lambda restriction, negative TdT, negative CD10,

negative CD34). FISH for MYC, BCL6, and t(8;14) were negative, but FISH for MLL rearrangement was positive. Despite the mixed B lineage immunophenotype that was initially reported on the bone marrow, the reference laboratory classified it as a B lymphoblastic leukemia. FISH of the facial mass was also positive for MLL rearrangement. As a result, we have classified his disease as B lymphoblastic leukemia with MLL rearrangement.
Conclusion: There have been cases of Burkitt-type lymphoblastic leukemia with precursor B cell immunophenotype, and B leukemia with morphologic and flow cytometry markers of both immature and mature phenotypes have been reported previously. B-acute lymphoblastic leukemic blasts with MLL rearrangement have been reported to be CD10 negative. We believe that this is the first case presentation of B-lymphoblastic leukemia demonstrating two distinct clonal populations at diagnosis from medullary and extramedullary sites.

Poster # 917

SIGNET RING CELL ADENOCARCINOMA OF THE STOMACH ACHIEVED PROLONGED LIFE WITH CRIZOTINIB, A TARGETED THERAPY FOR MET AMPLIFICATION

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Background: Signet ring cell adenocarcinoma of the stomach is an aggressive form of gastric cancer, which carries a poor prognosis. MET amplification in gastric cancer has been variously reported and clinical trials using MET-directed targeted therapy are ongoing in adults. There are, however, only a limited number of cases of pediatric gastric cancer reported and as of date, there is no report of treatment with MET inhibitor, as a single or multi-agent therapy, in children.
Objectives: Herein, we present a case of a 15-year old male with stage IV signet ring cell adenocarcinoma of the stomach who was treated with a MET inhibitor and conduct a review of the literature.
Design/Method: A retrospective chart review of the above case is performed and a review of the literature is conducted.
Results: Fifteen-year old male presented with a two-month history of epigastric and abdominal pain with emesis. Histopathology of endoscopic biopsy established the diagnosis of signet ring cell adenocarcinoma of the stomach. Genomic profiling of the primary tumor by Foundation Medicine revealed 31 copies of MET amplification, TP53 R273H mutation, and CDKN1B G97fs”22 mutation. He received the standard multi-agent chemotherapy, however he had recurrent tumors at the end of therapy. Crizotinib, a dual ALK/MET inhibitor, was selected for targeted therapy, which offered remission on PET imaging that was sustained for 8 months, after which he developed progressive disease.
Conclusion: This report illustrates the efficacy of therapeutically targeting a pediatric gastric cancer with a dual ALK/MET inhibitor. Crizotinib was well tolerated and the patient achieved 8 months of quality of life. With careful review of the literature, including personal communications with pharmaceutical companies, the targeted therapy approach could be a viable option for treating a subset of pediatric cancers. Our case demonstrates an urgent need for developing clinical trials that incorporate targeting aberrant gene alterations in childhood cancer.

Poster # 918

ACUTE MEGAKARYOBLASTIC LEUKEMIA PRESENTING AS AN UNDIFFERENTIATED SMALL ROUND BLUE CELL MASTOID MASS

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Background: Myeloid sarcoma (MS) is a rare extramedullary mass of myeloid blasts that can precede, coincide or follow the diagnosis of acute myeloid leukaemia (AML). Without an antecedent history of AML, MS can be missed. In particular, extramedullary acute megakaryoblastic leukemia (AMKL) is easily misdiagnosed as non-hematopoietic neoplasms/sarcomas due to overlapping morphology. To date, there is only one prior report of mastoid presentation.
Objectives: To illustrate the challenge of diagnosing AMKL in a child who presented with a mastoid mass.
Design/Method: Case report.
Results: A 2 year-old boy was consulted to St. Jude Children's Research Hospital for evaluation of Ewing-like undifferentiated small round cell sarcoma that presented as a mastoid mass. This child first presented with a right mastoid swelling 3 months prior, otherwise well. Two months later, he became febrile and unable to walk. CT/MRI revealed a 4x6 cm mastoid tumor with extensive osseous destruction and intracranial extension indenting the cerebellum. Innumerable pelvic and vertebral metastases with a T6 compression fracture were found. An open biopsy of the mass showed a small round blue cell tumor composed of cells positive for CD31, CD34, FLI-1, WT1, and negative for CD99, CD45, PAX-5, desmin, myogenin, MyoD1, and chromagranin. Fluorescent in-situ hybridization was negative for rearrangements in EWSR1, FUS, CIC or BCOR genes. A presumptive diagnosis of Ewing-like small round cell sarcoma was made. However upon transfer to our institution, further immunostaining demonstrated positivity for CD56, CD163, cKit, CD43, and CD33, and negativity for vimentin, EMA, cytokeratin AE1/AE3, CD68, CD1a, myeloperoxidase, lysozyme, and S-100. These findings were diagnostic of myeloid sarcoma, promoting bone marrow evaluation that showed increased myeloblasts. No MLL or RBM15/MKL1 translocation was found, and the only clonal abnormality was t(3;16)(p21;q24). By flow cytometry, blasts were positive for CD33, CD34, CD117, CD41 (dim), CD11b (subset) CD56 (bright), and CD16, while negative for CD4, CD14, CD11c, CD64, CD123, CD235a, CD19, cyCD3, and MPO. Immunohistochemical studies showed sheets of blasts with uniform expression of CD42b, compatible with AMKL. This patient is being treated with our frontline AML protocol, AML08.
Conclusion: AML, particularly AMKL, can present as extramedullary tumor with clinicopathological features mimicking sarcoma. Clinical suspicion is vital, and MS should be considered as a differential diagnosis of small round blue cell tumors especially in children. A broad and judicious immunohistochemical panel, including aberrant markers for MS such as CD43 and myeloid markers CD33 and CD34, will facilitate accurate diagnosis of undifferentiated tumors.

Poster # 919

MALIGNANT TRANSFORMATION OF TESTICULAR TERATOMA TO PRIMITIVE NEUROECTODERMAL TUMOR, ADENOCARCINOMA, AND OSTEOSARCOMA WITH COMPLETE REMISSION AFTER SURGERY AND COMBINATION CHEMOTHERAPY

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Background: Teratomas consist of pluripotent tissue capable of malignant transformation along germ cell lines. Rarely, mixed germ cell tumor (GCT) teratomas may also transform to somatic malignancies of histologies outside traditional germ cell lineages. Sarcoma is the most frequent histologic transformation, followed by adenocarcinoma and primitive neuroectodermal tumor (PNET). Osteosarcoma somatic transformation is rare and, based on our review, has been reported only once.
Objectives: To present a novel case of testicular GCT with transformation into multiple malignant histologies.
Design/Method: Case Report and Literature Review
Results: A 19 year old man presented with a three month history of an enlarging right testicle. After initial evaluation, a unilateral orchiectomy was performed. Pathology of the testicle revealed mature and immature teratoma with somatic PNET transformation (30-50%), yolk sac tumor (3%), and embryonal carcinoma (2%). Staging evaluation revealed retroperitoneal lymph nodes matted in a mass. Retroperitoneal lymph node dissection (RPLND) was performed and pathology revealed mixed teratoma with transformation to PNET (60-70%). 18 F-FDG-PET completed following RPLND revealed an avid 1 cm left lower lobe lung nodule. Combination chemotherapy was initiated with alternating vincristine/doxorubicin/cyclophosphamide (VDC) and ifosfamide/etoposide (IE). Wedge resection of the left lower lung lobe nodule after 9 cycles of chemotherapy revealed mature teratoma (40%), osteosarcoma (30%) and adenocarcinoma (30%). Treatment was subsequently amended to an osteosarcoma based treatment regimen that contained 4 cycles of cisplatin with doxorubicin again alternating with 3 cycles of ifosfamide and etoposide. Total cumulative dose included: doxorubicin 600mg/m2, cisplatin 360mg/m2, ifosfamide 54g/m2, etoposide 3g/m2, and cyclophosphamide 6g/m2. End of therapy evaluation was negative for any evidence of disease.
Conclusion: Patients with teratomas containing somatic PNET transformation have been reported to respond to VDC/IE therapy with 2-year cancer specific survival of 50%. There is currently no standard of care treatment for osteosarcoma somatic transformation. We have demonstrated that thorough surgical resection and combination chemotherapy targeted to the most aggressive subtype can lead to disease control and durable remission in patients with GCT containing somatic malignancy of multiple histologies. Further research is needed to adequately define treatment paradigms for patients with mixed GCT transformed to multiple somatic malignancies; however, directing treatment towards the most aggressive subtypes with targeted chemotherapy and surgical resection should be considered.

Poster # 920

A CASE OF DERMATOTOXICITY SECONDARY TO SKEWED 6-MERCAPTOPURINE METABOLISM IMPROVED WITH ALLOPurinol

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Background: Mercaptopurine (6-MP) is a crucial component of acute lymphoblastic leukemia (ALL) treatment. Major active metabolites of 6-MP include 6-thioguanine nucleotide (6-TGN) and 6-methymercaptopurine nucleotide (6-MMPN). 6-TGN is responsible for producing anti-leukemia effects, and 6-MMPN may lead to hepatotoxicity.
Objectives: To describe the rare clinical findings of dermatotoxicity and hypoglycemia in the setting of 6-MMPN toxicity as well as describe the use of allopurinol to prevent skewed thiopurine metabolism.
Design/Method: Case report
Results: A 4-year-old female with high-risk ALL presented for initiation of Cycle 4 of maintenance chemotherapy (oral methotrexate (125% dosing) and 6-MP (150% dosing)) with a 2-3 week history of peeling skin on her hands and feet, cracked lips, and onycholysis. Methotrexate was held due to concerns for skin toxicity; however, 6-MP was continued due to failure to achieve ANC goals. Dermatologic findings quickly progressed to ulcerations of the hands, feet, and perianal area. The patient was admitted to the hospital for skin biopsy and pain management. Biopsy revealed cytotoxic dermatitis, but no infectious organisms. Bone marrow aspirate and biopsy showed no evidence of leukemia. Thiopurine methyltransferase activity was normal but 6-MP metabolites returned abnormal with 6-MMPN elevated at 18,102 pmol/RBC (normal ≤5700 pmol/RBC) and 6-TGN decreased at 38 pmol/RBC (normal 230-400 pmol/RBC). It was also discovered that the patient was having early morning hypoglycemic episodes with glucoses 30-50 mg/dL. 6-MP was subsequently discontinued and the patient experienced a dramatic and rapid improvement in both her hypoglycemic episodes as well as her acral and perianal erythema. 6-MP was eventually restarted at 50% of previous dose with allopurinol added at 10 mg/kg/day without further episodes of hypoglycemia or return of her dermatologic manifestations. On repeat laboratory evaluation 2 months later, her thiopurine metabolites had improved with 6-TGN increased to 59 pmol/RBC and undetectable level of 6-MMPN.
Conclusion: Hepatotoxicity, pancreatitis, and hypoglycemia are known side effects of elevated 6-MMPN levels in patients that preferentially metabolize 6-MP to 6-MMPN. This case demonstrates a rare side effect of bullous acral erythema as a result of extremely elevated 6-MMPN levels. Allopurinol has been successfully used to prevent hepatotoxicity and pancreatitis in ALL patients with skewed thiopurine metabolism; the addition of allopurinol may improve dermatologic side effects and hypoglycemia associated with altered thiopurine metabolism, as well. Further work should be done to elucidate if the addition of allopurinol could also improve drug exposure, and thus, decrease relapse rate in patients with skewed thiopurine metabolism.

Poster # 921

AGENESIS OF THE CORPUS CALLOSUM AND HEPATOBLASTOMA: A NEW ASSOCIATION

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Background: Up to 20% of children with hepatoblastoma have associated congenital anomalies, including genitourinary abnormalities and defined genetic syndromes with specific chromosomal changes such as Familial Adenatomatous Polyposis and Beckwith-Wiedemann Syndrome.
Objectives: To report a possible new association between agenesis of corpus callosum and hepatoblastoma.
Design/Method: Case report.
Results: Case 1: A 7 month old male with a history of prematurity, developmental delay and multiple congenital abnormalities including agenesis of the corpus callosum, cleft palate, brachial dysplasia and short stature, presented with abdominal mass and AFP level of 250,000 ng/ml. Imaging and biopsy revealed PRETEXT stage III hepatoblastoma. He underwent chemotherapy with cisplatin, 5-flourouracil, vincristine, and doxorubicin, followed by complete surgical resection. He received two cycles of adjuvant chemotherapy, and has been in remission for 10 years from diagnosis. Case 2: A 6 month old female with multiple congenital abnormalities, including craniosynostosis, microcephaly, ASD/VSD, dysmorphic facial features, shortened first and fifth digits, and an anteriorly placed anus presented with acute respiratory failure and hypoxemia. The patient was born at approximately 36 weeks and was found to have severe IUGR with birth weight less than 1500 grams. She was diagnosed with likely Bohring-Opitz syndrome, although genetic testing for ASXL1 gene changes were negative. Abdominal ultrasound revealed incidental multifocal cystic liver mass with elevated AFP (17,700 ng/ml). Biopsy revealed localized epithelioid hepatoblastoma, PRETEXT stage IV. MRI brain showed multiple midline abnormalities, including complete agenesis of the corpus callosum with mild cystic expansion of the third ventricle, absent pituitary bright spot, hypoplasia of bilateral optic nerves, and mild hypoplasia of the inferior vermis. Additional findings were suspicious for polymicrogyria within the bilateral frontal and right anterior mesial temporal region. Chromosomal microarray and whole exome sequencing revealed multiple abnormalities, but none known to be associated with her clinical picture. Due to her clinical condition, no disease directed therapy was administered and she died secondary to respiratory failure.
Conclusion: We present two cases of hepatoblastoma in children with agenesis of the corpus callosum. Given the rarity of both conditions, this is likely a true association. Further investigation into the underlying genetic and molecular changes of this association is warranted.

Poster # 922

ACUTE MYELOID LEUKEMIA WITH MLL GENE REARRANGEMENT INITIALLY PRESENTING WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of intense immune activation leading to diffuse inflammation with prolonged fevers, bone marrow failure, hepatosplenomegaly, and signs of end-organ damage. HLH can be primary (familial) or secondary (triggered by disease processes such as infection and malignancy). Most malignancy-

related cases are of lymphoid origin. HLH as a treatment complication of acute myeloid leukemia (AML) or vice versa has also been reported. The presentation of HLH and AML concurrently, however, is rare.
Objectives: To discuss a patient with HLH triggered by undifferentiated AML with MLL gene rearrangement and approach to therapy.
Design/Method: Case report
Results: A previously healthy 10-year-old male presented with fever for 8 days, hemodynamic instability, respiratory distress, hepatosplenomegaly, and lymphadenopathy. Laboratory abnormalities included pancytopenia, hyponatremia, transaminitis, hypertriglyceridemia, hypofibrinogenemia, elevated lactate dehydrogenase, elevated uric acid, and ferritin above 30,000 ng/mL. His course was complicated by respiratory failure requiring mechanical ventilation and acute renal failure requiring dialysis.The patient met 5 of 8 diagnostic criteria defined by HLH-2004 trial with fever, splenomegaly, pancytopenia, hypertriglyceridemia and hypofibrinogenemia, and ferritin above 500 ng/mL. Results later showed elevated soluble CD163 and soluble IL-2 receptor levels. Low or absent natural killer cell activity and hemophagocytosis in bone marrow were not found. Testing for familial HLH and infectious triggers was negative. Peripheral blood smear showed circulating blasts. Bone marrow biopsy and aspiration confirmed undifferentiated AML. Cytogenetic analysis demonstrated a complex rearrangement involving chromosome 10p and 11q with detection of MLL/MLLT10 fusion protein. Dexamethasone was initiated for HLH therapy along with cytarabine, daunorubicin, and etoposide for AML induction therapy. At the end of induction, he achieved morphological and molecular remission with negative minimal residual disease and normalization of HLH markers. The patient has now completed three cycles of AML therapy and is awaiting hematopoietic stem cell transplantation.
Conclusion: HLH secondary to AML at presentation is not well studied. The role of the MLL gene rearrangement is also unclear; there is evidence of MLL gene rearrangement in etoposide-related AML following HLH treatment but limited information on the association of MLL gene rearrangement with concurrent HLH compared to other known chromosomal abnormalities. Given the rarity of this presentation, a standard of care has not been established. Treatment for HLH in the context of newly diagnosed AML should focus on the underlying disease process, and the addition of corticosteroids should be considered.

Poster # 923

INTRAVENOUS BEVACIZUMAB FOR THE TREATMENT OF SEVERE RECURRENT RESPIRATORY PAPILLOMATOSIS IN A PEDIATRIC PATIENT

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Background: Recurrent respiratory papillomatosis (RRP) is a rare disease caused predominantly by human papilloma virus (HPV) types 6 and 11 and is characterized by papillomatous lesions throughout the respiratory tract. Surgical removal of papillomas by laser microsurgical ablation is the treatment of choice. Adjuvant therapy has included alpha-interferon, acyclovir, ribavirin, intra-lesional cidofovir, indole-3-carbinol, Cox-2 inhibitors, and H-2 blockers. In severe cases of diffuse RRP and cases with pulmonary lesions, surgical and intra-lesional therapy is not feasible.

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), inhibiting angiogenesis. It is approved by the FDA for use in various malignancies. Evidence supports the use of intralesional bevacizumab in management of RRP and serves as the basis of investigating systemic bevacizumab as an effective adjuvant treatment. Only two case reports exist in literature describing the use of systemic bevacizumab for RRP.
Objectives: We report a case of a child with widespread laryngotracheal and pulmonary RRP successfully treated with intravenous bevacizumab.
Design/Method: Case Report.
Results: In this report, we describe a 7 year old male diagnosed with RRP at 11 months of age. Lesions were positive for HPV type 11. The patient was previously treated with alpha-interferon, celecoxib, intra-lesional cidofovir, and cimetidine. He had undergone approximately 150 procedures for surgical ablation of papillomas. Immediately prior to treatment with intravenous bevacizumab, the child had diffuse laryngotracheal papillomatosis and multiple pulmonary nodules and cavitary lesions consistent with RRP. He was started on bevacizumab 10mg/kg IV every 2 weeks. At bronchoscopy exam 6 weeks later, there were no papillomas seen in the larynx and few in the trachea. A chest CT six months after starting therapy revealed improvement of notable cavitary lesions. Subsequent exams showed no to rare papillomas and treatment was stopped after 11 months. Systemic bevacizumab was restarted one year later with return of diffuse papillomas. He again had quick resolution of papillomas and dosing was changed to every 3 weeks. During therapy, the patient developed hypertension requiring anti-hypertensives. This is a known side effect of bevacizumab, and the patient also had a family history of hypertension.
Conclusion: Severe cases of RRP may progress to diffuse papillomas throughout the respiratory tract. There is no standard medical management. Systemic therapy with intravenous bevacizumab may offer an effective option in medical management of laryngotracheal and pulmonary RRP. Further study is needed to define optional dosing and monitor side effects.

Poster # 924

DELAYED CLEARANCE OF HIGH DOSE METHOTREXATE ASSOCIATED WITH HYPERTRIGLYCERIDEMIA

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Background: High dose methotrexate is used in the treatment of many pediatric malignancies including leukemias, lymphomas, and solid tumors. Several factors have been associated with delayed clearance of methotrexate, including elevated creatinine levels, increased acidity of the urine, accumulation of methotrexate in fluid collections such as ascites and effusions, and concurrent use of medications that inhibit renal clearance of methotrexate, such as non-steroidal anti-inflammatory drugs, proton pump inhibitors, and several antibiotics. There is little data regarding lipid abnormalities and their potential impact on the metabolism and clearance of methotrexate.
Objectives: We report a case of delayed methotrexate clearance in the setting of significant hypertriglyceridemia (>5x the upper limit of normal) without other identifiable risk factors. After treatment of hypertriglyceridemia, the patient had a normal time to methotrexate clearance

following his subsequent high dose methotrexate infusion.
Design/Method: Case report.
Results: A six year old male with high risk acute lymphoblastic leukemia was given a 5g/m2 infusion of high dose methotrexate over 24 hours per protocol. When methotrexate levels remained elevated above the clearance threshold of 0.1 µmol/L at 176 hours after the start of the infusion, his case was further reviewed and his blood sample was noted to be lipemic. The methotrexate level measured in that lipemic sample was 0.42 µmol/L. When fat was separated from the sample, the level in the remaining serum measured only 0.08-0.1 µmol/L. When resuspended, the fat layer contained the residual methotrexate, ruling out a lipemia interference with the assay. The patient's triglyceride level was found to be elevated at 789 mg/dL, presumably related to a recent asparaginase dose. Treatment for hypertriglyceridemia was initiated with fenofibrate and fish oil. Triglyceride levels were followed concurrently with methotrexate levels for the remainder of his admission until he cleared, which finally occurred in the setting of decreasing triglyceride levels (371 mg/dL) 224 hours after the initiation of the methotrexate infusion. Triglyceride levels were lower during his next admission (range 94-387 mg/dL) and methotrexate cleared by hour 48.
Conclusion: High triglyceride levels may be associated with delayed clearance of methotrexate. In patients with delayed methotrexate clearance in the absence of renal dysfunction or other risk factors, practitioners should consider checking lipid levels, especially for those patients who have received medications known to affect lipid metabolism such as peg-aspariginase and propofol. Pharmacologic treatment of hypertriglyceridemia may improve methotrexate clearance in these patients, limiting their risk for toxicity, and decreasing hospital length of stay.

Poster # 925

CARNEY-STRATAKIS SYNDROME: A RARE CASE IN AN ADOLESCENT WITH BILATERAL RENAL CYSTS

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Background: Gastrointestinal stromal tumors (GIST) are a rare mesenchymal tumor of the gastrointestinal tract in children. The small subset without KIT or PDGFRA mutations are wild-type GIST, including succinate dehydrogenase (SDH)-deficient GIST. Even more rare is a germline mutation in the SDH genes, (SDHB, SDHC, SDHD), resulting in Carney-Stratakis Syndrome, the inherited cancer syndrome with GIST and paragangliomas.
Objectives: To highlight a SDH-deficient GIST with germline mutation and the need for pediatric management guidelines.
Design/Method: Case Report.
Results: 16 year old male presented with pallor, lightheadedness and headaches. He later reported early satiety and melanotic stool. Maternal family history was significant for grandfather with lung cancer. Paternal history was unknown. On exam, he was pale, with systolic flow murmur, without hepatosplenomegaly or palpable abdominal masses. Laboratory studies were significant for hemoglobin 6.6g/dL. Stool guaiac was positive. Chest x-ray was unremarkable, as were studies for celiac disease. Abdominal magnetic resonance imaging (MRI) revealed a large polypoid mass in the lesser curvature of the gastric antrum and bilateral simple

renal cysts. On esophagogastroduodenoscopy (EGD), a pedunculated submucosal mass was discovered in the stomach antrum. Pathology revealed wild-type GIST with no KIT, BRAF or PDGFRA mutations, mixed spindle and epithelioid histology and high grade mitotic activity. Immunohistochemistry showed loss of SDH activity. The patient underwent a subtotal gastrectomy for resection of the 9cm multifocal mass. Abdominal lymph nodes were disease positive. Genetic testing revealed a germline mutation in the SDHC gene, suggesting Carney-Stratakis Syndrome, but work up for paragangliomas was negative. Given the renal cysts and concern for polycystic kidney disease, sequencing of PKD1 and PKD2 genes was done but revealed only a benign variant in the PKD1 gene.
Conclusion: While very rare, GIST must be considered in adolescents with gastrointestinal blood loss. If SDH-deficient GIST is discovered, germline mutation testing is warranted due to the genetic implications. There are no consensus guidelines for the management of pediatric GIST, within Carney-Stratakis Syndrome or found sporadically. Surgical resection is the mainstay of treatment as they are not frequently responsive to tyrosine kinase inhibitors. We will follow our patient with physical exam, complete blood counts and 18-FDG-PET scan every 3 months for 2 years and then consider increasing that interval. Further studies are needed to determine better therapeutic and targeted approaches to these rare and unique tumors. Furthermore, while SHD-deficient renal call carcinoma has been documented with SDH germline mutations in older patients, renal cysts have not been described.

Poster # 926

WHEN LARGE PROBLEMS PRESENT IN SMALL PATIENTS: A CASE OF CHILDHOOD T CELL LARGE GRANULAR LYMPHOCYTIC LEUKEMIA

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Background: Large granular lymphocytic (LGL) leukemia is a disease of adults. It most commonly manifests as an indolent T cell lymphoproliferative disorder often coinciding with autoimmune findings. It is characterized by recurrent infections with neutropenia, anemia, and splenomegaly. With a mean age of onset of 60 years, its incidence in the pediatric population is effectively unheard of, with only a handful of adolescent cases ever having been reported.
Objectives: To describe the unique case of a pediatric patient with LGL leukemia, and to introduce this disease to the differential diagnosis of unexplained childhood cytopenias and splenomegaly.
Design/Method: A 13 year old girl presented with fatigue, worsening mouth sores, and massive splenomegaly. A CBC revealed an isolated neutropenia (absolute neutrophil count 100/mm3), and an extensive evaluation for infectious and autoimmune etiologies was negative. Review of the peripheral blood film revealed numerous lymphocytes with clusters of azurophilic granules, prompting evaluation for LGL leukemia. A clonal bone marrow population of mature lymphocytes revealed the characteristic immune phenotype of inverse CD4/CD8 and positive alpha-beta T cell staining, confirming the unlikely diagnosis of LGL leukemia. The presence of the Y640F STAT3 mutation was also identified. Review of the literature revealed no reports of a patient this young with this disease.
Results: Based on the adult standard of care for LGL leukemia, our patient began a therapeutic

trial of oral methotrexate and prednisone. After two months of therapy, her splenomegaly dramatically regressed, her mouth sores resolved, she had a modest increase in neutrophil count, and there was a decline in circulating LGL population.
Conclusion: Review of the peripheral blood film is essential in children with unexplained splenomegaly and neutropenia, and in this case was pivotal in directing evaluation for a very rare disease. Although this child has had a favorable initial response to therapy, challenges remain in controlling this chronic indolent leukemia for a lifetime.

Poster # 927

WHEN BIG KIDS GET LITTLE KID TUMORS: THE C0-OCCURRENCE OF A PLEUROPULMONARY BLASTOMA, NODULAR THYROID GOITER AND OBTURATOR MALIGNANT ESENCHYMAL NEOPLASM

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Background: Pleuropulmonary blastoma (PPB) is described as a sentinel disease of a distinct DICER1-related hereditary tumor syndrome; thus, the finding of PPB suggests the possibility of developing subsequent malignancies. Multinodular goiter and thyroid carcinoma have frequently been reported to occur in those with DICER1-related PPB although not simultaneously. We describe a novel presentation of DICER1 mutation in a 13-year-old female with co-occurrence of PPB, multinodular goiter and malignant mesenchymal neoplasm.
Objectives: Review the differential diagnoses of a pulmonary mass seen on chest CT.Recognize the association of DICER1 mutation and PPB and the predisposition to development of additional tumors.
Design/Method: 13-year-old Hispanic female presented with complaints of dizziness, chest pain, palpitations and shortness of breath for one day. She was recently admitted to the hospital for similar symptoms and was diagnosed with pneumonia with ipsilateral pleural effusion. Chest CT showed a right-sided lesion diagnosed as a congenital pulmonary airway malformation (CPAM) and a thyroid lesion. She was discharged on oral antibiotics. She returned to our institution four days later.
Results: The patient underwent a complicated VATS procedure for removal and analysis of the lesion, where she suffered an intraoperative cardiac arrest due to respiratory failure and, once stabilized, remained intubated and ventilated in the PICU until recovery. Pathological evaluation of excised lesion revealed a solid pulmonary mass with residual cystic areas consistent with a type II PPB. On further evaluation of the thyroid lesion by fine-needle aspirate the diagnosis of nodular goiter with a hyperplastic focus was made. Patient underwent a PET scan which had increased FDG uptake at the right obturator. A fine-needle aspirate and core biopsy of the lesion showed a malignant mesenchymal neoplasm morphologically similar to the right lung tumor. Subsequent genetic testing of the pulmonary mass revealed biallelic loss of function and RNAse IIIB missense DICER1 mutations.
Conclusion: Germline mutations in the micro-ribonucleic acid processing gene DICER1 are associated with increased risk of several tumors including PPB, cystic nephroma, ovarian Sertoli-Leydig cell tumors, pituitary blastoma, and thyroid carcinoma. Most cases of PPB are diagnosed

in childhood between the ages of 1-4 years. In newborns and infants the lesion is often mistaken for a CPAM and, since it is only rarely seen in older children, it can easily be misdiagnosed as with our patient. While PPB occurs infrequently, clinicians should be aware of the potential for additional malignancies in patients with diagnosis of PPB in which DICER1 mutation is commonly implicated.

Poster # 928

UNIQUE CASE OF CENTRAL NEROUS SYSTEM HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)FOLLOWING INDUCTION THERAPY FOR CNS-III T-ACUTE LYMPHOBLASTIC LEUKEMIA (T-ALL) IN A CHILD SUCCESSFULLY MANAGED WITH HLH-2004 PROTOCOL AND CNS RADIATION

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Background: In children, malignancy-associated secondary HLH (mHLH) is very rare, but most commonly reported with T lymphomas followed by B lymphomas and T-ALL. Management of mHLH is challenging due to heterogeneity of inciting factors and overlapping features of HLH and neoplasms. CNS-HLH is characterized by CNS symptoms, pleocytosis and elevated CSF protein. Most children reported with mHLH during ALL therapy are managed by withholding chemotherapy and instituting HLH specific therapy and BMT. We found 15 pediatric cases of T-ALL mHLH and none of CNS-HLH. Mortality amongst these patients was > 80%.
Objectives: Describe a case of CNS-III T-ALL asociated CNS-HLH managed with sequential specific HLH followed by T-ALL therapy, including cranial irradiation.
Design/Method: PubMed search for pediatric mHLH in T-ALL was performed.
Results: A 9 year old female presenting with blindness was diagnosed with CNS-III T-ALL and treated per AALL1231. End -induction bone marrow (BM) showed remission, CNS was negative, vision normalized, peripheral counts recovered and she was clinically well. On day 36 she presented with fever, anemia/thrombocytopenia, direct bilirubin of 13 and rapidly developing delirium, aphasia, and psychosis. Blood cultures were negative, urine grew E. coli and respiratory viral panel showed enterovirus. CSF showed 32 WBCs(no blasts), protein 95 (7-35mg/dL), negative bacterial/fungal/viral cultures/pcr. MRI was normal; EEG showed diffuse slowing. Due to persistent fevers despite broad spectrum anti-microbials, persistent hyperbilirubinemia, worsening pancytopenias, rising CRP, and worsening CNS symptoms,CNS-HLH was considered. Ferritin-5500, triglycerides-200,Soluble IL-2 receptor >4000,very low NK-cell activity, CNS pleocytosis with very high protein,BM hemophagocytosis confirmed CNS-HLH . Within one week of HLH specific therapy, she regained normal speech/mentation, all labs normalized. Familial HLH testing was negative. Planned AALL1231 cranial irradiation with a block of maintenance chemotherapy was given earlier then protocol specified because we/HLH experts believed the CNS-III leukemia was ultimately driving the CNS symptoms and that rapid eradication of residual CNS leukemia was necessary to prevent HLH recurrence. Since treatment she has maintained remission with no CNS issues and normal labs for 1 year.
Conclusion: Infection, CNS leukemia and neurotoxicity are considerations in ALL-patients with altered mental status. However CNS-HLH must also be considered when patients worsen while treated appropriately and labs fail to improve. In our patient, CNS-III T-ALL,

immunosuppression and infection or all triggered CNS-HLH. The challenging decision is whether to hold specific T-ALL treatment in favor of extended HLH therapy. Our experience is a unique example of aggressively managing CNS-leukemia to curtail the trigger for HLH.

Poster # 929

DIFFUSE LEPTOMENINGEAL GLIONEURONAL TUMOR: A DISTINCTIVE ENTITY WITHOUT CURRENT STANDARD TREATMENT. CASE REPORT AND LITERATURE REVIEW

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Background: Diffuse Leptomeningeal Glioneuronal Tumor (DLGT) is a rare neoplasm which was recently included in the revised WHO 2016 classification of tumors of the central nervous system (CNS). We report here a case of recurrent disseminated DLGT, its clinical presentation, molecular results and management.
Objectives: To describe the presentation of a rare CNS tumour, discuss the potential role of adjuvant therapy and literature review.
Design/Method: A MEDLINE search was conducted for queries including "Diffuse Leptomeningeal Glioneuronal Tumor". Relevant papers were selected for the literature review.
Results: An eight year-old male patient presented with bilateral leg pain that was progressively worsening to the point of inability to bear weight. Brain magnetic resonance images (MRI) showed a 2cm enhancing intramedullary neoplasm within the thoracic cord at T7-T8. There was no evidence of spinal metastasis or intracranial disease and lumbar puncture was negative for malignant cells. The patient underwent excisional biopsies and was diagnosed as papillary ependymoma at an outside institution. No further treatment was given, over the subsequent 14 months follow up magnetic resonance imaging revealed 3 new spinal lesions. Excisional biopsies were repeated and pathology reviewed at our institution demonstrated DLGT in both the initial and second biopsies. Immunophenotyping was positive for S100 protein, vimentin and synaptophysin, with no expression of EMA, GFAP, CK, NSE, or chromogranin, and low level of Ki67 staining. Among the complex cytogenetic alterations identified was a t(1;19)(q10;p10) translocation which corresponds with the diagnosis of DLGT. Due to the aggressive behavior of the tumor, the patient received craniospinal radiation to 36Gy(RBE) plus 7.2 and 5.4 Gy(RBE) boosts to the low and mid spine respectively followed by 6 cycles of temozolomide maintenance chemotherapy. Patient has been clinically stable with resolution of his symptoms and has stable residual disease on serial surveillance MRI imaging; one year since last surgery.
Conclusion: DLGT is a very rare type of glioneuronal tumor that has recently been classified in the WHO classification. A literature review of single case reports or small case series showed that although Diffuse Leptomeningeal Glioneuronal Tumors express low grade markers, clinically they behave aggressively as they disseminate and recur. Limited data is available on the use of adjuvant therapy in DLGT treatment. Additional data about disease course, relevant biomarkers, and treatment outcomes are needed for further understanding of these rare brain tumors. In our patient, the combination of surgical resection and adjuvant chemo-radiotherapy has maintained stable disease for a year post re-excision.

Poster # 930

LONGITUDINAL CLINICAL, BIOLOGICAL, AND IMMUNOPHENOTYPIC CHARACTERISTICS OF LINEAGE SWITCH ACUTE LEUKEMIA WITH KMT2A-REARRANGEMENT: A CASE SERIES

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Background: Acute leukemia undergoing lineage switch is rare, with a dismal prognosis and known association with KMT2A (formerly MLL) rearrangements. Lineage switch etiology is poorly understood. Proposed mechanisms include selection of a minor clone not detected at diagnosis, de-differentiation of the original clone, and reprogramming of a bipotential progenitor.
Objectives: To identify clinical and flow cytometric patterns that may signal increased risk for lineage switch in KMT2A-rearranged leukemia and to better understand the underlying mechanism.
Design/Method: We retrospectively reviewed cases of KMT2A-rearranged acute leukemia with lineage switch at our institution from 2010-2015. A detailed review of the medical record was performed and flow cytometry data was closely re-examined. Whole exome sequencing (WES) is being performed on pre- and post-lineage switch samples from two patients.
Results: We identified 5 patients with KMT2A-rearranged acute leukemia with lineage switch. One patient switched from acute myeloid leukemia (AML) to B-acute lymphoblastic leukemia (B-ALL), and four switched from B-ALL to myeloid lineage (two AML and two mixed phenotype acute leukemia (MPAL)). The median age of diagnosis was 7 months (range:3mos–16yrs), and the median time from diagnosis to lineage switch was 14 months (range:10mos-27mos). Four patients died, with median time from lineage switch to death of 4 months (range:<1mo-8mos). Two patients underwent hematopoietic stem cell transplant (HSCT) following lineage switch: one died in remission; the other remains in remission 15 months post-transplant. Close review of flow cytometry data identified atypical leukemia-associated immunophenotype (LAIP) patterns prior to lineage switch diagnosis in four patients. Three patients with B-ALL demonstrated a small population of blasts expressing CD13, 33, 64, and/or 117 at diagnosis (n=2) or B-ALL relapse (n=1). One patient with AML demonstrated co-expression of CD19 in a subset of blasts at diagnosis. None of these cases fulfilled the WHO 2008 criteria for MPAL prior to lineage switch. When complete, WES for trio samples (diagnosis, remission, and lineage switch) from two patients will be presented.
Conclusion: Our case series confirms that patients who undergo leukemic lineage switch tend to be young, harbor KMT2A rearrangements, and have a particularly poor prognosis. We also present the novel finding that KMT2A-rearranged acute leukemia may reveal subtle yet distinct aberrations in LAIP prior to lineage switch. This case series raises several questions that warrant further study, including the possible prognostic implications of LAIP aberrations in KMT2A-rearranged acute leukemia and the potential benefit of novel treatment strategies, including early HSCT, in patients with such aberrations.

Poster # 931

COMBINATION OF BEVACIZUMAB AND TAXANE CONTAINING REGIMEN, HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC) AND TYROSINE KINASE INHIBITOR (TKI) TRAMETENIB FOR THE TREATMENT OF AGGRESSIVE METASTATIC PEDIATRIC ANGIOSARCOMA

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Background: Angiosarcomas are extremely rare tumors in children. Little is known about their biology, natural history or optimal therapy. Angiosarcomas tend to behave aggressively with high rate of metastases, local recurrences and poor prognosis.
Objectives: To report the significant response of a metastatic pediatric angiosarcoma treated aggressively with a bevacizumab-containing regimen, cytoreductive surgery and HIPEC, followed by maintenance with an oral TKI.
Design/Method: Case report and literature review
Results: A 13-year-old female presented with complaints of diffuse abdominal pain and distention. An MRI was significant for diffuse ascites, the presence of abdomino-pelvic masses extending into the cul-de-sac and widespread peritoneal implants. Pathology studies confirmed a diagnosis of high grade angiosarcoma. Chemotherapy was initiated with ifosfamide-doxorubicin with initial response followed by progressive disease. The patient then received neoadjuvant gemcitabine-docetaxel-bevacizumab with significant response, followed by surgical resection with maximal tumor debulking and HIPEC with mitomycin. She then completed three adjuvant cycles of the same regimen achieving a complete remission. Molecular studies of the tumor revealed a known oncogenic mutation of NRAS that was targeted with the oral TKI trametinib, a RAS-RAF-MEK pathway inhibitor. The child has remained in remission for 10 months and is closely monitored.
Conclusion: Angiosarcomas are rare, aggressive, high grade tumor especially in children. Due to their low incidence there is no known optimal therapy and their prognosis remains poor (five-year overall survival ~20%). Preclinical studies have shown that angiosarcomas overexpress vascular endothelial growth factor-A (VEGF-A) and its receptors (eg, VEGFR-2), and its blockade results in tumor cell apoptosis. Few studies have shown efficacy of bevacizumab in angiosarcoma but its rarity in children, undermines the statistical ability to draw strong clinical conclusions. HIPEC is used for the treatment of peritoneal metastases, but there is no report of its use and efficacy in angiosarcoma. Targeted therapy with TKIs are increasingly integrated with standard modalities in oncology, showing promising results. Our case suggests that combined aggressive multi-modality therapy of metastatic angiosarcoma in children is feasible and possibly has significant efficacy with disease control and prolonged survival. Randomized trials are needed to establish the role of HIPEC, bevacizumab, TKIs and other therapeutic options in angiosarcomas.

Poster # 932

NEGATIVE INITIAL BONE MARROW ASPIRATE DOES NOT DEFINITIVELY RULE OUT ACUTE LYMPHOBLASTIC LEUKEMIA: A CASE SERIES

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Background: Patients with eventual diagnosis of acute lymphoblastic leukemia (ALL) may initially present with varying degrees of pancytopenia and hypoplasia on bone marrow aspiration (BMA), but without evidence of ALL or clonal abnormalities. Parvovirus B19 and non-A, non-B viral hepatitis have been implicated in case reports but significant clinical data are lacking.[1, 2].
Objectives: To describe the presentation and characteristics of patients with initial cytopenias but a normal BMA who were subsequently diagnosed with ALL.
Design/Method: We conducted a retrospective chart review of patients with ALL who presented with cytopenias but initial negative BMA at UCSF Benioff Children's Hospital Oakland over the last 15 years. We collected and descriptively analyzed data regarding initial cytopenia(s), BMA results, clinical symptoms at presentation, number of BMAs until diagnosis, and time to diagnostic BMA from initial BMA.
Results: Six children (median age 3.8 years), presented with peripheral blood cytopenias and initial normal BMA before progressing to ALL. This represented 2% of all ALL diagnoses during this time period. One patient presented with isolated anemia; one with isolated leukopenia with neutropenia; one with leukopenia (with neutropenia) and thrombocytopenia; and three with pancytopenia. All initially presented with fever and presumed infection.Proven infections included Salmonella enteritis, Epstein-Barr Virus adenitis and Streptococcus bacteremia. All patients had a negative chest radiograph on initial presentation. Patients had a median of three bone marrow evaluations before ALL was diagnosed, with a median time of 3.3 months to diagnosis. Of the initial BMAs, four were hypocellular and two hypercellular. All patients had normal initial cytogenetics, 4 of which progressed to clonal abnormalities at diagnosis (the other 2 had no growth for cytogenetic analysis at diagnosis). Two patients had increased "lymphoblast-like" cells at initial presentation which resolved on subsequent BMA before eventually progressing to definitive ALL.
Conclusion: Transient cytopenias without BMA findings may represent a prodrome prior to definitive diagnosis of ALL. In our population this represented 2% of patients with ALL, similar to previously reported studies.[3-4] All patients presented with proven or presumed infection which may have been due to the underlying cytopenias or represented the inciting event for the development of eventual clonal abnormalities with ALL. Practitioners must be aware that initial negative BMA does not definitively rule out ALL.1. Heegard E et al. Br J Haematol 2001;114:8102. Ireland R et al. Leuk Res 1998;12:7953. Hasle H et al. Leukemia 1995;9:6054. Breatnach F et al. Br J Haematol 1981;49:387

Poster # 933

GROWING TERATOMA SYNDROME IN A PEDIATRIC PATIENT WITH IMMATURE TERATOMA AND GLIOMATOSIS PERITONEI

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Background: Growing teratoma syndrome (GTS) is a rare phenomenon of enlarging benign tumor elements with normalization of tumor marker levels following successful treatment of the

primary tumor.
Objectives: We describe a rare case of a young child with likely GTS and present a discussion on the importance of early recognition and appropriate treatment.
Design/Method: Case Report
Results: A 2-year-old female presented with increasing abdominal girth for one month. Imaging revealed a large ovarian mass and AFP was found to be elevated. The mass was completely resected and pathology revealed an immature teratoma stage 1, grade 1 with gliomatosis peritonei. AFP decreased to near normal at this time. Two months later imaging revealed new enlarging perihepatic and abdominal lesions along with significant rise in AFP, so chemotherapy was initiated. One cycle of BEP chemotherapy was given, but the mass continued to rapidly increase by three times the original size three weeks following initiation of chemotherapy. AFP again approached normal. A second complete resection of the perihepatic and abdominal masses was completed. The pathology revealed predominance mature elements with rare immature foci, without malignant elements. The patient is now four years out from her second resection, and AFP remains within normal limits with no evidence of recurrence or tumor growth.
Conclusion: This case represents the interesting phenomenon of GTS in a young child after suspected recurrence of original disease with initial increase in tumor markers and tumor growth. Following chemotherapy there was a normalization of tumor markers but a persistence of impressive tumor volume, suggesting treatment of malignant elements with growth of the benign component. The mechanism behind GTS is unclear, but is hypothesized to either be due to chemotherapy eliminating malignant elements, leaving behind only the benign component, or differentiation of the immature tissue to a resistant benign state. Unfortunately, GTS often is misinterpreted as chemoresistant tumor or recurrence. Early recognition of GTS in the young pediatric patient can prevent further unnecessary chemotherapy, mass affect, and intraoperative complications.

Poster # 934

OMALUZIMAB IN COMBINATION THERAPY WITH BEACOPP IN STAGE IV PULMONARY HODGKIN DISEASE

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Background: Lymphoproliferative disorders are known associations of the hyper-IgE syndrome, however a marked elevation of IgE as an initial manifestation of a lymphoproliferative disease is rare. Hodkgin Disease (HD) lymph nodes with eosinophilia often contain substantial deposits of IgE, which are generally not detectable in benign hyperplastic lymph nodes. Eosinophils and Reed Sternberg (RS) cells have been shown to express the CD23 antigen, which is a cell-surface receptor for IgE. Therefore - IgE antibodies targeted to tumor cells may cause a marked effect on tumor development and growth. We describe for the first time the observational successful treatment of Omaluzimab (monoclonal IgE Ab) in combination therapy with BEACOPP in a patient who presented with stage IV HD and unexplained severe urticaria with elevated IgE.
Objectives: To discuss an observational treatment of Omalizumab in combination with BEACOPP chemotherapy for Stage IV HD.
Design/Method: An 18-year-old male was evaluated for chronic urticaria with significant

neutrophilia and elevated IgE (>1600) for 18 months. Infectious causes and parasites were excluded and he was diagnosed with chronic urticaria NOS. The patient was lost to follow up for 6 months, subsequently returning to clinic with new onset cough, night sweats, and a 20lb weight loss. CXR showed multiple bilateral pulmonary masses with widening mediastinum, confirmed by CT and suggestive of pneumonia or lymphoma.
Results: Pathology confirmed HD, nodular sclerosis, stage IV. Massive pulmonary nodules in HD are more often seen at relapse than at initial presentation in a treatment-naïve patient. B-symptoms for lymphoma might include itching but not histamine-resistant urticaria with spontaneous widespread recurrent hives and persistent neutrophilia without infection. Omalizumab is a monoclonal Ig-E antibody that is FDA approved for chronic urticaria and asthma. This is the first report where Omaluzimab 300mg IV was initiated to control chronic urticaria (x1 dose), but then -after diagnosis of HD- successfully continued in synergy with intensified BEACOPP chemotherapy every 14 days as targeted anti-tumor activity (x7 doses). Patient achieved CR with resolution of urticaria and normalization of IgE levels and remains in remission on maintenance with monthly Omalizumab.
Conclusion: Rare cases have reported that hyper-immunoglobulin E may be a manifestation of Hodgkin's Lymphoma. In those patients, combination therapy with standard chemotherapy and Omaluzimab might be considered, to target the IgE production by RS cells as well as the eosinophilic tumor microenvironment.

Poster # 935

LINEAR NEVUS SEBACEOUS SYNDROME AND ASTROCYTOMA: 2 CASE REPORTS AND REVIEW OF LITERATURE

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Background: Linear Nevus Sebaceous Syndrome (LNSS) is a very rare genetic syndrome characterized by pigmented papules at birth, developmental delay, CNS abnormalities including seizures, ocular abnormalities, brain hemi-megalencephaly, and skeletal and cardiac defects. It is associated with post-zygotic HRAS and KRAS mutations, and a predisposition to diverse ectodermally-derived malignancies in diverse tissues, including skin, breast, salivary gland, stomach, esophagus and bladder. Interestingly, reports of CNS neoplasms are limited to only 3 children with low grade gliomas.
Objectives: To report two pediatric patients with LNSS-associated CNS neoplasms, one low grade and one anaplastic glioma, thus expanding the spectrum of LNSS-associated neoplasms.
Design/Method: Review of patient medical records, including radiographic imaging and pathology, and literature review.
Results: Case 1: A 15 year-old female with known LNSS, right eye cataract, and cutaneous linear facial nevus, and no focal neurologic abnormalities, underwent brain magnetic resonance imaging (MRI) following possible concussion. MRI showed left subinsular, caudate head and paramedian frontal lobe enhancing nodules. She underwent gross total resection (GTR) of one nodule. Pathology was consistent with WHO grade I astrocytoma. Six months later, MRI showed local recurrence, again treated with GTR yielding identical pathology, though complicated by stroke. MRI 4 years later showed local recurrence. She was treated with monthly carboplatin and

vincristine, developed anaphylaxis after 6 courses and was changed to temozolomide before elective discontinuation after 3 courses. MRI remains stable 5 years following chemotherapy cessation.Case 2: A 15 year-old female with known LNSS and unilateral coloboma, underwent brain MRI for headaches associated with recent concussion that revealed a localized 4 cm left frontal lobe abnormal T2 signal abnormality. Following GTR, tumor pathology showed anaplastic astrocytoma WHO grade III. She was treated on ACNS0822 with involved field radiation and vorinostat, then 12 courses of temozolomide and avastin. MRI 18 months later showed local recurrence, and she underwent GTR, and pathology showed glioblastoma WHO grade IV. Despite hypo-fractionated re-irradiation and adjuvant chemotherapy, she died of tumor progression 6 months later.
Conclusion: These 2 case reports of CNS gliomas, including the first reported anaplastic glioma, expand the known spectrum of neoplasms associated with LNSS. Combined with 3 previously reported LNSS-associated pediatric low grade gliomas, abnormal developmental glial migration and cortical differentiation, and/or disturbed astro-glial proliferation is implicated in this very rare syndrome. When evaluating patients with LNSS, consideration of surveillance brain MRI for potential asymptomatic glial neoplasms is warranted.

Poster # 936

VINORELBINE-INDUCED PANNICULITIS IN A PATIENT WITH HIGH-RISK HODGKIN DISEASE

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Background: With the advancement of chemotherapeutic agents used to treat childhood cancers, side effect profiles continue to expand. Panniculitis is a disease state characterized by inflammation of subcutaneous tissue, frequently diagnosed with a deep skin biopsy. Classification is determined by histological characteristics and location of the inflammatory cells. Panniculitis has been reported secondary to extravasation of cytostatic chemotherapeutic agents, most frequently in association with Vinorelbine. Despite the benign course associated with panniculitis, the presentation can often be misinterpreted for disease recurrence.
Objectives: To describe a case of panniculitis secondary to Vinorelbine in a patient with recurrent Hodgkin disease. To broaden the differential of firm mass identified in a patient receiving chemotherapy.
Design/Method: We describe a 16-year-old male with recurrent high-risk Hodgkin disease, receiving Vinorelbine and Gemcitabine as a bridge to stem cell transplantation. During interval visits, the patient was found to have two palpable submandibular nodules measuring 1.5cm x 2cm, and 1.5cm x 1.5cm. Imaging confirmed two soft tissue masses with evidence of inflammation and edema, without evidence of abscess. Despite antibiotic therapy, the patient had minimal response on follow-up examinations. With concern for refractory lymphoma, a fine needle aspiration (FNA) was completed. Pathology confirmed the diagnosis of panniculitis with unidentifiable etiology. As the patient continued to have active disease after 4 cycles of Vinorelbine and Gemcitabine, alternative therapies were used and the panniculitis ultimately resolved.

Results: 16 year-old male with Vinorelbine-induced panniculitis, resolving after completion of chemotherapy. Although previously described in adult patients receiving Vinorelbine, we report this case of a pediatric patient with recurrent Hodgkin disease.
Conclusion: Pediatric cancer patients are exposed to multiple chemotherapeutic agents with risks of both common and rare side effects. Specifically, patients with relapsed disease are treated with newer agents and are at risk for further medical morbidities. Many of these side effects are manageable, however, the presentation can be misinterpreted as limited pediatric reports have been described. Vinorelbine toxicity can lead to capillary leak syndrome within the endothelial cells, and cause the development of clinically palpable panniculitis. Despite the self-limiting nature of panniculitis, the development of palpable nodules in patients fighting aggressive malignancies is concerning for recurrent disease and should be thoroughly worked up. During this time, it is necessary to consider panniculitis and other benign processes, in order to best expand the differential beyond refractory disease.

Poster # 937

PEDIATRIC PATIENT WITH END-STAGE KIDNEY DISEASE SECONDARY TO EAGLE BARRETT SYNDROME AND METASTATIC UNRESECTABLE HEPATOBLASTOMA TREATED SUCCESSFULLY WITH CHEMOTHERAPY AND LIVER-KIDNEY TRANSPLANT

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Background: Hepatoblastoma is the most common malignant liver neoplasm in children. The etiology is unknown, but it has been associated with Beckwith-Weidemann syndrome, familial adenomatosis polypi, and low birth weight. Eagle Barrett (Prune Belly) syndrome is a congenital anomaly characterized by lax abdominal musculature, bilateral cryptorchidism and carries significant renal pathology requiring dialysis in some patients due to abnormalities of the kidney and urinary tract. There are very few reports in the literature of association between Eagle Barrett syndrome and hepatoblastoma. The use of chemotherapy has improved survival in patients with unresectable hepatoblastoma by increasing the number of patients whose tumors can be resected, but the use of nephrotoxic chemotherapy in patients undergoing dialysis can be challenging. We report a particular case of a 3-year-old patient with Eagle Barrett syndrome with end stage renal disease (dialysis dependent) also diagnosed with metastatic unresectable hepatoblastoma.
Objectives: To report the case of a pediatric patient with hepatoblastoma with associated Eagle Barrett syndrome and end stage kidney disease treated successfully with neoadjuvant chemotherapy while on dialysis and liver-kidney transplant followed by adjuvant chemotherapy.
Design/Method: Case report and literature review
Results: A 2-year-old male with stage IV- M unresectable hepatoblastoma and Eagle Barret syndrome resulting in end stage renal disease was treated with doxorubicin, cisplatin, fluorouracil and vincristine while on dialysis (doses were adjusted accordingly) then underwent a liver-kidney transplant and right side nephrectomy followed by two cycles of adjuvant chemotherapy at full dose of the same regimen following COG protocol AHEP0731. The patient now is remission and has normal renal function.
Conclusion: Though hepatoblastoma is a common liver neoplasm, it is infrequently found in

association with Eagle Barrett syndrome. Further awareness of this association can ultimately further investigation of potential genetic association between these two diseases.

Poster # 938

MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMA IN PEDIATRIC PATIENTS WITH SJÖGREN SYNDROM

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Background: MALT lymphoma accounts for 7-8% of all B-Cell lymphomas, has a female predilection, and is associated with immunodeficiency and immunologic disorders. The median age of presentation is 67 years and it is extremely rare in pediatric patients. MALT lymphoma is the most prevalent Non-Hodgkins Lymphoma (NHL) among patients with Sjögren Syndrome (SS), with an incidence around 40% higher compared to the general population. The pathophysiology of lymphoproliferation in MALT lymphoma patients (with or without SS) is unclear. However, it was hypothesized that chronic antigen-driven immune stimuli, together with oncogene mutations and translocations, result in B-cell malignant clonal expansion. The clinical course of localized tumors is generally indolent and patients respond well to different treatment modalities with a 5-year overall survival (OS) of around 95%. Therapy for MALT-SS has not been well established. However, treating the underlying SS in addition to MALT lymphoma is preferred.
Objectives: To report two cases of extranodal MALT lymphoma in pediatric patients with Sjögren Syndrome (SS).
Design/Method: Review of electronic medical record and recent medical literature.
Results: 15 year-old female patient with Celiac disease and recurrent parotiditis underwent biopsy of parotid gland, which revealed MALT lymphoma. Given the association between MALT lymphoma and SS, autoantibody testing was done confirming the diagnosis of Sjogren Syndrome. Examinations for HIV, hepatitis B, hepatitis C and for immunologic disorders were negative. She was treated with four once-weekly doses of rituximab preceded by methylprednisolone, and oral hydroxychloroquine daily. She achieved remission and has since been stable without recurrence. A 15 year-old boy with Sjögren Syndrome, complicated by inflammatory arthritis, presented with tender swelling of the right parotid gland. MRI showed homogeneous bilateral swelling that was minimally suspicious for malignancy. As swelling persisted, a fine-needle aspirate and a subsequent partial parotidectomy were done, confirming the diagnosis of MALT lymphoma. He was treated with bendamustine monotherapy after having an anaphylactic reaction to rituximab. Patient successfully achieved remission without recurrence.
Conclusion: Although primary pediatric SS is a rare disease, its importance is magnified by its association with MALT lymphoma. Pediatric oncologists must maintain vigilance for lymphoma in children with known or possible SS. Fortunately, with early diagnosis and appropriate treatment, good outcomes can be expected for most patients with Sjogren–associated non-Hodgkins lymphoma.

Poster # 939

GASTRIC ADENOCARCINOMA AND CHRONIC MYELOID LEUKEMIA IN THE SETTING OF IPEX SYNDROME

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Background: Immune dysregulation, polyendocrinopathy, enteropathy X-linked syndrome (IPEX) is a rare disease characterized by poor regulatory T cell function. Symptoms include autoimmune enteropathies, dermatitis, and diabetes mellitus. Mutation in FOXP3 gene is present in up to 25% of patients. Although FOXP3 is known to act as a tumor suppressor gene in human cancers, only one case of EBV related lymphoma in the setting of immunosuppression has been described in a patient with IPEX syndrome. This may be due to low incidence of this disease and short life span of patients with IPEX syndrome.
Objectives: To further describe the presentation and treatment options in malignancies arising in the setting of IPEX syndrome.
Design/Method: A retrospective review of two case reports
Results: Patient 1: 14 year-old male with history of IPEX syndrome and chronic gastritis that presented with a history of vomiting, abdominal distention, and weight loss. MRI abdomen with contrast demonstrated a 1.6 x 1 cm focal polypoid-like mass near the antrum. Endoscopic biopsy revealed a signet ring adenocarcinoma (T3N1M0). He received eight cycles of 5-fluorouracil and oxaliplatin followed by total gastrectomy. He continued antifungal prophylaxis during treatment, and did not develop any infectious complications. He is in remission 8 months from diagnosis.Patient 2: 6 y.o. male who presented with high fevers, pneumonia, and eczematous rashes at 2 years of age, subsequently diagnosed with IPEX syndrome. Shortly after diagnosis, he presented with fever leading to further work up and diagnosis of CML (BCR/ABL positive). He was started on imatinib and went into remission. He later developed generalized lymphadenopathy with leukocytosis and blasts on blood smear. The differential diagnosis included AML versus a blast crisis of his CML. He completed induction chemotherapy per AAML0531 and was transferred to our institution to complete a a matched related donor bone marrow transplant 11 months ago. Complications post transplant include initial grade II graft vs. host disease, and is still intermittently receiving donor lymphocyte infusions for mixed chimera. He has otherwise done well, with his IPEX syndrome in remission since that time.
Conclusion: As patients with IPEX syndrome survive longer due to improved bone marrow transplant and supportive care options, it is likely that we will encounter more cases of cancer in these patients. Moreover, it appears that IPEX patients tolerate conventional chemotherapy without significant infectious complications or systemic toxicity. These cases thus demonstrate the need for closer monitoring of potential malignancies in patients with IPEX syndrome.

Poster # 940

INTRATHECAL RITUXIMAB: A PROMISING THERAPY FOR ADVANCED STAGE B-CELL LYMPHOMA WITH CNS INVOLVEMENT

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Background: Non Hodgkin lymphoma (NHL) accounts for approximately 25% of neoplasms in children age 15 to 19 years. The most common subtypes of pediatric NHL are derived from B cell progenitors. CNS involvement is associated with an adverse outcome in patients with NHL. Rituximab monoclonal antibody therapy is an effective treatment for B-cell NHL. Preclinical study has demonstrated that intrathecal (IT) Rituximab is able to concentrate in and eradiate tumors without significant acute or delayed toxicity.
Objectives: To examine the effect of IT/Intravenous (IV) Rituximab on the prognosis and outcome of a patient with advanced stage NHL with CNS involvement
Design/Method: The patient received combination treatment of conventional chemotherapy (COG protocol #ANHL1131) with IT/IV Rituximab. Tripple IT during 2 cycles of Induction was replaced by IT Rituximab.CSF was analyzed for tumor cells at each IT procedure. PET scan was done mid cycle and at end of treatment to check for residual disease. No extracranial radiation therapy was given
Results: A fifteen-year-old Hispanic healthy boy presented with 4-months of headache, acute onset of right facial focal seizure followed by ipsilateral facial drooling and difficulties with articulation. Physical exam was significant for dysarthria, asymmetric face with right lower half facial weakness and significant splenomegaly. Head CT demonstrated multiple enhancing masses in both hemispheres and cerebellum, a large mass (2.1 x 2.8 cm) in the left frontal lobe with significant surrounding edema, and 5 mm rightward midline shift. He also had multiple space-occupying lesions in lungs, liver and spleen. Bone Marrow biopsy, liver lesion Biopsy, and lumbar puncture were negative for malignant cells. Biopsy of intracranial lesion revealed CD20 positive diffuse large B cell lymphoma. The patient was started on a combinational treatment of conventional chemotherapy with IT/IV Rituximab. He tolerated his chemotherapy well without any significant toxicity. He has been in complete remission for 12 months without receiving any extra-cranial radiation therapy.
Conclusion: IT Rituximab therapy can be used as an effective alternative to radiation therapy in CD20 positive NHL. It circumvents the blood brain barrier and targets CNS lymphoma cells which express CD20. The long-term adverse effects of radiation therapy such as cognitive problems, hypopituitarism, and secondary cancer can thus be avoided in these patients. Rituximab may improve prognosis and outcome of patients with NHL with CNS involvement without the use of radiation.

Poster # 941

A CASE OF NEUROBLASTOMA SECRETING VASO-INTESTINAL PEPTIDE RESISTANT TO CHEMOTHERAPY

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Background: Neuroblastoma is the most common extra-cranial solid tumor in children. Its behavior is heterogeneous, ranging from cases that can be cured with minimal therapy or observation alone to others that require intense, multi-modal treatment. Symptoms are typically related to the location of the primary tumor and metastases. However, rare patients have symptoms related to paraneoplastic syndromes. Opsoclonus-myoclonus occurs in about 3% of neuroblastoma cases, and diarrhea due to tumor vasointestinal peptide (VIP) secretion occurs in less than 1% of patients. This subset of patients may require a different treatment approach than other neuroblastoma patients.
Objectives: We describe our experience treating a child with VIP-secreting neuroblastoma resistant to chemotherapy.
Design/Method: Case Report
Results: A previously healthy 17-month-old male presented with diarrhea, fever, decreased appetite, and lethargy. Computed topography scan revealed extensive retroperitoneal, mesenteric, and pelvic masses with calcification. Biopsy of the retroperitoneal mass revealed favorable histology neuroblastoma without MYCN-amplification. Urinary catecholamines were elevated. Due to extensive diarrhea, we evaluated the VIP level, which was determined to be 486 pg/mL (normal < 75 pg/mL). Tumor evaluation revealed no evidence of metastatic disease to the bone marrow or bone, and his tumor was classified as stage 3 by the International Neuroblastoma Staging System with favorable biologic features. After 2 cycles of intermediate-risk chemotherapy per ANBL0531, no change in the size of his primary tumor was observed. The patient then underwent surgery. However, the tumor encased numerous blood vessels including the aorta and inferior vena, resulting in only 50% tumor resection. Post-operatively, the VIP level decreased to 154 pg/mL, and the patient's diarrhea improved. Six weeks following surgery, the diarrhea recurred, causing significant wasting of potassium and bicarbonate. The patient was subsequently treated with octreotide, but his stool output did not decrease, and he continued to require aggressive fluid management due to large volume of stool losses. Six months after diagnosis, a second surgery was performed, and >90% of this residual tumor was resected, with minimal gross disease remaining in neural foramina L2-L4 near his spinal cord. After surgery, his diarrhea resolved immediately. He has remained stable with normal urine catecholamines and VIP levels 8 months since repeat resection of his tumor.
Conclusion: VIP secretion is a rare paraneoplastic syndrome associated with neuroblastoma. Treatment can be difficult as these tumors are commonly differentiated and resistant to chemotherapy and radiation. This case highlights the importance of aggressive surgical resection in this subset of neuroblastoma patients.

Poster # 942

PEDIATRIC CD5+ DIFFUSE LARGE B CELL LYMPHOMA (DLBCL): A CASE REPORT AND REVIEW OF LITERATURE

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Background: CD5 positivity in DLBCL has been well reported in the adult literature. Up to 10% of the total DLBCL adult cases are CD5 positive which is associated with an aggressive clinical outcome. It is virtually unknown in the pediatric population with only one prior report

describing such a case.
Objectives: This case report will describe the clinical features and the initial response to therapy of a pediatric CD5 + DLBCL and compare it to the existing literature
Design/Method: Retrospective case study
Results: We describe a 13 year old previously healthy male patient who was diagnosed with Stage III DLBCL of the nasopharynx after he presented with difficulty in breathing and swallowing. While histochemical studies confirmed that he had a DLBCL, immunohistochemistry demonstrated that the lymphoma was positive for the CD5 marker proving that he had a mature B cell lymphoma with a high proliferation index and an aberrant CD5 positivity. He was treated with the high risk COG ANHL 1131 protocol with Rituximab due to pretreatment with corticosteroids prior to diagnosis. He has shown an excellent response. He is currently in remission for about 12 months after the end of therapy.
Conclusion: About 800 new cases of pediatric NHL are diagnosed every year in the US. NHL is a wide group of lymphoma with varied genotypes, phenotypes and clinical behaviors. De Novo CD5 positivity is rarely reported in pediatric DLBCL. Its presence in the adult population has prognostic implications. Little is known about its clinical significance in pediatric DLBCL. This is only the second described case of a pediatric CD5 + DLBCL. Thus, there is a need for identifying and characterizing more such cases in the future. Reporting and studying these cases may help us learn more about the prognostic significance and biological implications of CD5 positivity in pediatric DLBCL.

Poster # 943

PRIMARY INTRACRANIAL SARCOMAS: WHAT IS THE OPTIMAL TIME FRAME TO INITIATE THERAPY?

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Background: Primary CNS sarcomas are exceedingly rare pediatric malignancies without a well-defined standard of care. A 2016 Canadian retrospective case series in the Journal of Neurosurgery: Pediatrics described treatment of these tumors with the Ifosfamide, Carboplatin and Etoposide (ICE) chemotherapy regimen along with focal radiation therapy after surgical resection. While the outcomes were encouraging, the time frame for initiation of adjuvant therapy after resection remains variable. Some neurosurgeons request postponing chemotherapy to allow the patient to recover from the operation and possibly undergo physical therapy, while some teams prefer early adjuvant therapy to prevent tumor regrowth.
Objectives: To describe a pediatric case of primary undifferentiated CNS sarcoma and complications of chemotherapy initiation after surgical resection.
Design/Method: Case Report.
Results: A 6-year-old boy with a history of an arachnoid cyst was admitted with worsening headaches and vomiting. CT and MRI demonstrated a right frontotemporal subdural mass confirmed by pathology to be an undifferentiated high-grade sarcoma. Further radiographic inquiry revealed no extracranial tumor sites, and a PET scan was negative, confirming a primary intracranial sarcoma measuring approximately 4.3 x 3.7 x 4.4 cm. Neurosurgery resected the tumor; however, given the extensive involvement of the MCA, it was a sub-total (approximately

95 percent) resection. The patient suffered an intraoperative CVA and is now hemiplegic. The patient was transferred from the neurosurgical service to rehab post-op for physical therapy to help with recovery. Approximately 5 weeks later, his baseline scans prior to initiating chemotherapy showed extensive tumor regrowth, measuring approximately 5.3 x 5.8 x 5.4 cm. He underwent a second resection with chemo initiated 72 hours later. However, he suffered from status epilepticus just after the initial ifosfamide dose (3000 mg/m2), leading therapy to be altered to a "baby" cycle with etoposide 150 mg/m2 and Carboplatin at 360 mg/m2. Once counts recovered on day 16, he was admitted for the first full cycle of ICE therapy, which was well-tolerated.
Conclusion: Given the aggressive nature of primary intracranial sarcomas, the potential for regrowth of the tumor should be balanced with the risk of starting adjuvant therapy before the brain has recovered post-operatively. Larger studies are needed to develop a standard of care for treating intracranial sarcomas.

Poster # 944

NOVEL EXON-6 MUTATION OF FACTOR-8 GENE PRESENTING IN A NEONATE WITH HEEL STICK BLEEDING AND SPONTANEOUS SUBDURAL HEMATOMA IN EARLY INFANCY

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Background: Hemophilia- A is an X-linked genetic disorder. Genotyping is important to determine risk of inhibitors, prenatal testing, carrier detection, and research in gene therapy.
Objectives: To describe the genetic and clinical characteristics of two cases in a family with hemophilia-A associated with a new mutation.
Design/Method: We reviewed the medical records of two cases with hemophilia-A, including clinical presentation, laboratory evaluation, complications, and management.
Results: Case-1. A male infant, uncle of the patient in case-2, presented at age 6 months with history of excessive bruising and limb hematoma. First maternal cousin has hemophilia. Laboratory study showed aPTT 104 sec, factor-8 assay 2% (baseline factor-8 level 1.0- 3.3%), consistent with moderate factor deficiency. However, clinically he had severe disease with multiple spontaneous soft tissue bleedings requiring factor replacement at 6 months and prophylactic factor replacement at 11 months. He had a low responder inhibitor at 4 yrs of age (0.50 BU), with negative repeat inhibitor testing and remained negative until his last visit at age 9yrs. Factor-8 gene sequencing showed a novel mutation in exon-6, characterized by the insertion of 29 base pairs at codons 227-228 (c.738_739ins). The mutation was included in CDC data base, but clinical description of the case was not published.Case 2. A male newborn presented with persistent bleeding at 10 hours of life from heel stick site obtained at birth. On day of life 3 he developed a large hematoma of the thigh after saphenous venipuncture for bilirubin. Laboratory test showed aPTT 41 sec (repeat 97) and factor-8 assay 3%. He received recombinant factor-8 for the thigh hematoma. Targeted F8 gene sequencing of exon-6 showed hemizygosity for a variant designated c.738_739ins29, confirming inherited disease. The mutation is predicted to result in a frameshift and premature protein termination (p.Trp247Profs*21). At 4 months repeat factor-8 assay was 1%. He had minor soft tissue

bleedings until 4 months, then received factor-8 for hand hematoma. At 5 months he presented with seizure and CT scan showed a large subdural hematoma. He received intensive factor replacement therapy with good response, then prophylactic factor replacement. At his last visit, at age 11 months, had negative inhibitor.
Conclusion: The two cases illustrate that this novel mutation results in a severe clinical phenotype presenting in early infancy, with discordance in classification of severity based on factor level and clinical manifestations. We recommend early initiation prophylactic factor replacement in cases with this mutation to prevent life threatening bleeding.

Poster # 945

MULTIFOCAL PERIVASCULAR MYOID TUMOR TREATED WITH CRYOABLATION: A RARE PRESENTATION AND UNIQUE APPROACH TO TREATMENT

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Background: Perivascular myoid tumor (also referred to as myopericytoma or glomangiopericytoma) is a rare benign soft tissue tumor featuring proliferation of perivascular myoid cells that support or invest blood vessels. Presentation typically occurs as a painful solitary lesion most often in the lower leg. Surgical resection is generally curative. There is little data on appropriate treatment approach for multi-focal lesions.
Objectives: We describe a case of multi-focal perivascular myoid tumor that recurred after attempts at resection and eventually responded to therapy with cryoablation.
Design/Method: The discussion includes clinical presentation and diagnostic features noted on initial disease evaluation such as magnetic resonance imaging (MRI). We also have provided histologic findings from biopsies.
Results: A 14-year-old African American female presented with several weeks of right ankle pain with swelling. MRI showed a 2cm soft tissue mass in the posterior right lower leg. The mass was resected with pathology consistent with benign perivascular myoid tumor. While symptoms initially resolved several months later she once more developed pain and swelling in her right lower leg. MRI demonstrated multiple soft tissue masses (largest 8cm) concerning for recurrence. Largest lesion was removed with pathology again consistent with perivascular myoid tumor. She was managed for several months with analgesics and anti-inflammatory medications but continued to have pain from residual lesions. Since amputation with a prosthetic was the only surgical option to remove remaining lesions other therapies were sought. She was referred to Interventional Radiology for cryoablation. After two courses of cryoablation she had shrinkage in her tumors with markedly decreased swelling and pain.
Conclusion: Although perivascular myoid tumors are benign, multifocal lesions present a treatment dilemma since surgical resection may not be feasible. Since these tumors are slow growing, cytotoxic chemotherapy may not be effective. In this patient cryoablation proved to be very effective in shrinking the tumor and improving her quality of life.

Poster # 946

CLINICAL FEATURES AND OUTCOMES OF PEDIATRIC PATIENTS WITH MAY-THURNER SYNDROME

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Background: May-Thurner Syndrome (MTS) is an anatomic variant that results in impedance of venous flow due to venous compression of the left iliac vein by the right iliac artery. Frequently under-recognized, patients with MTS are at continued risk of developing recurrent deep venous thrombosis (DVT) or post thrombotic syndrome (PTS).
Objectives: We aim to discuss the clinical presentation and outcomes of seven pediatric patients with MTS.
Design/Method: A retrospective chart review of pediatric patients with MTS diagnosed and treated at one institution between 2005 and 2016.
Results: Among seven patients with MTS, the mean age was 15 years (range 13-17). Three patients were male (42.8%) and six were Non-Hispanic Black (85.7%). All but one patient had an occlusive left lower extremity DVT at presentation, while one asymptomatic patient had MTS incidentally diagnosed on imaging. Presenting symptoms among those with DVT included left lower extremity pain (100%), leg swelling (67%), and fever (33%), which closely mirrored physical exam findings. All with suspected DVT underwent initial Doppler ultrasound. MTS was confirmed either by additional image studies (n=3 including MRA, CTA, CT), or by interventional radiology venogram (n=4). Two patients (28.5%) were diagnosed with MTS after a recurrent thrombosis. We identified risk factors for thrombosis in 5 of 6 patients that developed a clot. Four had obesity (57%), three of four women were on oral contraceptive pills (42.8%), two had periods of immobility (28.5%), and two had prediabetes or diabetes mellitus (28.5%). We identified four patients with a thrombophilia risk factor (57%) including 2 patients with heterozygous Factor V Leiden and 2 with elevated Factor 8 levels. The 6 patients with DVT were started on anticoagulation with heparin or low-molecular-weight heparin. Stent placement was eventually performed in all patients with history of DVT. Duration of anticoagulation was variable, ranging from 3 months to indefinite. Three patients had recurrent episodes of DVT, one following stent placement. Two patients later developed symptoms suggestive of PTS.
Conclusion: Pediatric patients with MTS usually present with thrombosis during teenager years, in the setting of additional risk factors for thrombosis. Approaches to anticoagulation for secondary prevention of thrombosis post stent placement are variable.

Poster # 947

FAMILIAL NON-WNT/NON-SHH MEDULLOBLASTOMA

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Background: Medulloblastoma (MB) is an embryonal tumor of the cerebellum that accounts for around 20% of pediatric brain tumors. Four subgroups of MB with distinct gene expression

profiles, methylomes and clinicopathological features, have been identified: WNT, SHH, Group 3 and Group 4. Most MB cases are sporadic but some arise in the context of genetic syndromes that include: familial adenomatous polyposis (APC mutation), constitutional mismatch repair deficiency (MLH1, MSH2, MSH6, PMS2 biallelic mutations), Gorlin (PTCH1, SUFU mutation), Rubenstein-Taybi (CREBBP, EP300 mutations), and Li Fraumeni syndromes (TP53 mutation).
Objectives: To report 2 cases of MB in siblings without an identified genetic predisposition.
Design/Method: Retrospective chart review.
Results: Two male, Hispanic full siblings were diagnosed with MB 4 years apart. Patient A presented at 7 years of age with 3 weeks of nausea and vomiting, concurrent with a 3cm x 2cm x 3cm posterior fossa mass on brain magnetic resonance imaging (MRI). He was diagnosed and treated for high-risk MB, and remains in remission 4 years after therapy. Patient B presented at 4 years of age with headache, ataxia, vomiting, and increased somnolence for 10 days. MRI of the brain revealed a 3cm x 4.5cm x 2cm mass in the posterior fossa. He is currently undergoing treatment for average-risk MB. In both cases, histological findings were consistent with classical MB morphologically. Immunohistochemical staining was performed and both tumors had cytoplasmic β-catenin without nuclear staining, and were negative for YAP-1, GAB-1, and p53, supporting the diagnosis of non-WNT/Non-SHH MB. On physical examination, neither patient had a syndromic phenotype; family history was negative for consanguinity and unremarkable for cancers. Next generation sequencing of patient B's tumor for exons of 405 cancer-related genes and select introns of 31 rearrangements was performed and did not reveal any reportable alterations. Germline DNA testing for cancer predisposing genes with deletion/duplication analysis was performed on patient B. No aberrations were found in 28 genes including: APC, MLH1, MSH2, MSH6, PMS2, TP53, PTCH1, and SUFU among others. In view of the siblings' history, an asymptomatic 3-year-old male sibling underwent brain MRI that was unremarkable.
Conclusion: Familial MB in the absence of a characterized genetic syndrome has previously been reported in 11 cases. We hypothesize that the familial case we report here is likely part of a cancer predisposition syndrome that has yet to be identified. The family has been enrolled on a germline whole exome sequencing study that aims to answer this question.

Poster # 948

PLATELET CHARACTERISTICS AND BLEEDING PATTERNS IN CHILDREN WITH JACOBSEN SYNDROME: A SINGLE CENTER REPORT

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Background: Jacobsen Syndrome (JS) is caused by a deletion involving the long arm of chromosome 11 (11q). Clinical features of JS vary widely and can include: characteristic facies, cardiac malformations, renal and gastrointestinal abnormalities, developmental and behavioral issues, and thrombocytopenia and platelet dysfunction. Although a wide array of abnormal features are reported, 90% of patients are reported to exhibit platelet dysfunction and Paris-Trousseau syndrome (PTS). PTS is associated with increased bone marrow megakaryocytes with slow megakaryopoiesis, giant alpha-granules in peripheral platelets, and an increased risk of clinical bleeding. The clinical bleeding characteristics in patients with JS are often referred to,

yet are poorly described in the medical literature.
Objectives: To report the bleeding characteristics and laboratory features of platelets in children with genetically proven JS.
Design/Method: Patients with JS were identified through a STRIDE database query. Subjects with diagnosis by genetic testing were included. Data on subject characteristics, results of platelet laboratory testing, surgeries, and bleeding episodes were collected by chart review. Significant hemorrhage was defined as a spontaneous bleed requiring presentation to a medical professional and any bleeding continuing for over 20 minutes.
Results: Eight eligible subjects were identified (6 female) with 296.5 months of observation (median 22 months per patient). LABORTATORY: Median platelet count was 119 k./uL (range 63-244). Two subjects had normal platelet function testing performed by PFA-100. BLEEDING: Five subjects (62.5%) reported bleeding incidents ranging from mild to severe, and 3 had no bleeding. Significant spontaneous hemorrhagic events occurred in 2 patients (25%), and significant prolonged bleeding occurred in 2 subjects, for a bleeding rate of 0.44 significant bleeds per 1000 patient days. Five patients (62.5%) underwent a total of 14 invasive procedures with two patients receiving perioperative platelet transfusions with operative bleeding complications present in one patient (14% of total procedures). Three patients (37.5%) received 28 platelet transfusions, with one patient receiving 21 of the total transfusions.
Conclusion: Current literature suggests up to 90% of JS patients have thrombocytopenia and platelet function abnormalities consistent with PTS. However, laboratory and clinical features of JS children have not been well described. In our small JS cohort, we observed a rate of 0.44 significant bleeds per 1000 patient days. While this case series demonstrates that the incidence of clinically significant bleeding may be less than previously postulated, larger studies of this rare disease are needed to fully describe the bleeding characteristics and laboratory abnormalities seen in JS.Breton-Gorius, et al, Blood 1995.

Poster # 949

MALIGNANT TRANSFORMATION OF A PLEXIFORM NEUROFIBROMA IN A PATIENT WITH NEUROFIBROMATOSIS TYPE 2 (NF2)

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Background: Malignant peripheral nerve sheath tumor (MPNST) is a rare soft-tissue sarcoma with an unfavorable prognosis and limited therapeutic options. MPNSTs can be sporadic, but approximately one half are associated with NF1 and usually arise from pre-existing neurofibromas. MPNSTs in patients with NF2 have only been reported in exceedingly rare cases. The mechanisms by which a neurofibroma transforms into an MPNST are not fully elucidated.
Objectives: To describe the clinicopathological and genomic features of a plexiform neurofibroma as it transforms into an MPNST in the context of NF2.
Design/Method: Retrospective chart review.
Results: An 8-year-old male diagnosed at age 6 with sporadic NF2 with bilateral vestibular schwannomas, meningiomas, and a paraspinal plexiform neurofibroma extending from C3 to C7, underwent multiple debulking surgeries to relieve neurologic symptoms. For almost 2 years, the

initial plexiform neurofibroma demonstrated typical histology. Genetic sequencing of the tumor identified a somatic EGFR missense mutation and the germline NF2 mutation. Twenty months after diagnosis, increased proliferation (Ki67+ 10%) and loss of p16 on immunohistochemistry were first identified, but diagnostic criteria for MPNST were not met morphologically. In view of recurrences, and with the identification of a variant of uncertain significance in MAPK2 in the tumor, the patient was started on trametinib. He demonstrated stable disease for 4 months before presenting acutely with left arm paralysis. At that time, magnetic resonance imaging (MRI) showed tumor extension through neural foramina C5-C7 with severe cord compression. Histology of the intradural portion showed multiple changes, including abnormal proliferation (Ki67+ 10-20%), consistent with low-grade MPNST. Six months later, the patient presented with a rapidly enlarging left neck mass associated with severe pain radiating down the arm. MRI showed dramatic tumor growth and fluorine-18-fluordeoxyglucose positron emission tomography demonstrated new multifocal activity, SUV maximum 3.4. Pathology examination showed fascicles of alternating cellularity, loss of S100, necrosis, and increased proliferation (Ki67+ 53%), consistent with high-grade MPNST. Tumor sequencing revealed acquisition of a somatic frameshift mutation in NOTCH2, predicted to be inactivating. NOTCH2 is involved in cell fate decisions and has been described in oncogenic and tumor suppressor roles. Other novel, potentially oncogenic mutations were also identified. No NF1, TP53, or SMARCB1 alterations were documented.
Conclusion: In the extremely rare setting of NF2, a plexiform neurofibroma transformed into an MPNST. In this case, targeted genomic analysis provided insight into the transformation process. Deeper genetic sequencing is underway and will provide a better understanding of the genomic evolution of this tumor.

Poster # 950

ECULIZUMAB FOR DELAYED HEMOLYTIC TRANSFUSION REACTION IN A PEDIATRIC PATIENT WITH SICKLE CELL DISEASE

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Background: Delayed hemolytic transfusion reactions (DHTR) are potentially life-threatening complication seen in 4% to 11% of patients with sickle cell disease (SCD) within 5-20 days of transfusion. Patients with DHTR present with the acute onset of destruction of both transfused and autologous red blood cells (RBC) often concurrent with reticulocytopenia and symptoms of severe vaso-occlusive crisis. Alloimmunization to RBC antigens is a major cause of DHTR, but one-third of the patient antibodies are undetectable. There is no optimal treatment for DHTR.
Objectives: To present a case report of a 7-year-old African American female child with SCD with DHTR who was successfully treated with Eculizumab.
Design/Method: The medical record was reviewed and the case is presented. One week prior to the acute presentation, patient underwent a preoperative transfusion of phenotypically-matched PRBC prior to dental rehabilitation. Hemoglobin (Hgb) before discharge was 9.3 g/dL. One week later, she presented with severe fatigue, jaundice, and generalized body pain. Physical examination showed scleral icterus. Hemoglobin levels and absolute reticulocyte count were 4.6 g/dL and 73 x 109/L, respectively, with an elevated lactate dehydrogenase (LDH) of 1738 IU/L

(normal, 192-321 IU/L). She was admitted for management of a possible DHTR, and received intravenous (IV) fluids, pain medication, and intravenous immunoglobulin. She was started on dexamethasone (10 mg/day x 5 days) and erythropoietin (2000 units/day x 3 days). On day 3 of admission, she developed hemodynamic instability with hypoxia, fever, and severe tachycardia. Hemoglobin further decreased to 3.4 g/dL and chest X- ray showed left lower lobe infiltrate.
Results: Additional extended phenotyping and direct coombs test were negative. At the nadir of 3.4 g/dL received PRBC transfusion and a single dose of 600mg (30mg/kg) IV Eculizumab. We contacted the medical director at Alexion to request compassionate use approval for Eculizumab. The patient received the meningococcal vaccine before the medication was administered. Hgb stabilized at its baseline level of 7 g/dL within 24 hours of therapy. It remained stable as LDH decreased and reticulocytes recovered.
Conclusion: Eculizumab is FDA approved in pediatrics for atypical hemolytic uremic syndrome. This is the first case where Eculizumab, a potent C5 inhibitory antibody, has been successfully used in the treatment of DHTR in a young child with SCD. Based on the response seen in our case, we believe Eculizumab is an effective therapy for life threatening DHTR and the role of complemented mediated mechanisms in its pathophysiology need to be studied.

Poster # 951

GLIOFIBROMA: FIRST DESCRIPTION OF METASTATIC GLIOFIBROMA OF THE BRAIN IN AN INFANT

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Background: Gliofibroma of the brain is a rare, low grade glioma. It is classified separately from other low grade gliomas as "Other Glioma" in the 2015 CBTRUS scheme. This very rare tumor usually presents in childhood as a solitary mass. A case presenting with metastatic disease has never been reported.
Objectives: Description of first presentation of metastatic gliofibroma in an infant, treated and presumably cured with chemotherapy alone.
Design/Method: Chart review.
Results: A five month old female presented to the emergency room with failure to thrive. She had a nonfocal neurological exam. MRI brain and spine revealed a fourth ventricle mass with numerous metastases throughout the brain and spine. Biopsy confirmed a diagnosis of gliofibroma. She was treated with carboplatin, vincristine and temozolmide for one year with an excellent response to therapy but not a complete response. Two years after completing therapy, she presented with a palpable nodule on the face. The lesion was resected, pathology was pilomatrixoma. Six months later, she presented with new CN VI palsy. MRI imaging revealed a new tumor nodule at the exit point of CN VI on MRI. Therapy with carboplatin, vincristine and temozolomide was given for another year and she again had an excellent response but not a complete response to chemotherapy. Three years after completing her second round of chemotherapy, she remains well with stable disease. She has not been treated with radiation therapy.
Conclusion: Metastatic gliofibroma has not been described before. This tumor presented in infancy and, despite widespread metastases, the disease was controlled with chemotherapy alone.

As is the case with many low grade gliomas, and illustrated here, a good response to therapy can be achieved using the same chemotherapy regimen with recurrent disease. The finding of a second neoplasm (pilomatrixoma) in this young child raises the possibility of an underlying syndrome, such as Gardner syndrome; no syndromes have been identified so far.

Poster # 952

HYPEREOSINOPHILIA-ASSOCIATED THROMBOSIS AS PRESENTING FINDING IN PATIENT WITH GATA2 MUTATION

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Background: GATA2 mutations are associated with a broad spectrum of disease including primary marrow failure, neoplasia, immunodeficiencies, venous thrombosis, lymphedema, pulmonary disease, sensorineural hearing loss, and hypothyroidism. Described GATA2-related immunologic abnormalities include monocytopenia, B cell and natural killer cell lymphopenias.
Objectives: We discuss a unique case of a teenage female with recurrent massive thromboembolism and hypereosinophilia who developed cytopenias leading to further workup revealing GATA2 mutation. Eosinophilia has not been previously described in patients with GATA2-related disease.
Design/Method: This is a single case report from retrospective review of the patient's electronic medical record. Literature search was conducted via PubMed and Ovid Medline using the following search terms: GATA2 mutation, eosinophilia, thrombosis, hypereosinophilic syndrome.
Results: A previously healthy 13-year-old African-American female presented with extensive deep vein thrombosis (DVT) of the right leg. Hypercoagulability workup was positive only for lupus anticoagulant (resolved on follow-up). Over the next 3 years, her course was complicated by poor compliance. She had multiple hospitalizations for recurrent bilateral lower extremity DVTs, pulmonary emboli, atrial thrombi, and underwent procedures including surgical embolectomy and IVC filter placement. Multiple anticoagulation therapy changes were made. During her course, persistent eosinophilia was noted (absolute eosinophil count >1500 cells/L); tryptase, IL-5 and IgE were normal. Initial bone marrow biopsy was normocellular with eosinophilia and presence of trisomy 8. Hypereosinophilic syndrome was considered the likely etiology of the thromboembolic events. No significant improvement was seen with oral steroids and interferon alpha therapy. Mepolizumab (anti-IL5) was started, after which the eosinophilia resolved. There have been no thromboembolic events since resolution of the eosinophilia, and she is maintained on rivaroxaban, aspirin, and imatinib.Other findings have included monocytopenia, B cell lymphopenia, hypergammaglobulinemia, B cell clonality, and decreasing marrow cellularity. Molecular diagnostics included negative testing for JAK2, BCR/ABL, CHIC-2, and FIPIL1/PDGFRA rearrangement. GATA2 missense mutation at C.1061C>T[p.T354M] was found. Our patient has many findings consistent with GATA2 deficiency including thrombosis, monocytopenia, lymphopenia, trisomy 8, and Thr354Met mutation. Eosinophilia, however, has not been described in GATA2-related disease.
Conclusion: Our patient demonstrates a case of GATA2 mutation that is remarkable for

hypereosinophilia and extensive recurrent thromboses in addition to previously described features of GATA2-related disease. (Spinner, Blood, 2014; Mir, Cancer Medicine, 2015; Wlodarski, Blood, 2016)

Poster # 953

A CASE REPORT OF SUCCESSFUL SYSTEMIC THERAPY WITH BEVACIZUMAB FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

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Background: The human papilloma virus can cause recurrent respiratory papillomatosis (RRP). RRP is characterized by benign but incurable papillomas in the respiratory tract. RRP is treated with surgical local control (removal/debulking), which often needs to be repeated. Bevacizumab (Bv) is a vascular endothelial growth factor (VEGF) antibody. Its proposed mechanism is preventing the binding of VEGF to its target receptor on endothelial cells, thus preventing soft tissue neovascularization. There is evidence that RRP-associated papillomas have increased expression of VEGF. We present the case of a 19 year old female who was diagnosed with RRP treated with bevacizumab after repeated surgeries and progressive disease.
Objectives: To report our experience treating a patient with refractory RPP with Bv.
Design/Method: Between May, 2016 and January, 2017, a 19 year old female with RRP received Bv. The patient was initially diagnosed with RRP at the age of 4 after presenting with hoarseness and dyspnea. She underwent multiple surgical attempts at local control with very poor response, and ultimately developed widespread disease that included the lung parenchyma, larynx, nasopharynx, and sinuses. As she aged, she required debulking of the papillomas every 6 weeks. Other attempted therapies included intralesional cidofivir and oral celecoxib. Starting in May, 2016 the patient received Bv at 10 mg/kg/dose every 2 weeks for 3 months, then every 4 weeks for 3 months and then maintained with Bv every 6 weeks.
Results: Interval assessment of the patient was performed by direct visualization at 1, 2, and 6 months. Nasal endoscopy after 2 doses revealed no evidence of papillomas in the nasopharynx. Bronchoscopy performed after 4 doses of bevacizumab revealed no visible papillomas. Chest CT scans showed no new growths or change in size of any pre-existing parenchymal lesion at 2 and 6 months when compared to pre-treatment scans. Clinically the patient reported no snoring as well as improved exercise tolerance.
Conclusion: The systemic use of Bv for RRP improved this patient’s quality of life and eliminated the need for surgical intervention. Given the response on visual inspection, we speculate that the residual imaging findings may be consistent with scar tissue. While more data is required, the use of Bv to provide life-prolonging and morbidity-reducing treatment for RRP warrants further clinical investigation.

Poster # 954

INFANT WITH SEVERE ALPHA-SPECTRIN LINKED NON-DOMINANT HEREDITARY SPHEROCYTOSIS (HS) CAUSED BY A UNIQUE DOUBLE HETEROZYGOUS MUTATION IN THE SPTA -1 GENE

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Background: HS is a hemolytic anemia characterized by autosomal dominant inheritance and impaired erythrocyte membrane vertical protein interactions due commonly to moderate deficiency of spectrin resulting in mild to moderate hemolysis. In contrast, recessive or more commonly referred as non-dominant HS (ndHS) accounting for <5% cases is a near-fatal form of HS in infancy or childhood, requiring frequent blood transfusions and early splenectomy [Agre,NEJM]. Erythrocytes in ndHS exhibit a marked deficiency of spectrin due to SPTA-1 mutations. An extremely rare form of ndHS demonstrating a variant spectrin called α-spectrin Bughill (α-BH)due to point mutation on codon 970(A970D) of α-spectrin gene has been described. This variant while itself not responsible for ndHS is in linkage disequilibrium with another variable α-spectrin gene defect responsible for ndHS. Parents of affected individuals are hematologically normal with normal spectrin levels. The α-BH variant has only been reported in 8 patients with HS, 6 of whom were found to be double-heterozygous for the α-BH allele and a second, abnormal, α- spectrin defect[Tse ,AJH].
Objectives: To report a case of severe ndHS with a rare double-heterozygous SPTA-1 mutation.
Design/Method: Literature review on Google/PubMed for all cases of ndHS was performed.
Results: A 5-month old late-preterm Hispanic male with severe hyperbilirubinemia at 24 hours of life managed with phototherapy and IVIG for presumed ABO incompatibility, presented with growth failure, progressive jaundice, lethargy and poor feeding. The baby had chronic pallor and jaundice since birth but no significant family history of hemolytic anemia. Exam showed jaundice with liver 5 and spleen 8 cm below costal margin. Labs were, hemoglobin- 2.7 g/dL, bilirubin- 5 mg/dl, reticulocyte-18%, LDH-5199 u/l, haptoglobin <4 mg/dl and platelet count -66 k/ul secondary to hypersplenism,. Peripheral smear showed 30% nucleated RBCs, marked anisocytosis and large number of spherocytes. Work up excluded G6PD and Pyruvate kinase deficiency, Hemoglobinopathy, and Congenital dyserythropoietic anemia. Target gene mutation analysis by Next-generation sequencing revealed double heterozygous mutations in SPTA-1,first , mutation on exon 3 leading to premature termination of α-spectrin and second the A970D mutation (α-BH)confirming non-dominant severe HS.The patient is now 9 months, on 3-weekly transfusions and in preparation for splenectomy.
Conclusion: Double-heterozygous mutations in SPTA-1 for the α-BH allele and a second variable defect leading to severe ndHS are extremely rare. Rare mutations associated with HS should be investigated in patients presenting with severe congenital hemolytic anemia without a family history. This can determine need for early splenectomy and direct family counselling.

Poster # 955

SUCCESSFUL USE OF CRIZOTINIB IN TREATMENT OF A PULMONARY INFLAMMATORY MYOFIBROBLASTIC TUMOR WITHOUT ANY ALK REARRANGEMENT OR OTHER KNOWN GENETIC TARGET, CASE REPORT

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Background: Inflammatory myofibroblastic tumor (IMT) is a rare neoplasm. About 50% of IMT's have ALK rearrangements. More recently, other rearrangements, such as those involving ROS1, RET and NTRK3, have been found in IMT. Crizotinib which was initially developed as a MET inhibitor, is a potent ALK inhibitor and ROS1 inhibitor.
Objectives: We report a patient with pulmonary IMT without any ALK rearrangement, or other known molecular target of crizotinib, but had a complete response to it.
Design/Method: Case report.
Results: An 8 year old male with several year history of repeated left lower pneumonias and wheezing. Chest CT revealed a large mass in left lower lung consistent with IMT, which was confirmed by biopsy. Intraoperatively, during attempted resection, the mass had replaced the left lower lobe, invaded the lingula, abutted the hilum and encased the main branch of the pulmonary artery and left main stem bronchus. There were numerous small masses studding the pericardium and diaphragm, as well as a large tumor on his left diaphragm. He underwent left lower lobectomy and was left with significant gross residual disease after surgery. No ALK rearrangement or ALK gene amplification was detected by fluorescence in situ hybridization. No further genomic profiling was unable to be done. He was treated with 6 cycles of ifosfamide, vincristine, dactinomycin, and celecoxib, with no change in tumor size. Crizotinib, 500 mg/m2/day divided twice a day, was empirically started, and decrease to 430 mg/m2/day due to toxicities, which resulted in tumor shrinkage. After approximately 6 months on crizotinib, second look surgery confirmed resolution of all of his tumors. The pathology on the remnants of tumor did not reveal any residual IMT. He was placed on celecoxib post operatively. He remains tumor free 18 months post-surgery.
Conclusion: The list of immunotherapies that have molecular targets is growing. While the importance of molecular profiling of tumors, not just malignant ones, is starting to be recognized, it may not be able to be performed in all cases. If traditional cytogenetics does not reveal any ALK rearrangement, a trial of crizotinib may be considered in unresectable, refractory IMT.

Poster # 956

VITAMIN B12 DEFICIENCY MASQUERADING AS EVAN'S SYNDROME?

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Background: Vitamin B12 deficiency, usually presents in the adult population and is a known cause of megaloblastic anemia with neurological symptoms. Vitamin B12 deficiency rarely causes pancytopenia and psychiatric manifestations. Severe B12 deficiency causing symptomatic transfusion dependent pancytopenia is extremely rare in the pediatric population.
Objectives: We present a case of B12 deficiency presenting with transfusion dependent pancytopenia with evidence of hemolysis and neuropsychiatric symptoms.
Design/Method: Case report
Results: A 16 year old African American male presented with gradual pancytopenia (with a normal MCV), jaundice and dark urine. Bone marrow performed showed dyserythropoeitic changes, decreased megakaryocytes and mixed myeloproliferative changes but no clonal

abnormality. Chromosomal analysis and cytogenetics was normal. Red cell enzyme assay showed no enzyme deficiency. Direct Coombs test was initially negative, lactate dehydrogenase levels was 12,071 U/L (normal 100-300 U/L) and haptoglobin was <10 mg/dL. Autoimume work-up was positive for Cyclic Citrullinated Peptide. Coombs became positive within 3 months of diagnosis of pancytopenia; steroids were started with a diagnosis of Evans syndrome. Blood counts improved on steroids but patient developed an acute psychotic episode necessitating inpatient psychiatry treatment. Patient continued to be transfusion dependent post cessation of steroids with continued signs of hemolysis. Different treatment options utilized: IVIG (no response), rituximab (transient response but not sustained), cellcept (no response) and rapamune. Repeat bone marrow showed no clonal abnormality. Patient was admitted again to inpatient psychiatry with acute paranoia and concerns for schizophrenic disorder; risperidone was started per psychiatry. He developed dystonic reactions, leg weakness and refusal to walk. Due to worsening neurological status, MRI brain and spine was done. MRI showed diffuse symmetric T2 hyperintense signal abnormality throughout dorsal columns of spinal cord which was typical for a patient with B12 deficiency. Vitamin B12 levels were 53 pg/ml (normal 180-914 pg/ml). Antibody testing was positive against intrinsic factor confirming diagnosis of pernicious anemia. Vitamin B12 supplementation was started with cyanocobalamin injections daily for a week, weekly injections for 4 weeks and then monthly maintainance supplementation. After 6 weeks on B12 supplementation blood counts were completely normal. Patient's neurological status showed gradual signs of improvement in lower extremity weakness and increased alertness.
Conclusion: This case demonstrates vitamin B12 deficiency in a pediatric patient causing pancytopenia, transfusion dependence and neurological symptoms including neuropsychiatric problems. Vitamin B12 needs to be considered in refractory pancytopenia in pediatric patients.

Poster # 957

INFANTILE HOLOCORD IMMATURE TERATOMA UNDIAGNOSED ON PRENATAL ULTRASOUND

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Background: Immature intramedullary teratoma is an exceeding rare malignancy with the majority of cases occurring in the lumbosacral area. There are very few cases of congenital holocord lesions in the literature that were not suspected based on pre-natal ultrasounds.
Objectives: To describe a rare newborn intramedullary holocord immature teratoma.
Design/Method: Case Report.
Results: A previously healthy 27 day old full term female born via spontaneous vaginal delivery after an uncomplicated pregnancy presented to the emergency department with concern for poor feeding and increasing irritability over the previous 10 days. Family also reported that muscle tone and infant reflexes appeared to be diminished, especially in her upper extremities. Her initial neuro exam was significant for spontaneous movement in both legs, minimal movement in left arm, and no movement in right arm. Due to initial suspicion of meningitis, a lumbar puncture was performed in the emergency room, with xanthochromic CSF. MRI brain and spine revealed an expansive heterogeneous intramedullary mass involving the lower medulla, cervicomedullary

junction, cervical spinal cord, and thoracic spinal cord to the T12 level with areas of hemorrhage. Additional imaging studies were negative for further tumor foci. Labs included HVA and VMA which were not elevated, beta-HCG was not elevated. AFP was normal for age at 113.1 ng/mL. A gross total resection of the spinal cord tumor was achieved, and pathology was consistent with a grade 1 immature teratoma. Postoperatively, she subsequently regained spontaneous movement of her upper extremities and continues to work with physical therapy while being carefully observed for recurrence.
Conclusion: We report a 27 day old with a rare newborn intradural intramedullary immature teratoma, with no suspicion of abnormalities on prenatal ultrasound. Despite the more common etiology being infection in newborns presenting with hypotonia, spinal tumors should remain on the emergent differential.

Poster # 958

BABESIOSIS LEADING TO SEVERE HEMOLYSIS IN TWO PATIENTS WITH SICKLE CELL ANEMIA

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Background: The intracellular parasites Babesia microti and Babesia duncani can lead to severe life-threatening hemolytic anemia in high-risk patients, including those with sickle cell disease. The rarity of the diagnosis, as well as its similar clinical presentation to delayed hemolytic transfusion reaction, may lead to a delay in diagnosis, as well as inappropriate treatment with steroids or other immunosuppressive agents.
Objectives: The goal of this case report is to describe transfusion-associated babesiosis in two patients with sickle cell anemia who were on chronic transfusion therapy for secondary stroke prophylaxis.
Design/Method: We retrospectively analyzed the clinical and laboratory information of these two patients, including blood bank records.
Results: A 21-year-old female with HbSS presented 26 days after her last transfusion with a hemoglobin of 5.2 gm/dl and reticulocyte count of 17%. Patient had history of anti-C and anti-K RBC allo-antibodies but had been transfused with phenotype matched pRBC without evidence of new alloantibodies; however direct antiglobulin test (DAT) was positive for IgG and C3 complement, consistent with warm autoimmune hemolytic anemia. Eluate was positive with some reagent red cells but showed no specificity. She received 2 units of pRBCs and was started on prednisone 60 mg BID for hemolysis due to autoantibodies. She continued to have persistent hemolysis despite steroid therapy, so thick and thin smears were sent, which revealed babesia infection with a parasitic load of 3.9%. An 11 year-old male with HbSβ°thalassemia presented to the ED with fever. Initial hemoglobin was 8.5 gm/dl with 15% reticulocytes. Repeat CBC 24 hours later showed a significant drop in hemoglobin to 6.5 gm/dl with 11% reticulocyte count. Patient had history of positive DAT for IgG but negative for complement, eluate was a panagglutinin, consistent with a warm autoimmune process. Admission blood bank serology was not changed and no new alloantibodies were identified. Intracellular parasites were identified on peripheral smear with a parasitic load of 10%.Both patients were treated successfully with

azithromycin and atovaquone until parasitic load was persistently 0%. Lookback testing of the blood donors for both cases showed donors with high titer B. microti antibody. New York State recently began a nucleic acid-based ELISA screening program of all donated blood.
Conclusion: As demonstrated in these two cases, evidence of a warm autoimmune process should not preclude other causes of hemolysis. Intracellular parasitic infections should be considered in the differential diagnosis of accelerated hemolysis after a transfusion.

Poster # 959

EXTRANEURAL METASTASIS OR SECOND PRIMARY? A CASE REPORT OF AN ABDOMINAL GERM CELL TUMOR FOLLOWING A SUCCESSFULLY TREATED INTRACRANIAL GERM CELL TUMOR IN A 9 YEAR-OLD GIRL

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Background: Intracranial germ cell tumors (GCTs) rarely recur with extraneural metastases.
Objectives: We report the case of a child successfully treated for an intracranial nongerminomatous GCT who developed an abdominal GCT two years after initial therapy completion.
Design/Method: Case review of clinical information, results of relevant laboratory investigations, and management course.
Results: A previously healthy 9-year-old girl with a maternal family history of breast and ovarian cancer presented with a two-month history of headache, photophobia, fatigue, morning vomiting, polydipsia, and polyuria. A brain magnetic resonance imaging (MRI) revealed a large sellar and suprasellar mass with hydrocephalus. Spine MRI was negative and a ventriculoperitoneal (VP) shunt was inserted. Serum and cerebrospinal (CSF) alpha-fetoprotein (AFP) were elevated (3866 and 158 μg/L respectively) as were serum and CSF beta-human chorionic gonadotropin (β-hCG) (137 and 52 IU/L respectively). CSF cytology was suspicious for malignant cells. Based on tumor location and elevated tumor markers, the diagnosis of nongerminomatous GCT was made without biopsy. She was treated with chemotherapy (carboplatin, etoposide, ifosfamide) and craniospinal radiation including tumor boost as per protocol COG ACNS0122. Complications from tumor location included panhypopituitarism. Head imaging post therapy showed a residual suprasellar lesion but overall response with normalization of serum tumor markers. Two years later, she developed abdominal pain and distension with imaging demonstrating a large left upper quadrant soft tissue mass. Head imaging was unchanged. Serum β-hCG was markedly elevated (3372 μg/L) and AFP mildly elevated (10 IU/L). Cytology performed on peritoneal fluid confirmed a GCT, favoring a seminoma. CSF tumor markers and cytology were negative. Her karyotype was normal (46,XX) and testing for the sex-determining region Y (SRY) locus was negative. DICER1 sequencing was negative. She was treated successfully as per protocol COG ACGT0132 with chemotherapy (bleomycin, cisplatin, etoposide). She is 3.5 years and 15 months off-therapy for the intracranial and abdominal GCTs, respectively, and remains in biochemical and radiological remission. Therapy complications included asymptomatic decreased pulmonary and renal function, and high frequency hearing loss.
Conclusion: It is unclear if the abdominal GCT represents a hematogenous or VP shunt

metastasis versus a second primary tumor, although timing of the abdominal tumor would favor a second primary. This case brings into question whether children with intracranial GCTs and VP shunts require surveillance with abdominal imaging.

Poster # 960

A CASE REPORT OF AN INFANT WITH PEARSON SYNDROME: A RARE CAUSE OF BONE MARROW FAILURE SYNDROME AND SIDEROBLASTIC ANEMIA

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Background: Pearson marrow pancreas syndrome (PMPS) is an exceedingly rare, often fatal, mitochondrial disorder caused by a large deletion in mtDNA. Because of its rarity the prevalence of PMPS is unknown. Affected children typically present in infancy with a hematologic disturbance consistent with an inherited bone marrow failure syndrome and congenital sideroblastic anemia. Inherited bone marrow failure syndromes (IBMFS) are relatively rare and estimated to occur in 40-65 per million live births. Congenital sideroblastic anemia's (CSA's) are an uncommon form of inherited hematopoietic disorder characterized by pathological deposition of iron in the mitochondria of erythroid precursors in the bone marrow (ringed sideroblasts). Anemia is often the sole manifestation of the disease, making it difficult for the clinician to distinguish CSA from more common causes of anemia. Important clues to the diagnosis of Pearson syndrome include cytoplasmic vacuolization of erythroid and myeloid precursors along with the presence of ringed sideroblasts on bone marrow evaluation. Another hallmark clinical feature is exocrine pancreatic insufficiency. Currently there is no cure for this disease. The most common causes of death include overwhelming infection, lactic acidosis, and multi-organ failure.
Objectives: To describe a rare cause of pancytopenia in a young child
Design/Method: Case Report.
Results: A 3 month old previously healthy Caucasian male presented to the hospital with decreased appetite over the preceding 2-3 weeks with new onset fatigue and minor nosebleed that began the day prior. Physical examination was notable for severe pallor and lethargy. Initial laboratory work-up revealed hemoglobin of 2.6 g/dL (10.2-12.7), hematocrit 7.7% (30.9-37.9), mean corpuscular volume 104 fL (71.3-82.6) white blood cell 4200/uL (240/uL neutrophils and 3860/uL lymphocytes), platelets 50,000/uL (140-400), reticulocyte 1.31% (1.55-2.7). Serum PCR for Parvovirus B19 returned negative. He had normal immunoglobulin levels and lymphocyte subsets, which ruled out an immunologic cause for his pancytopenia. Work-up for bone marrow failure syndromes was notably negative for Fanconi anemia (negative DEB chromosomal breakage study), Dyskeratosis congenita (normal telomere length), and paroxysmal nocturnal hemoglobinuria. Bone marrow examination revealed increased cellularity with cytoplasmic vacuolization of myeloid and erythroid precursors. Iron staining of bone marrow biopsy revealed numerous ringed sideroblasts. Fecal fat content was elevated. Hemoglobin A1C and amylase/lipase were normal. Deletion/duplication analysis of mitochondrial genome revealed a 4.9kb deletion, m.11027_15950del4923, consistent with mitochondrial DNA

(mtDNA) deletion syndrome, also known as Pearson syndrome.
Conclusion: PMPS is a rare mitochondrial disease that is of interest to Pediatric Hematologists because of its striking cytopenias along with CSA.

Poster # 961

AFP-SECRETING EXTRA-RENAL TERATOID WILMS TUMOR

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Background: Teratoid wilm's tumor is a rare variant of the most common renal malignant tumor in children. Only 32 cases have been reported in the literature, only 4 previously reported originating from extra-renal locations, 1 prior case in which such a tumor was AFP-secreting, and none before found post-natally. While classic Wilm's alone is known to recapitulate nephrogenesis, the addition of other tissue-types has led some authors to theorize that teratoid Wilm's derives from embryologic rather than neoplastic tissue.
Objectives: To describe a case of extra-renal teratoid AFP-secreting wilm's tumor.
Design/Method: Single case report.
Results: A 6 year old female presented to her pediatrician following 3 days of decreased appetite, constipation, and mild dysuria, and one day of fever and abdominal pain. She was found to have a palpable abdominal mass. Initial blood work was significant for a white blood cell count of 23 x 109/L with 88% neutrophils, elevated inflammatory markers (ESR 28, CRP 57.88), LDH of 446, Alpha fetoprotein of 521.9 ng/ml (normal <15 ng/ml) , normal hCG, and otherwise normal serum chemistries. US of the abdomen showed a 10.2 cm x 6.6 cm x 8.7 cm heterogeneous mass in the lower mid abdomen, superior to the urinary bladder, with demonstrated blood flow on color doppler, as well as left hydroureteronephrosis. CT showed a large ovoid mass in the pelvis extending to the lower abdomen with left hydroureterneprhosis, abutting the left adnexa but not communicating with the uterus, with no lymphadenopathy or metastases. At subsequent laparotomy the mass was found to originate in the retroperitoneum rather than from the ovary, with normal ovaries and no renal involvement. Pathology after excision was consistent with areas of classic wilm's tumor along with teratoid elements rather than a classic germ cell tumor as expected. Due to spillage of contents during excision she was treated according to COG Wilm's tumor stage 3 standard risk protocol, with regimen DD-4A, with Vincristine, dactinomycin, doxorubicin and radiation therapy to the whole abdomen. Complications during treatment included small bowel obstruction requiring small bowel resection. She has since completed treatment and is free of residual disease at 33 months following diagnosis.
Conclusion: Teratoid Wilm's is an unusual clinical entity, and extra-renal AFP secreting teratoid Wilm's even more so. The outlook appears to be favorable, and the AFP level can be a helpful tumor marker to monitor the progress of treatment.

Poster # 962

SUCCESSFUL USE OF ROMIPLASTIM FOR A PATIENT WITH DOWN'S SYNDROME WITH APLASTIC ANEMIA

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Background: Patients with aplastic anemia have ineffective hematopoiesis due to impairments of the hematopoietic stem cell (HSC) compartment. Thrombopoietin is a critical regulator of hematopoiesis. The insight that the TPO receptor c-mpl is expressed on HSCs gave the impetus to explore the role of TPO mimetic drugs, eltrombopag and Romiplastim, for conditions associated with acquired disorders of hematopoiesis. Thrombopoietin (TPO) receptor agonists have shown to enhance hematopoiesis through its direct action on hematopoietic stem cells (HSC). Thrombopoietin (TPO) receptor agonist, eltrombopag, has been successfully used for the treatment of refractory aplastic anemia in adults and clinical trials are underway in pediatrics. In this context, we report our experience of using Romiplastim in a patient with aplastic anemia.
Objectives: Study course of a patient with aplastic anemia treated with Romiplastim
Design/Method: Prospective data-collection during the therapy with Romiplastim
Results: A 9 year old female with history of trisomy 21 and epilepsy who presented with an acute onset of petechial rash and epistaxis and with severe pancytopenia. CBC: WBC 1.2 K/MM3, ANC 462 /MM3, Hemoglobin 5.8 mg/dl, Platelet 2 K/MM3. Prior CBC showed mild leucopenia due to anticonvulsant medication. The etiology of present episode was thought to be related to recent addition of Lamotrigine along with Ethosuximide and Levetiracetam. Subsequently Lamotrigine and Ethosuximide were discontinued. Bone marrow biopsy confirmed severe aplastic anemia with hypocellularity <5%. Workup was negative for inherited bone marrow failure syndromes. Due to the concerns for irreversible bone marrow failure related to anticonvulsant, the therapeutic options for stem cell transplantation and immune-suppressive therapy were offered to family. She was commenced on weekly Romiplostim to reduce her platelet transfusion requirement. Patient showed gradual improvement in her cytopenia and remained transfusion independent after 4 weeks of therapy. Follow up bone marrow evaluation at 12 weeks of therapy showed 50% recovery without reticulin fibrosis. Recent CBC: WBC 3.8 K/MM3, ANC 2400 /MM3, Hemoglobin 12.7 mg/dl, Platelet 179 K/MM3. No side effects from Romiplostim were noted. Since her blood counts returned to her baseline, she is being weaned of Romiplastim without any significant drop in her blood counts.
Conclusion: Our experience showed that Romiplastim was safe and effective in a pediatric patient with aplastic anemia. It is possible that removal of an inciting event may have helped recovery of hematopoiesis. Therefore, efficacy of Romiplastim in children with aplastic anemia deserves further evaluation.

Poster # 963

MANAGEMENT OF BEVACIZUMAB INDUCED COLON MICRO-PERFORATION IN A PATIENT WITH NEUROBLASTOMA

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Background: Vascular endothelial growth factor (VEGF) is a tumor angiogenesis regulator known to support the proliferation of many malignancies. Increased expression of VEGF and VEGF receptor is correlated with poor prognosis and high stage neuroblastoma. Bevacizumab, a humanized anti- VEGF monoclonal antibody inhibits tumor vasculature and proliferation. It is currently FDA-approved for the treatment of several adult malignancies, and is being investigated in several early phase trials in children. Common adverse events are moderate: epistaxis, hypertension, and proteinuria. However, it is important to be aware of serious, rarer complications associated with bevacizumab.
Objectives: We describe a case of colon micro-perforation after administration of bevacizumab in a 5-year-old male with refractory neuroblastoma who received prompt surgical therapy.
Design/Method: This is a retrospective case review of a single case at Memorial Sloan Kettering Cancer Center.
Results: The patient presented at age four with stage 4 neuroblastoma. He received induction chemotherapy and underwent a partial resection of his abdominal tumor requiring a partial pancreatectomy with roux-en-y pancreaticojejunostomy. After first and second line chemotherapy, he had refractory soft tissue disease and enrolled on an institutional phase I protocol of 131I-3F8mediated radioimmunotherapy and bevacizumab (NCT00450827). He received 128 mCi 131I-3F8 on day 0 followed by bevacizumab 15 mg/kg on days 1 and 15. On day 27 he developed diffuse, cramping abdominal pain. Same day CT scan revealed severe pneumatosis with evidence of free air under the diaphragm. He underwent emergent laparotomy hours after presenting with symptoms which revealed small bowel adhesions and an extensive amount of pneumatosis around the cecum. A diverting loop ileostomy was performed. Postoperative care included metronidazole, gentamicin, piperacillin/tazobactam. No post-operative complications were observed. He underwent reanastomosis of his colon 16 months later, but needed parenteral nutrition for 6 years post-surgery due to bowel dysfunction. He currently tolerates all nutrition orally, and is on pancreatic enzyme supplements. The patient went on to receive additional anti-neuroblastoma therapy including high-dose chemotherapy, 3F8, abdominal radiotherapy, and perifosine for 3.5 years. He remains well without progression two years off therapy.
Conclusion: Incorporating new therapeutic agents such as bevacizumab into multimodality therapy might improve outcomes in high-risk pediatric cancers. However, providers must have a thorough understanding of potential rare adverse events. Bowel perforation has been described in adults receiving bevacizumab, often with dismal outcomes, but has not been reported in children. By describing this rare complication and the rapid intervention, we illustrate that prompt intervention can lead to a favorable outcome.

Poster # 964

DIFFERING NEONATAL PRESENTATIONS OF EPSILON GAMMA DELTA BETA THALASSEMIA WITHIN A FAMILY

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Background: Epsilon gamma delta beta thalassemia (EGDBT) is a rare condition caused by a large deletion within the beta-globin gene locus. It is characterized by neonatal anemia that

improves within the first few months of life.
Objectives: The aim of this report was to describe the differing neonatal presentations of a family with EGDBT.
Design/Method: A retrospective chart review was performed on a child and her father, both of whom presented with neonatal anemia. A deletion/duplication analysis of the beta-globin gene locus by multiplex-ligation-dependent probe amplification (MLPA) was then performed on the child, father and mother. Beta-globin gene locus sequencing was also performed on the father to determine if a clinically significant variant was present.
Results: The child was born full term with mild anemia (hemoglobin 10.5 g/dL) and stress erythropoiesis. Her newborn screen showed FA hemoglobin. She did not require transfusion prior to discharge from the newborn nursery. By 8 weeks, her hemoglobin trended down to 6.7g/dL and hemoglobin HPLC showed no variant hemoglobins. Red blood cell transfusion was given. She did not require further transfusions. By 2 years, her CBC and HPLC were consistent with beta thalassemia trait. Her hemoglobin was 9.8 g/dL and MCV 52.5 fL. Her family history revealed the father and paternal aunt were hydropic at birth. The paternal aunt had an exchange transfusion at 1 hour of life. Initial CBC showed hemoglobin of less than 4 g/dL and retic of 26.4%. She died at 5 hours of life. The father required intrauterine transfusions and immediate exchange transfusion at birth. He did not require further transfusions and by 7 months of age his CBC and HPLC were consistent with beta thalassemia trait. The duplication/deletion assay of the beta-globin gene locus revealed a deletion in the beta locus that extends from upstream of the HBB-HS5 region in the locus control region to a point at least 15kb 3' of the beta globin gene in the child and father. The mother's was normal. Beta-globin gene locus sequencing on the father did not reveal any clinically significant variants to explain the difference in neonatal presentations in the child and father.
Conclusion: Despite identical genotypes, patients with EGDBT can have differing prenatal and neonatal clinical courses ranging from hydrops fetalis to mild anemia at birth. Therefore, despite the clinical course of other family members, fetuses and neonates at risk for inheriting EGDBT should be monitored closely as their presentation may be markedly different.

Poster # 965

PRIMARY SPINAL PRESENTATION OF EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES (ETMR)

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Background: CNS tumors comprise approximately 20% of all pediatric malignancies. Of these, the diagnosis of embryonal tumor with multilayered rosettes (ETMR) represents a rare entity, newly recognized by the 2016 update of the WHO classification of CNS tumors. The diagnosis of ETMR is based on both histomorphologic appearance (i.e. ependymoblastic rosettes) and in most cases, amplification of C19MC, an oncogenic miRNA cluster on chromosome 19 (19q13.42). ETMRs generally arise in the supratentorial region of the brain, with primary spinal disease exceedingly rare. Clinically, ETMRs show aggressive behavior and strikingly poor prognosis despite multi-modality therapy, most often based on high-risk PNET protocols.
Objectives: To describe a unique case of primary spinal ETMR in a pediatric patient

Design/Method: Case Report.
Results: A three-year-old male patient presented with a two-month history of worsening broad-based gait, along with acute weakness of the legs, inability to walk and urinary retention. An MRI of the spine demonstrated an intradural, intra- and extra-medullary lesion spanning T10-S2, with vertebral involvement and extension through the neural foramen with invasion through the right psoas muscle. An additional intradural, extramedullary lesion was noted at the C6 spinal cord level. The brain MRI was negative for malignancy except for a 4 mm, solid and enhancing pineal gland concerning for possible metastasis. Due to cord compression and impending paralysis, the patient underwent emergent laminoplasty and tumor debulking. Bone marrow biopsies were negative for malignancy. Despite initial suspicion for neuroblastoma, urine VMA and HVA were negative and there was no uptake on MIBG scan. Pathologic analysis confirmed a diagnosis of ETMR, NOS as per the 2016 WHO Classification. The patient was started on therapy per HeadStart II consisting of high-dose methotrexate, vincristine, cisplatin, cyclophosphamide and etoposide, with a plan to proceed to high dose chemotherapy with autologous stem cell rescue if the disease proves to be chemo-responsive, followed by radiation. By the end of his first cycle of this therapy, our patient has improving neurological status, is urinating spontaneously and cruising.
Conclusion: We present an exceedingly rare case of primary spinal ETMR. . Optimal treatment strategies have not been identified.

Poster # 966

A CASE SERIES OF PYRUVATE KINASE DEFICIENCY AND HEPATIC FAILURE: THE EXPERIENCE OF A PEDIATRIC TERTIARY CARE CENTER IN QUEBEC

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Background: Pyruvate kinase deficiency (PKD) is an autosomal recessive disorder characterized by an enzymatic defect of the glycolytic pathway. PKD may present with severe neonatal hyperbilirubinemia and anemia, but in very rare cases a severe hepatic failure have been reported.
Objectives: To report three cases of hepatic failure associated with pyruvate kinase deficiency.
Design/Method: Case series in a single tertiary center and literature review.
Results: Case 1: this male term baby presented at birth with severe anemia, thrombocytopenia, conjugated hyperbilirubinemia, normal GGT, hepatosplenomegaly, liver failure with coagulopathy, and hypoalbuminemia causing generalized edema. Liver biopsy revealed important intralobular cholestasis, ductular proliferation and mild extramedullary hematopoiesis. Two pathogenic mutations in the PK-LR gene were found: c.721G.T [p.Glu241*] and c.1195del [p.Ala399Leufs*20]. He died at 3 months of age of a fulminant sepsis before splenectomy and liver transplant could be performed. Case 2: this full-term newborn boy showed at birth a very similar presentation. Two pathogenic mutations in the PK-LR gene confirmed the diagnosis: c.1091G>A [p.Gly364Asp] and c.1529G>A [p. Arg510Gln]. He is currently alive and well 15 months after splenectomy along with a cadaveric liver transplant. His hemolytic anemia is now controlled without repeated transfusions. Histopathologic examination of the patient liver revealed severe fibrosis, important neoductular proliferation in portal tracts with canalicular and

cellular cholestasis, and moderate iron overload. The spleen showed extramedullary hematopoiesis. Case 3 is a male infant born at term from consanguineous parents, who also had similar clinical presentation. Genetic analysis of PK-LR gene revealed that he was homozygous for c.1436G>A pathogenic mutation. Liver biopsy showed important lobular and portal fibrosis associated with neoductular proliferation and intracanalicular bile deposition. He also died of a fulminant sepsis at 4 months of age while he was waiting for liver transplant along with splenectomy.
Conclusion: The above reported three cases of PKD illustrate that in rare cases, severe mutations can be responsible of neonatal hepatic failure. The underlying pathophysiology is possibly multifactorial. Severe prenatal and neonatal hemolysis may have contributed to biliary canaliculi obstruction. PK-LR mutations may have affected the expression of both PK-L and PK-R in liver and red blood cells, respectively. This PK-L defect may have altered the hepatocyte energetic metabolism and increase the susceptibility of hepatocytes to different insults. Also, the expected compensatory overexpression of PKM2 in the liver may have not been achieved for unknown reason. Finally, severe extramedullary hematopoiesis may have cause a supplementary damage to the lobular architecture.

Poster # 967

TRANSLOCATION ASSOCIATED RENAL CELL CARCINOMA AS A SECONDARY MALIGNANCY IN A PEDIATRIC PATIENT PREVIOUSLY TREATED WITH ALLOGENEIC STEM CELL TRANSPLANT FOR PHILADELPHIA CHROMOSOME POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Renal cell carcinoma (RCC) is infrequent in children and only accounts for 2-5 % of pediatric renal masses with an overall incidence of 0.01 per 100,000 population. Translocation associated RCC is the most common form of pediatric RCC. These translocations results in gene fusions involving MiTF/TFE transcription factor genes. There have been rare reports of translocation associated RCC in patients with previous exposure to chemotherapy particularly topoisomerase II inhibitors or alkylating agents.
Objectives: We present an exceptional observation of an 8 year old boy with translocation associated RCC who had a previous history of allogeneic stem cell transplant (SCT) for Philadelphia Chromosome positive (Ph+ve) Acute lymphoblastic leukemia (ALL) at 2 years of age.
Design/Method: Case report.
Results: An 8 year old male with history of Ph+ve ALL diagnosed at the age of 2 years and was treated with chemotherapy and underwent allogeneic SCT after achieving complete remission. Conditioning regimen was myeloablative consisting of total body irradiation, thiotepa and cyclophosphamide. Patient's post-transplant course was complicated by Veno-Occlusive disease of the liver with hepatorenal syndrome. He developed nephrotic range proteinuria necessitating a renal biopsy which showed some residual left renal scarring on the lower pole. Due to this finding, patient was being followed with yearly renal ultrasound. Ultrasound done at 6 years post-transplant visit revealed an incidental finding of 1.5cm mass on upper pole of right kidney

that was confirmed on contrast enhanced CT angiogram to be a solid lesion with no lymph node or renal vein involvement. Urology was consulted and patient underwent partial nephrectomy with lymph node sampling. Pathology of the lesion revealed signet ring like cells having clear cytoplasm with eccentric nuclei interspersed in normal renal polygonal cells. This sample was positive for Xp11.23 translocation in 40% cells confirming the diagnosis of Xp11.23 translocation associated RCC (clear cell variant) Stage T1A.
Conclusion: Children who survive cancer are more than 20 fold-increased risk of developing another malignancy. Still, RCC occurring as a secondary malignancy is uncommon. Cytotoxic chemotherapy may predispose to the development of translocation associated RCC. Surgery is the best treatment option and prognosis is favorable for a localized tumor with complete resection. Nodal disease is common and seen with small primary tumors. Failure to sample LN results in incomplete staging and potentially inadequate disease control. Our patient had a localized tumor with no lymph node involvement and underwent nephron sparing surgery. He is doing well 6 months post-surgery with no complications.

Poster # 968

NOVEL CUBN MUTATION IN A YOUNG CHILD WITH MEGALOBLASTIC ANEMIA

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Background: Inherited disorders of cobalamin (Cbl, vitamin B12) metabolism are rare causes of megaloblastic anemia and neurologic abnormalities. More prevalent in certain ethnic groups, these disorders occur despite adequate Cbl intake and usually result from abnormal vitamin cell transport or processing. Cubilin (CUBN, intrinsic factor-cobalamin receptor, IFCR) is the intestinal receptor for the endocytosis of the intrinsic factor (IF)-Cbl complex. Its gene is localized to chromosome 10p13 and mutations involving CUBN have been described in patients with congenital megaloblastic anemia (Megaloblastic anemia-1, Finnish type or Imerslund-Grasbeck syndrome (IGS)). The clinical features of affected children involve development of early anemia that is responsive to Cbl therapy, and varied degree of proteinuria.
Objectives: To describe a novel CUBN pathogenic variant mutation in a child with megaloblastic anemia
Design/Method: Case Report.
Results: A 2-year-old female of Arabic origin presented with a three-day history of bilateral eye swelling, two weeks of decreased activity level and appetite, and progressive paleness. Reported diet was age appropriate and included animal products and cows milk. Parents denied consanguinity. Physical exam was remarkable for irritability and pallor. Initial laboratory work-up revealed hemoglobin 5.7 g/dL (10.2-12.7), hematocrit 17.7% (30.9-37.9), mean corpuscular value 96.7 fL (71.3-82.6), white blood cell 7,390/uL (670/uL neutrophils and 6500/uL lymphocytes), platelets 61,000/uL (140-400), reticulocyte 1.8% (0.82-1.45), lactate dehydrogenase 9,953 U/L (460-1,060), urinalysis with 2+ protein, normal uric acid and iron studies. Peripheral smear revealed anisopoikilocytosis, hypersegmented neutrophils, and giant band neutrophils. Folic acid was normal (>24 ng/mL) and Cbl level was 101 pg/mL (200-1100

pg/ml), post red cell transfusion. Bone marrow was hypercellular with erythroid hyperplasia and megaloblastic maturation. Homocysteine was 55.2 umol/L (<10.4), with plasma propionyl (C3) carnitine of 6.48 umoles/L (0.1-1.48), and urine methylmalonic acid was 1,100 mmole/mole creatinine (0-6), suggesting a defect in the Cbl metabolism. Karyotype was normal. Cobalamin metabolism gene panel sequencing revealed two copies of a novel, pathogenic CUBN variant mutation, c.2496dupT (homozygous). The c.2496dupT variant created a frameshift in the CUBN protein at codon 833 in exon 19 which resulted in a premature termination codon, and likely a truncated/absent protein product. Pathogenic variants of CUBN are inherited in an autosomal recessive manner, as demonstrated in this case. Our patient was initiated on Cbl supplementation with complete resolution of symptoms and normalization of laboratory results.
Conclusion: The c.2496dupT CUBN variant mutation has not been previously reported in patients with megaloblastic anemia. This variant leads to the clinically significant Imerslund-Grasbeck syndrome.

Poster # 969

H3K27M-MUTANT PEDIATRIC MIDLINE GLIOMA WITH EPENDYMAL AND LOW-GRADE ASTROCYTIC COMPONENTS

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Background: K27M mutation in genes encoding histone H3 isoforms (H3K27M) is detectable in the majority of pediatric diffuse intrinsic pontine gliomas and 20-30% high-grade gliomas (HGG) arising in midline structures. When present in this setting, it has been associated with more aggressive clinical behavior and poor prognosis. H3K27M mutations have rarely been reported in low-grade gliomas (LGG). The limited available data on the prognostic significance of this mutation in LGGs suggests it may be a negative marker, especially in thalamic tumors.
Objectives: To report an unusual case of an H3K27M-mutant pediatric glioma with combined ependymal differentiation and low-grade astrocytic features.
Design/Method: Retrospective chart review and review of the literature.
Results: A 7-year-old previously healthy female presented with a 2-month history of intermittent headaches, morning emesis and increased sleepiness. Brain magnetic resonance imaging (MRI) showed a large partially calcified, centrally necrotic and partially enhancing mass centered within the left hypothalamus, left globus pallidus and left thalamus with significant hydrocephalus. Following a subtotal resection of the tumor, pathologic examination revealed a modestly cellular infiltrative glioma lacking significant mitotic activity, vascular proliferation and necrosis supporting the diagnosis of a low-grade infiltrative astrocytoma. Tumor cells were uniformly bland and ribbon-like strips of tumor surfaced by an ependymal-like epithelial lining were identified. Immunohistochemical (IHC) staining was diffusely positive for GFAP in tumor cells, while EMA labelled many cells in a perinuclear dot-like pattern. H3K27M IHC staining showed strong nuclear positivity in both infiltrative cells and the ependymal-like epithelial cells, confirming that both were components of the tumor. The tumor was subsequently classified as an H3K27M-mutated glioma with ependymal and low-grade astrocytic features. Next Generation Sequencing confirmed the H3F3A K27M mutation and did not identify any BRAF aberrations. The patient is being treated per the Children’s Oncology Group protocol A9952 Regimen A and

is currently in maintenance therapy, 7 months after resection. She is being monitored with serial MRIs of the brain that have so far shown stable residual mass.
Conclusion: H3K27M mutation occurs uncommonly in LGGs, but when present, it may confer a poor prognosis. Clinicians must be aware of this entity as closer or longer-term monitoring of patients with H3K27M-mutated LGG may be warranted. This report also highlights a case of genomic overlap between histologic diagnoses of pediatric LGG and HGG.

Poster # 970

NOVEL GERMLINE NIJMEGEN BREAKAGE SYNDROME MUTATION IN AN ARAB PATIENT

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Background: Nijmegen Breakage Syndrome (NBS) is an autosomal recessive chromosomal instability syndrome characterized by microcephaly, growth retardation, immunodeficiency, predisposition to cancer, and DNA repair defect. Its causal mutation is in the NBN gene which encodes for the protein NBS1 (nibrin), a tumor suppressor. Pathogenic mutations are most frequent in Eastern European populations. NBN mutations have not been reported in patients of Arab descent. We report a four-year-old Saudi Arabian boy with poor growth who presented with Burkitt Lymphoma. He experienced significant toxicity to chemotherapy both in Saudi Arabia where he received three cycles of therapy including cyclophosphamide, vincristine, prednisone, doxorubicin, etoposide, carboplastin, and rituximab and in the United States after a cycle of COP-R (cyclophosphamide, vincristine, prednisone, rituximab). Due to extreme toxicity from chemotherapy including prolonged cytopenias, renal failure, multiple invasive infections, and severe mucositis, the patient was evaluated for germline DNA repair defects.
Objectives: We report a novel NBN gene mutation in the first Arab patient diagnosed with Nijmegen Breakage Syndrome.
Design/Method: Clinical genetic testing was performed using the Chromosome Breakage Disorders next-generation sequencing (NGS) panel (Molecular Genetics Laboratory, Cincinnati Children’s Hospital). The identified NBN gene mutation was evaluated in the context of prior reports of patients with NBS. The function of the resulting hypomorphic protein product was predicted based on NBS protein domains.
Results: NGS testing identified a novel point mutation (c.589delT; p.Y197fs) in both of the patient’s NBN alleles. This is the first report of a patient of Arab descent with NBS. NBN mutations that result in NBS have been reported mostly in Slavic populations and occur in exon 6 (c.657_661del5). The wild-type NBS1 protein is 754 amino acids and binds MRE11 and RAD50 to form the MRN complex which is essential to double-stranded break (DSB) repair. Additionally, NBS1 is phosphorylated at amino acids 278 and 343 by ATM which contributes to cell cycle checkpoint control. The Y197fs mutation results in a hypomorphic protein of 229 amino acids, which is truncated prior to the MRN binding and ATM phosphorylation target sites. Thus, the resulting hypomorphic protein is predicted to be deficient in DSB repair and cell cycle checkpoint functions. This is consistent with dysfunction of the NBS1 protein leading to genomic instability. Our patient displayed symptoms consistent with this phenotype including development of malignancy and extreme chemosenstivity.

Conclusion: Nijmegen Breakage Syndrome should be considered in Arab patients with malignancy and symptoms consistent with constitutional DNA repair defects.

Poster # 971

YOUNG CHILD WITH INFANTILE FIBROSARCOMA AND INTRACRANIAL CAVERNOMAS: A CASE REPORT

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Background: Infantile fibrosarcoma (IF) is a rare soft tissue sarcoma that typically develops prior to one year of life. It carries a good prognosis with complete surgical resection being the treatment of choice. Most cases are associated with t(12;15)(p13;q25) translocation, creating ETV6/NTRK3 gene fusion, which can be used for definitive diagnosis. Occasionally, it may be initially mistaken for a cutaneous vascular malformation (VM), as these lesions may be hypervascular and radiographically resemble VMs. To date, there are no reported cases or literature supporting any causal relationship between infantile fibrosarcoma and vascular malformations.
Objectives: To report a clinical presentation of vascular malformation with history of IF, outlining the pathology and genetics of the case.
Design/Method: Electronic medical record review of the patient's case.
Results: We outline the case of a 16 month old boy who presented for evaluation of persistent emesis with a previous diagnosis of IF. The right chest wall IF was diagnosed and resected at 10 months of age. Pathology revealed a cellular spindle cell neoplasm with thin walled branching vessels and multifocal hemorrhage. The diagnosis was confirmed by fluorescence in situ hybridization demonstrating ETV6 gene rearrangement. He recovered well despite decreased strength in his right arm. Six months later he evaluated for persistent emesis. A head CT with contrast demonstrated a 5.2cm heterogeneous mass in the right temporal lobe with left midline shift. An MRI identified a partially calcified hemorrhagic mass with an additional 8mm lesion and few small hemorrhagic lesions in the bilateral occipital, frontal, and left parietal lobes. He underwent a right frontotemporoparietal craniotomy for mass resection and drain placement. A diagnosis of recurrent IF was considered but final pathology was consistent with VM. Upon follow-up, imaging demonstrated post-surgical changes of the mass resection and stable hemorrhagic lesions that radiographically represented cavernomas.
Conclusion: This case demonstrates the challenges that revolve around the diagnosis of IF and VM which further delineates the importance of a multimodal diagnostic approach. The distinction between these diagnoses relies on the differing histomorphology, with IF being characterized by highly cellular spindle proliferation with a herring bone pattern, and VM showing a mixture of variable sized dilated vessels lacking a solid spindle cell component. This case poses the unique opportunity for discussion regarding the remaining intracranial lesions that radiographically represent cavernomas, and the potential need for biopsy and genetic testing in the future. Therefore, follow-up and re-imaging with broader consultation to discuss management will be warranted.

Poster # 972

MEDIASTINAL MASS AS AN UNUSUAL PRESENTATION OF EXTRAMEDULLARY HEMATOPOIESIS IN A CHILD WITH OSTEOPETROSIS

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Background: The differential diagnosis of a mediastinal mass in children is broad and most commonly includes lymphomas, lipomas, cysts, thyroid masses, thymic masses, germ cell tumors, and sympathetic nervous system tumors (including neuroblastoma). Extramedullary hematopoiesis is most commonly noted in the liver and spleen and in patients with hemoglobinopathy or thalassemia syndromes. Rarely, intrathoracic extramedullary hematopoiesis can occur in lymph nodes leading to a mediastinal mass.
Objectives: To describe an extremely unusual presentation of extramedullary hematopoiesis.
Design/Method: Literature and medical record review
Results: We report the case of an 8-year-old boy with infantile malignant osteopetrosis with resultant anemia, blindness, and developmental delay who presented with a mediastinal mass. He was initially diagnosed with osteopetrosis as an infant after rib abnormalities were noted on CXR. Genetic analysis confirmed a homozygous mutation in the TNFRSF11A gene (RANK). The family declined bone marrow transplantation and patient received ongoing supportive care. The patient developed neck pain, and cervical MRI revealed a large paravertebral soft tissue mass with extension to the epidural space and paraspinal musculature at the cervicothoracic junction. The mass demonstrated heterogeneous T2 signal. CT scan of the chest demonstrated a mediastinal bilobed heterogeneous mass with its epicenter anterior to the vertebral bodies. The appearance of the mass was consistent with extramedullary hematopoiesis
Conclusion: Infantile malignant osteopetrosis patients suffer from an increase in bone density that leads to progressive replacement of the bone marrow, with subsequent anemia and pancytopenia. The abnormal expansion of bone interferes with medullary hematopoiesis, resulting in life-threatening anemia, thrombocytopenia and increased susceptibility to infections. Hypoplastic bone marrow leads to extramedullary hematopoiesis and secondary expansion of extramedullary hematopoiesis sites such as the liver and spleen. Extramedullary hematopoiesis in the mediastinum has rarely been reported in patients with hemoglobinopathies and thalassemia syndromes. There are no previously published cases of intrathoracic extramedullary hematopoiesis in a pediatric patient with osteopetrosis. Extramedullary hematopoiesis presenting as a mediastinal mass is an important diagnostic consideration in any patient with an underlying marrow disorder and ongoing stress erythropoiesis.

Poster # 973

A TALE OF TWO CASES - BRAF-V600E TARGETED THERAPY IN IOWA

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Background: The BRAF-V600E mutation occurs in multiple malignancies, including brain tumors, histiocytic disorders, and melanoma. BRAF is a regulatory serine/threonine protein kinase in the MAPK/ERK pathway. RAS/RAF/MEK/ERK facilitates communication between the extracellular and nuclear environment. Combination therapy with BRAF/MEK inhibitors has shown superior outcomes compared to monotherapy with BRAF inhibitors, and is now FDA approved for treatment of cancers in adult patients. Their use has not been reported in children.
Objectives: We report 2 patients with BRAF-V600E mutations who received targeted therapy with BRAF and MEK inhibitors.
Design/Method: Between 2014 and 2016, FoundationOne testing was used to identify targetable genetic alterations in pediatric cancers diagnosed at our center.
Results: Case 1: Fourteen year-old Caucasian male, who presented with right-sided neck swelling. He was initially diagnosed with stage 3 Peripheral T-cell Lymphoma-NOS without CNS or bone marrow involvement and treated with multiagent chemotherapy. Tumor was refractory to two chemotherapy regimens targeted against lymphoblastic lymphoma. Tumor exome profile of the original biopsy specimen revealed a BRAF-V600E mutation and was consistent with malignant histiocytosis. He received Dabrafenib and Trametinib as targeted therapy without side effects. Repeat functional imaging after 57 days of treatment showed complete response. At the time of preparation of this report, he has been in CR1 for five months without any evidence of toxicity. Case 2: Sixteen year-old Filipino male, who presented with sudden onset headache, left sided paralysis, and seizure. Magnetic resonant imaging (MRI) showed a right thalamic hemorrhagic mass, which was consistent with an infiltrating, high grade astrocytoma, WHO grade III with BRAF-V600E mutation. He was initially treated with the standard chemoradiation but showed disease progression after 10 months. He was started on Vemurafenib; due to intolerable side effects, we switched to combination therapy with Dabrafenib and Trametinib. He showed clinical improvement in two weeks, manifested by improvement in left arm paralysis, facial droop and drooling. Follow-up MRI showed decrease in thalamic enhancement and resolution of leptomeningeal enhancement. He experienced multiple side effects during treatment; after four months, he presented with increased tumor burden and hydrocephalus consistent with progression.
Conclusion: Targeted therapy against BRAF-V600E mutation can be considered for cancers harboring the mutation regardless of histological diagnosis. Combination therapy with BRAF/MEK inhibitors has shown promising response with variable side effects among patients. Future trials should focus on upfront genomic profiling and integration of targeted treatment with traditional chemotherapy.

Poster # 974

CONCURRENCE OF ALLOIMMUNE NEUTROPENIA AND THROMBOCYTOPENIA IN TWO NEONATES

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Background: Neonatal alloimmune thrombocytopenia (NAIT) and alloimmune neutropenia (NAN) are caused by transplacental passage of maternal alloantibodies against incompatible fetal platelet or neutrophil antigens, respectively. These are well-defined entities, however

simultaneous occurrence of both in the same patient has been rarely described (1, 2, 3).
Objectives: To describe two premature infants with extremely rare concurrence of NAIT and NAN.
Design/Method: Case report.
Results: Patient #1 was born at 31 weeks of gestation after an otherwise uncomplicated pregnancy to an Asian mother and Caucasian father. Shortly after birth, a complete blood count (CBC) demonstrated thrombocytopenia (60,000/µL), a white blood cell count of 5,300/µL and neutropenia (300/µL). The platelet count spontaneously increased and normalized by age 5 days without related complications. However, the absolute neutrophil count (ANC) fell to <100/µL by the second day of life and profound neutropenia persisted. Parental platelet and neutrophil antigen genotyping and antibody analysis (BloodCenter of Wisconsin, Milwaukee, USA) demonstrated maternal antibodies against HNA-1b and HPA–15b. A single dose of filgastrim (10 µg/kg) yielded a transient rise in ANC to 3,900/µL. Neonatal intensive care unit (NICU) course was complicated by mild omphalitis responsive to a one-week course of intravenous antibiotics. Neutropenia gradually resolved by 13 weeks of age. Patient #2 was that of a precipitous home delivery at 32 weeks of gestation after an uncomplicated pregnancy. As with patient #1, mother was Asian and father was Caucasian. CBC at the time of hospital admission demonstrated neutropenia (600/µL) and moderate thrombocytopenia (96,000/µL). By the third day of life the ANC fell to <100/µL. Thrombocytopenia spontaneously resolved by age 8 days without any related complications, however profound neutropenia persisted. Parental neutrophil and platelet antigen genotyping and antibody analysis revealed alloantibodies in the mother against HNA-1b and HPA-5b. A single dose of filgastrim (10 µg/kg) provoked a transient neutrophilic response. NICU course was uncomplicated. At the time of hospital discharge on day 23 of life, the ANC had risen to 1,300/µL.
Conclusion: NAIT and NAN are well-described entities. Although rarely reported, their concurrence in the same patient should be considered in neonates with otherwise unexplained bicytopenia. 1. Marin, Pediatr Allergy Immunol, 20052. Gramatges, Pediatric Blood Cancer, 20093. Taaning, Acta Paediatrica, 2012

Poster # 975

CASE REPORT: LIVING DONOR LIVER TRANSPLANTATION FOR SEVERE SOS AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

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Background: Despite recent advances, sinusoidal obstructive syndrome/veno-occlusive disease of the liver (SOS) remains a potentially fatal complication after hematopoietic cell transplantation (HSCT) with limited available treatment modalities.
Objectives: Describe an unusual albeit extreme treatment for refractory SOS.
Design/Method: Patient was a 2 year old male diagnosed with acute pre-B lymphoblastic leukemia. He underwent standard induction therapy, and quickly achieved morphologic remission. He continued on standard therapy, until during maintenance he suffered bone marrow relapse. After re-induction and achievement of CR-2, he was admitted for matched related donor

bone marrow transplant. He received high dose cyclophosphamide/TBI as a preparative regimen and tacrolimus/methotrexate for GVHD prophylaxis. Around day + 11 he began having fluid retention and right upper quadrant tenderness despite normal bilirubin; defibrotide was started on day + 15. He began to experience marked respiratory distress due to pulmonary edema, pleural effusions and decreased pulmonary compliance related to his marked abdominal distention and ascites. At this point he remained in remission with full donor chimerism, resolution of neutropenia and minimal transfusion requirements. Extensive infectious workup for viral, fungal and bacterial disease remained negative. Liver function continued to deteriorate with rising bilirubin, transaminase and ammonia levels. Liver biopsy confirmed presence of SOS and absence of GVHD. Due to ongoing clinical worsening without additional therapies known to be effective, patient was referred to an organ transplant center and underwent living donor liver transplant on day + 61.
Results: Patient tolerated liver transplant well, and received routine post bone marrow and post liver transplant care without unexpected morbidity. He continued to thrive with good quality of life until he suffered a bone marrow relapse of his ALL approximately 9 months post BMT. He was sent home with hospice care and died of sepsis shortly thereafter.
Conclusion: The prognosis remains poor in post HSCT patients that develop severe SOS resulting in multi-organ dysfunction. In our patient liver transplant gave him many months of active, quality time with family. In fact, had his malignancy not returned this therapy likely would have meant the difference between long term survivorship and early transplant related death. Numerous difficult ethical issues are raised from our experience, ranging from appropriate utilization of resources to morbidity/risk to the liver donor. We show, however, that in extreme cases liver transplantation can be curative of severe SOS.

Poster # 976

RECURRENT STROKE IN A CHILD WITH ATLANTOAXIAL INSTABILITY FOLLOWING CHIROPRACTIC MANIPULATION

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Background: The incidence of stroke in the pediatric population is approximately 2 to 8 in 100,000 per year in North America. Medical therapies (secondary stroke prophylaxis) aim at preventing recurrent arterial ischemic strokes. The risk for recurrence in the first 5 years after non-neonatal arterial ischemic strokes varies between 19% and 40%.
Objectives: To describe an unexpected cause of recurrent arterial strokes in children
Design/Method: Literature and medical record review
Results: A previously healthy 6-year-old boy who developed lethargy and altered mental status. He was found to have a large acute infarct of his left posterior cerebellar artery as well as multiple smaller infarcts. He underwent thrombectomy and was started on Enoxaparin. He had a normal MR angiogram of the neck, echocardiogram with bubble study and unremarkable coagulation panel (Antithrombin III, PT, aPTT, protein c, protein s , beta-2 glycoprotein antibodies, cardiolipin antibody , dilute Russell viper venom, factor 5 Leiden, prothrombin g20210a mutation), as well as normal CBC, antinuclear antibody, negative antiphosphatidylethanolamine antibody, fibrinogen gene mutation analysis ,C3 and C4, factor

XIII gene mutation analysis, von Willebrand factor antigen, Homocysteine and MTHFR. Despite multiple medical interventions including, enoxaparin, warfarin, aspirin, heparin drip, Abciximab, clopidogrel and thrombectomies, the child succumbed to multiple repeated infarcts requiring multiple hospitalizations. In neuroangiography, with the movement of his neck side-to-side, vertebral arteries were completely occluded on the opposite side of whichever way the head was turned. The patient was placed in C-collar for prevention of further clots and later had 2 stents placed in both vertebral arteries. After those events, the mother finally reported he had a significant fall resulting in torticollis 1 year prior and had his C-spine manipulated by a chiropractor. The patient's recurrent strokes were likely related to a hypermobile neck secondary to unhealed rotary subluxation. For the last 8 months, the patient has not had any new strokes.
Conclusion: This case demonstrates that with normal hypercoagulable workup, mechanical causes for thromboembolism should be investigated thoroughly. Around half of pediatric strokes are caused by arteriopathy. It is the major prognostic factor for recurrence. Delay in diagnosis, despite adequate anticoagulation, results in further morbidity and mortality.

Poster # 977

TREATMENT OF PEDIATRIC PLASMA CELL MYELOMA TYPE POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER WITH MODERN RISK-DIRECTED THERAPY INCLUDING AUTOLOGOUS STEM CELL TRANSPLANT

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Background: Post-Transplant Lymphoproliferative Disorder (PTLD) related plasma cell neoplasms have been reported in nine pediatric patients, with either normal cytogenetic profile or favorable changes. These patients showed good response to minimal therapy, with the majority reporting disease free survival at extended follow-up. Plasma cell myeloma type PTLD in a pediatric patient with high risk cytogenetic findings has not been reported. In adults with multiple myeloma, translocations involving immunoglobulin heavy-chain locus, deletions of chromosome 17, and abnormalities of chromosome 1 have been associated with poor prognosis and requirement for aggressive initial therapy. We report the case of a pediatric patient receiving this modern myeloma treatment regimen.
Objectives: To describe the case of a pediatric patient with plasma cell myeloma type PTLD with high risk cytogenetic findings including 1q duplication and translocation (8,14) and to establish the tolerability and efficacy of bortezomib, dexamethasone, and lenalidomide chemotherapy followed by autotransplant in a pediatric patient.
Design/Method: Case report
Results: The patient originally presented at three years of age with fulminant hepatic failure of unknown etiology and underwent deceased donor liver transplant. He was Epstein-Barr virus (EBV) negative pre-transplant, but developed EBV viremia while on tacrolimus immunosuppression. At nine years of age imaging obtained to evaluate for biliary collections showed multiple lytic bone lesions and epidural mass at T11-T12. Biopsy of the bone lesion showed myeloma type monomorphic PTLD with kappa light chain restriction. Bone marrow biopsy cytogenetics were positive for duplication 1(q32q21) and translocation 8;14 (q24;32), and urine protein electrophoresis was positive. Initial treatment consisted of chemotherapy with

bortezomib, dexamethasone, and lenalidomide plus zoledronic acid for presence of bony lesions. He subsequently received autologous bone marrow transplantation with melphalan conditioning as consolidation. Treatment was well tolerated and he remains in remission at five-year follow up. Complications from biliary strictures and cirrhosis in his transplanted liver pre-dating PTLD diagnosis persist and he is re-listed for liver transplant.
Conclusion: Extrapolating from adult data, the cytogenetic findings of 1q duplication and t(8;14) are important prognostic factors in plasma cell myeloma type PTLD and indicated risk-directed therapy including the use of an immunomodulator and proteasome inhibitor. The bortezomib, dexamethasone, and lenalidomide chemotherapy regimen was well tolerated and together with autologous stem cell transplant was effective in achieving five-year remission in this patient. Continued study in patients with high-risk cytogenetic findings is necessary to develop appropriate risk stratification for pediatric patients and predict therapeutic response.

Poster # 978

RETROPERITONEAL AND INTRACRANIAL BLEEDING IN A NEONATE WITH HEMOPHILIA A PRESENTING AS SEVERE HYPERBILIRUBINEMIA

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Background: Hemophilia A is an X-linked inherited bleeding disorder affecting all ethnic groups. Although hemophilia is the most common inherited bleeding disorder presenting in the neonatal period, bleeding in neonatal hemophilia patients is relatively rare. The majority of bleeding at this age is iatrogenic from venipuncture, traumatic delivery, intramuscular vitamin K or circumcision. When spontaneous bleeding does occur in neonates, it is often difficult to recognize due to the non-specific symptoms. This presents unique challenges to hematologists and other treating physicians.
Objectives: We describe our experience treating a neonate with hemophilia A who presented with severe hyperbilirubinemia, and acute bilirubin encephalopathy found to have a large retroperitoneal hematoma and several small intracranial hemorrhages.
Design/Method: Case Report
Results: A 7 day old post term neonate with severe hemophilia A, delivered via spontaneous vaginal delivery without complication, presented to his pediatrician with poor feeding and a high-pitched cry. Jaundice was noted and the total bilirubin was found to be 41 mg/dL, mainly unconjugated. Complete blood count was unremarkable, other than a hemoglobin of 11.3 gm/dL, and Coombs was negative. There were no signs of trauma or overt bleeding. He was admitted to the pediatric intensive care unit where he demonstrated opisthotonus and high shrieking cry. He was given factor VIII replacement and underwent a double exchange transfusion with triple phototherapy, while we investigated the source of hyperbilirubinemia.Head ultrasound was unremarkable. Abdominal ultrasound showed a left retroperitoneal hematoma, later confirmed by CT to be a large (4.4 x 2.2 cm) left mesenteric or anterior pararenal space hematoma. Subsequently the patient developed apneic episodes and seizures requiring phenobarbital. Brain MRI showed punctate subacute subdural and probable subarachnoid hemorrhages. He was continued on factor VIII replacement throughout his 2 week admission and discharged home on prophylactic factor VIII concentrate infusions.Three months later, follow up brain MRI

demonstrated no residual intracranial hemorrhages and the retroperitoneal hematoma had resolved on abdominal ultrasound. The patient continues on prophylactic factor VIII replacement and has been meeting his developmental milestones.
Conclusion: To our knowledge, this is the first reported case of a neonate with hemophilia presenting with hyperbilirubinemia requiring exchange transfusion, found to be due to a retroperitoneal hematoma and intracranial hemorrhages. This unusual presentation illustrates the need for a high index of suspicion with careful investigation of signs and symptoms of bleeding in this high-risk population.

Poster # 979

IS POST-CHEMOTHERAPY IDIOPATHIC HYPERAMMONEMIA TRULY IDIOPATHIC?

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Background: Idiopathic hyperammonemia (IHA) is a rare adverse occurrence, with unknown cause, that has been described in immunocompromised patients. Specifically, in pediatric oncology this complication has been documented following BMT and chemotherapy. There is growing literature supporting the association of IHA with Ureaplasma infections. There are no published case reports on Ureaplasma- associated hyperammonemia in children.
Objectives: We describe a case of a child with AML post chemotherapy presenting with IHA. In the absence of other explanations for her IHA, she screened and tested positive for Ureaplasma.
Design/Method: Case Report
Results: An 11 yo old immunocompromised female with a history of high risk AML treated per COG protocol AAML 1031 was admitted to the PICU for altered mental status. Her ammonia level was 901. She was started on Ammonul, arginine, and non-protein based nutrition. Liver function tests remained normal throughout hospitalization and no evidence for underlying metabolic disease was found. Ammonia levels continued to rise despite hemodialysis, CVVHD, and Carbaglu®. On hospital day 29 cerebral edema progressed to brain herniation and hemodynamic collapse. The day prior to her death a tracheal aspirate was collected for Ureaplasma Parvum PCR and subsequent confirmation was received a week post-mortem.
Conclusion: Current articles on IHA contain a common theme of an immunocompromised state, with varying pathways from immunosuppressive medications, chemotherapeutics, and post SOT and BMT. The lack of consistent features has led to a hypothesis that there is an underlying organism in association with or causing hyperammonemia when immunocompromised. Ureaplasma parvum, a urea hydrolyzing organism, was detected in our patient. Previously, Ureaplasma was isolated from lung transplant patients with IHA, but not found in those without IHA. Further confirmation of this relationship is ureaplasma parvum was recently discovered to cause hyperammonemia in immunocompromised murine models. Ureaplasma- associated hyperammonemia is a rare phenomenon seen in immunocompromised patients and is often undiagnosed due to lack of knowledge and understanding of the disease process and potential etiologies. Ureaplasma is a fastidious organism and does not grow on routine bacterial cultures so this can result in a delay in diagnosis. IHA in an immunocompromised patient should prompt

immediate testing and treatment for Ureaplasma. We hope the early identification of Ureaplasma in pediatric oncology patients with IHA will prevent future morbidity or mortality.

Poster # 980

PLUMMER-VINSON SYNDROME: A RARE CASE IN AN ADOLESCENT

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Background: Plummer-Vinson Syndrome, the association of iron deficiency anemia, dysphagia, and esophageal webs of the proximal esophagus, is very rare in children. The pathophysiology of this association remains unclear, though some hypothesize that high cell turnover makes the esophageal mucosa susceptible to iron deficiency, leading to mucosal damage and web formation. Some propose that the webs cause mechanical obstruction, while others believe dysregulation in esophageal motility causes dysphagia. This association confers an increased risk of squamous cell carcinoma of the pharynx and proximal esophagus, but the incidence of malignancy in pediatric cases is unknown.
Objectives: As the symptoms of anemia may predominate the clinical picture, pediatric hematologists and general pediatricians must be alert to this condition and the longstanding risk of malignancy.
Design/Method: Case Report.
Results: A 14 year old previously healthy female presented with headaches, fatigue and lightheadedness. She later reported dysphagia, odynophagia and glossal pain. She was pre-menarchal and denied any bleeding symptoms. She had appropriate growth and no dietary restrictions. Her physical exam was significant for pallor, lack of papillae on the tongue and a systolic flow murmur. No hepatosplenomegaly was appreciated. Labs were significant for hemoglobin of 6g/dL, MCV 51.6fL, RDW 22.1%, ferritin 0.9ng/mL. Chest x-ray, stool guaiac and celiac studies were negative. Due to dysphagia, she underwent a barium swallow, revealing a proximal esophageal web from the anterior wall of the esophagus at C4-C5. Thus, the presentation was consistent with Plummer-Vinson Syndrome. Oral ferrous sulfate therapy for two months resulted in a normalization of her hemoglobin, but worsening of the dysphagia. She underwent esophagoscopy with dilatation of the esophageal web. Biopsies revealed normal mucosa. Her symptoms of dysphagia and odynophagia resolved following the procedure and hemoglobin remained normal.
Conclusion: This case highlights a rare syndrome in pediatrics. Unlike many other reports, this patient had no etiology for iron deficiency, such as nutritional deficiency or blood loss. Despite resolution of anemia with iron supplementation, her dysphagia persisted, necessitating esophageal dilatation. Glossitis is reported more common in adults than children and painful dysphagia is unusual. This condition must be considered in children with unexplained iron deficiency anemia. Symptoms of dysphagia must be screened for by history as they may not be initially reported, as in our patient. The malignant potential also raises the question of surveillance guidelines. We intend to screen with annual blood counts and esophagoscopy with mucosal biopsies to monitor for malignant changes.

Poster # 981

THE USE OF DENOSUMAB IN THE TREATMENT OF GIANT CELL TUMOURS

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Background: Giant cell tumours (GCTs) are rare, locally aggressive bone tumours. Recently, a novel human monoclonal antibody (denosumab) that inhibits a receptor activator of NF-kB ligand (RANKL) has been explored for its clinical utility in tumour regression. RANKL and its receptor, RANK, are expressed by the stromal cells and osteoclasts comprising GCTs and also by osteoclasts in adjacent bone tissue.
Objectives: To describe the safety and efficacy of denosumab in two adolescent boys with near inoperable GCTs.
Design/Method: Case report
Results: Patient 1 was a 16 year old boy with a large GCT of the distal femur; patient 2 was a 17 year old boy with a GCT of the T5 vertebral body and large soft tissue masses. The tumours in both boys were surgically challenging due to their size and location. Denosumab was administered at doses of 120 mg weekly for three weeks, followed by monthly dosing (for 8 months in Patient 1 and for one year in Patient 2; 11 to 15-fold higher drug exposure than the typical adult osteoporosis dose of 60 mg every 6 months). In Patient 1, the tumour measured 11.6 cm (craniocaudal), 7.3 cm (transverse) and 6.2 cm (anterio-posterior); the tumour regressed by 20%, 18% and 10% in these dimensions on denosumab, with complete reconstitution of the deficient cortices. He then underwent successful resection of residual tumour and full recovery of mobility. A slow recurrence was noted (off denosumab) 2 years after the index surgery. In Patient 2, symptoms of lung and spinal cord compression (cough and right-sided lower limb weakness) resolved within 72 hours of denosumab administration; the tumour volume decreased by 3% (cradiocaudal), 24% (transverse) and 27% (anterior-posterior) on denosumab, followed by successful resection and spinal stabilization without recurrence in the following 2 years. To mitigate hypocalcemia on denosumab, both boys were treated with 1,25-dihydroxyvitamin D3 as well as calcium and cholecalciferol supplements. Patient 1 experienced mild, asymptomatic hypocalcemia which responded to increasing doses of cholecalciferol whereas patient 2 remained eucalcemic throughout. Rebound hypercalcemia was absent in the 24 months following treatment discontinuation. Serum c-telopeptide of type I collagen Z-scores fell by 91% percent between baseline and the nadir at 1 week in both patients.
Conclusion: High dose denosumab can be a safe and effective approach to achieving GCT regression, bone reconstitution and symptom control in adolescents, allowing for surgery in patients with anatomically challenging tumours.

Poster # 982

NOVEL VARIANT OF THE SERPINC1 GENE IN ANTITRHOMBIN DEFICIENCY

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Background: Antithrombin (AT) is a plasma serine protease inhibitor (serpin), and is a major inhibitor of thrombin and other anticoagulation proteinases. There are different types of AT deficiency, both genetic and due to other diseases. An inherited AT deficiency is an autosomal dominant disorder that predisposes patients to form clots. Patients typically present their first episode of venous thromboembolism before the age of 30 years. Most cases with AT deficiency carry genetic defects affecting exons or flanking regions of SERPINC1. Within the SERPINC1 gene, more than 200 variants have been identified. Data from one of our patients who presented with cerebral venous sinus thrombosis (CVST) and a strong family history of thrombophilia prompted us to investigate the genetic contribution to his disease.
Objectives: To describe a novel variant of SERPINC1 gene in inherited AT deficiency.
Design/Method: Case report and review of literature. The medical record, radiological studies and thrombophilia work up followed by next generation sequencing was reviewed.
Results: An 11 year old male with history of seasonal allergies was evaluated for headache, vomiting, dehydration and ataxia. Brain magnetic resonance imaging (MRI) revealed CVST. His thrombophilia work up was negative for protein C and protein S deficiency, Factor V Leiden and Prothrombin G20210A. AT III activity was 50% and AT antigen was 46%. He was started on low molecular weight heparin therapy but showed resistance to treatment and required AT infusion to get therapeutic. Paternal grandfather had history of AT deficiency and paternal great uncle and second cousin have been treated for deep vein thrombosis with warfarin. Patient's fraternal twin brother and father were also found to have AT deficiency. Upon discovering low AT levels and family history, he was switched to warfarin with full recovery and resolution of CVST. Gene sequencing discovered a heterozygous SERPINC1 gene variant c.1154-14G>A of intron 5. This introduces a splice site mutation that creates a cryptic splice site. This novel pathogenic variant in the SERPINC1 gene has been reported to segregate in individuals with recurrent venous thromboembolism and family history of AT deficiency and thromboembolism.
Conclusion: When evaluating patients with thrombosis with inability to achieve therapeutic Anti-Xa levels on heparin, it is important to consider AT deficiency. Family history of thrombosis may also raise suspicion for AT deficiency. This has important implications for prophylactic anticoagulation and genetic counseling. Description of novel genetic variants helps to identify pathologic variants in genes associated with AT deficiency.

Poster # 983

DYSFUNCTIONAL IMMUNE RECONSTITUTION AFTER CHEMOTHERAPY AND RITUXIMAB EXPOSURE IN UTERO

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Background: Rituximab is a monoclonal antibody directed against the CD20 surface antigen on B lymphocytes. It is used to treat a wide variety of disease processes, from lymphoma to multiple sclerosis. Biological therapies are being used at an increasing rate to treat various diseases during pregnancy. Rituximab, like other IgG immunoglobulins, is able to cross the placenta. There is

limited data on the safety of rituximab during pregnancy.
Objectives: Previous case series have demonstrated diverse clinical presentation following rituximab exposure in utero. Our case illustrates the potential for dysfunctional immune reconstitution presenting with severe autoimmune neutropenia and prolonged hypogammaglobinemia.
Design/Method: A retrospective chart review and review of the literature was performed.
Results: Our patient was born to a mother diagnosed with B cell acute lymphoblastic leukemia diagnosed at 18 weeks gestation. The infant was born via scheduled induction at 30 weeks gestation, two weeks after completing three courses of cyclophosphamide, doxorubicin, vincristine, and dexamethasone with rituximab (Hyper CVAD regimen). The mother had complete count recovery prior to delivery and the infant had a normal CBC following delivery. On day of life ten, the infant was noted to have an absolute neutrophil count of zero which was thought to be autoimmune neutropenia since patient had normal neutrophil count after birth. She was treated with IVIG and had rapid recovery of her ANC. At 1 month of life, her immunoglobulin G was <100 mg/dL and required scheduled IVIG infusions which also helped her neutrophil count. At 12 months of life, despite normal B and T cell subsets, she did not demonstrate a normal response to immunizations and continues to require scheduled IVIG.
Conclusion: Our case highlights the risk of rituximab exposure in utero with an infant presenting with dysfunctional immune reconstitution, as evident by autoimmune neutropenia and prolonged hypogammaglobulinemia.

Poster # 984

A RARE PRESENTATION OF HEMOPHILIA IN AN INFANT WITH NO IDENTIFIABLE GENE MUTATION

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Background: Pediatricians should be aware of rare presentations of bleeding disorders. A spinal epidural hemorrhage (SEH) as the presenting sign of hemophilia is extremely rare, especially in patients with few symptoms and no family history.
Objectives: Discuss the unusual case of an infant who developed a spontaneous SEH.
Design/Method: Description of the case and literature review of relevant topics.
Results: A previously healthy five-month-old male presented with a two-day history of irritability that progressed to hypotonia with a weak cry. On physical exam he resisted movement of his head and had decreased tone in the lower extremities. No suggestion of trauma by history or physical exam.Initial imaging included x-rays of the extremities and an abdominal ultrasound, which were negative. Providers noted excess bruising after a lumbar puncture and coagulation labs were sent. The PTT was prolonged, FVIII level was <1%, and von Willebrand factor antigen and activity were normal. MRI of the spine revealed an extensive epidural hemorrhage causing anterolateral displacement of the cervical spinal cord. He was treated with high dose recombinant FVIII replacement and close observation. After three days his neurologic symptoms resolved. Next generation sequencing and multiplex ligation-dependent probe amplification of the FVIII gene was performed, and no mutation or structural variants were identified. He developed an inhibitor after 18 exposure days, and started immune tolerance induction (ITI) with FEIBA

prophylaxis. However, a high titer inhibitor persists after one year of ITI, though his bleeding episodes are currently rare.
Conclusion: This case is unusual for several reasons. First, the incidence of CNS bleeds in hemophilia is rare, particularly those hemorrhages involving the spine. SEH can occur without a history of prior trauma and symptoms vary from irritability to extremity paralysis. Second, SEH as the first sign of hemophilia in an otherwise healthy infant is extremely rare. In this case, the presence of excess bruising following the LP was the first indication of a coagulation disorder. No previous cases of a SEH in a previously undiagnosed infant presenting with few symptoms, without any preceding trauma or family history of hemophilia, have been reported in the hemophilia literature. Prompt initiation of therapy with aggressive factor replacement is critical to minimize permanent neurologic injury, even with the known risk of early inhibitor development. However, patients who develop an inhibitor are more likely to have an identifiable genetic abnormality. Thus, the lack of a mutation or structural variant in this patient is exceedingly unusual.

Poster # 985

HOW DOES DFMO EFFECT SUBSEQUENT DINUTUXIMAB THERAPY AND PAIN MANAGEMENT?

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Background: Dinutuximab is a chimeric antibody used in the treatment of high-risk neuroblastoma. It binds to disialoganglioside GD2, which is highly expressed in neuroblastoma, as well as normal peripheral sensory nerve fibers. It has a known adverse side effect of pain, usually treated with morphine, with gabapentin recommended for additional pain management. Difluoromethylornithine (DFMO) is an inhibitor of L-ornithine decarboxylase and arginase, as well as a stimulator of L-ADC, and is currently being studied in a clinical trial as a means of maintaining remission in neuroblastoma. It is known to significantly increase the pain threshold, enhance morphine analgesia and inhibit acute morphine tolerance, but its interaction with gabapentin has not been documented.
Objectives: To describe a case of over-sedation in a pediatric patient receiving previously tolerated doses of morphine and gabapentin for dinutuximab-induced pain shortly after participating in the DFMO trial.
Design/Method: Case Report
Results: A 6-year old boy was found to have relapsed disease after 3 months on DFMO and he was admitted for chemotherapy and immunotherapy on COG ANBL1221. He had pain that was difficult to control with morphine alone and so gabapentin was added during cycle 1. He had received both drugs with sufficient pain control during his initial treatment on COG ANBL0032. On day 1 of cycle 2, he received a bolus dose of morphine 0.05 mg/kg before chimeric antibody started and a morphine infusion starting at 0.08mg/kg/hour (1.2mg/hour), as this dosing had been previously effective and tolerated during cycle 1. The patient experienced urinary retention and bradypnea with hypoxia during sleep. He required 3 doses of naloxone the following day (one was 0.001mg/kg, the others 0.01mg/kg) due to over-sedation (RR <10, pinpoint pupils) several

hours after discontinuation of the morphine infusion. He did not require morphine for pain control during day 2. On day 3, he received only two doses of morphine at 0.05 mg/kg. The morphine drip was reinitiated on day 4 at 0.033 mg/kg/hour (0.5mg/hour), well below the dose he had received with Gabapentin when he was treated on ANBL0032. However, naloxone was again required due to bradypnea. Despite receiving full doses of dinutuximab for 2 courses, he suffered from progressive disease.
Conclusion: Most patients receiving dinutuximab require morphine +/- gabapentin for pain control. However, studies have not been done to evaluate how lasting effects of DFMO may interact with gabapentin or how it may alter the efficacy of dinutuximab.

Poster # 986

CATASTROPHIC DELAYED HEMOLYTIC TRANSFUSION REACTION IN A PATIENT WITH SICKLE CELL DISEASE: CASE REPORT AND REVIEW OF LITERATURE

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Background: While red blood cell (RBC) transfusion therapy is a mainstay in the treatment of certain patients with sickle cell disease and the standard of care for pre-operative management, there are associated risks. Delayed hemolytic transfusion reaction (DHTR) is a risk of RBC transfusion occurring 2-20 days from transfusion and presents with severe pain characteristic of vaso-occlusive crisis, fever, and hemolytic anemia. DHTRs are rare, occurring in only 4-11% of transfused patients with sickle cell disease, but may be catastrophic in nature with progression to multi-organ failure within hours. In about one-third of cases, the direct antiglobulin test (DAT) is negative and there are no new detectable antibodies. Our case if the first reported catastrophic DHTR in a pediatric sickle cell patient with no known or new alloantibodies.
Objectives: To increase the clinical suspicion of DHTR in patients with sickle cell disease.
Design/Method: Case report and review of literature.
Results: 20-year-old female with a hyperhemolytic phenotype of sickle cell SS disease presented with severe back and leg pain, 5 days post-operative from a laparoscopic cholecystectomy. She was transfused 2 units of ABO, RH, and Kell matched packed RBCs one day prior to surgery with a pre-transfusion hemoglobin of 7.3 g/dl and reticulocyte count >20%. Upon presentation to the emergency department, her hemoglobin was 7.2 g/dl with reticulocytes >20% and she had a severe direct hyperbilirubinemia. She was initially treated for a vaso-occlusive crisis with intravenous fluids and pain control, but then developed tachypnea, tachycardia and an oxygen requirement. Repeat hemoglobin at that time was 4.1 g/dl and she was transferred to the intensive care unit for presumed delayed transfusion reaction. DAT and antibody screen were negative. Labs showed an elevated LDH, hemoglobinuria and metabolic acidosis. She was treated with IV methylprednisolone, but developed complications of multi-organ failure, including acute renal failure with refractory metabolic acidosis and disseminated intravascular coagulation. Due to critical illness and cardiorespiratory instability, the patient was transfused a further 6 units of RBCs over 24 hours with no increase in hemoglobin level (final hemoglobin 5.5 g/dl). Patient failed attempts of continuous veno-venous hemofiltration and eventually suffered multiple episodes of cardiac arrest and died one day after presentation.

Conclusion: The initial presentation of DHTR may mimic that of vaso-occlusive crisis and the clinician must be aware of this entity, especially in a patient who recently received an RBC transfusion. Early recognition and aggressive management with supportive care and immunosuppression may be life-saving.

(PBMTC Poster Platform 1000)

PSEUDOTUMOR CEREBRI AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN: A RARE COMPLICATION OF CYCLOSPORINE

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Background:Pseudotumor cerebri (PTC) is a rare neurologic disorder characterized by intracranial hypertension without identifiable cause on brain imaging. Left untreated, PTC may evolve to permanent visual loss. PTC has been very rarely related to the use of cyclosporine A (CsA) and exceptionally reported after hematopoietic stem cell transplantation (HSCT).
Objectives: We report the presentation, evolution and treatment of 2 children who experienced PTC related to CsA after HSCT.
Design/Method: The medical charts of the 2 patients were retrospectively reviewed and data were extracted. The clinical description of both patients was compared to medical literature of PTC in childhood.
Results: None of the children had a previous familial history of PTC. Both children were male, they didn't have entered puberty and they were obese. Patient 1 had a malignant disease whereas patient 2 suffered from a non-malignant disease. CsA blood levels were in the target range for both patients. The main symptoms in both patients were headache and blurred vision. Patient 1 had also cervicalgia with pain in the neck and shoulder, while patient suffered from protracted nausea and vomiting associated with severe alteration of consciousness. Symptoms began within the first month for patient 1, whereas patient 2 didn't have symptoms of PTC before the 9th month after HSCT. Lack of awareness about the risk of PTC, as well as possible differential diagnosis, led to delays of 11 days (patient 1) and about 1 month (patient 2) in diagnosing PTC. Finally, PTC was evoked after discovery of papilledema and was confirmed by an opening pressure higher than 250mm of H2O during lumbar puncture. In both cases, corticosteroids weaning (patient 1) or discontinuation (patient 2) in the previous weeks may have contributed to the development of PTC. Clinical evolution was rapidly favorable within 2 days after discontinuation of CsA and introduction of acetazolamide. Changing to tacrolimus was not associated with relapse of PTC despite withdrawal of acetazolamide. Ophthalmologic examination returned to normal at 1 year after HSCT in patient 1, whereas unilateral optic nerve atrophy was documented 2 months after diagnosis of PTC in patient 2.
Conclusion: CsA-induced PTC can occur after HSCT in children. Physicians should be aware of this possible complication in order to avoid delayed diagnosis which may put patients at risk of permanent visual loss. Changing from CsA to tacrolimus appears effective in preventing PTC.

(PBMTC Poster Platform 1001)

CYCLIN DEPENDENT KINASE 5 (CDK5) MEDIATES T-CELL ACTIVATION AND IMMUNE REGULATION IN APLASTIC ANEMIA

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Background: Aplastic anemia (AA) is a bone marrow failure (BMF) syndrome characterized by immune mediated destruction of hematopoietic stem cells leading to severe pancytopenia. Activated T-cells play an important role in triggering the immune response. Role of T helper (Th) and T regulatory (T reg) cells has been previously explored with a reduced T reg and an increased Th1/Th17 response. Cyclin dependent kinase 5 (Cdk5) is a non-cell cycle dependent serine-threonine kinase, which has been shown to have a role in immune activation via suppression of Forkhead box protein 3 (Foxp3) expression, leading to reduction in T regs. P35 is a known activator of Cdk5.
Objectives: Investigate the role of Cdk5 in immune mediated activation of T-cells in pre-clinical AA model.
Design/Method: AA mice were generated using previously described BMF model. C57Bl/6 and Balb/c mice were bred for CbyB6F1 generation. Recipient CByB6F1 mice were exposed to 5 Gy of total body irradiation at day 0. Lymph node (LN) cells were obtained from C57Bl/6 donors, and infused into recipients 4-6 hours post irradiation, at 5.0 Ã— 106 cells per mouse. P35 knock out mice were used to investigate the role of Cdk5 in T-cell activation. Cell counts were done serially to identify pancytopenia as an indicator for marrow failure. Fluorescence activated cell sorting (FACS) was used to study quantitative difference in T-cell subgroup percentages on days 10, 14 and 16. Reverse transcriptase polymerase chain reaction (RT-PCR) was used to identify Cdk5 and p35 expression. CByB6F1 mice with irradiation only were used as controls (n=3). P35 knock out (p35 ko) mice were used to investigate the effect of reduction in Cdk5.
Results: BMF was established between days 10-14 and progressed in AA mice (n=8) while control group (n=3) recovered cell counts by day 14. P35 ko mice (n=8) showed relatively lesser reduction in cell counts after irradiation and infusion as compared to AA mice. RT-PCR showed increased expression in spleen and bone marrow of Cdk5 and p35 in AA mice. FACS results showed significantly increased CD4 and CD8 infiltration in bone marrow of AA mice as compared to p35 ko mice. There was also significant increase in Th17 and reduction in T reg count in AA group as compared to p35 ko mice.
Conclusion: Increased Cdk5 expression was noted in AA murine model which can be targeted to reduce T-cell mediated immune activation in AA.

(PBMTC Poster Platform 1002)

OUTCOMES OF MATCHED RELATED AND UNRELATED BONE MARROW TRANSPLANTATION AFTER REDUCED-TOXICITY CONDITIONING FOR CHILDREN SUFFERING FROM CHRONIC GRANULOMATOUS DISEASE

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Background: Chronic Granulomatous Disease (CGD) is a life threatening immune deficiency related to a defect of oxidative burst in phagocytes. Patients experience severe bacterial or fungal infections, associated with chronic granulomatous inflammation of various organs. The only curative treatment is a Hematopoietic Stem Cell Transplantation (HSCT).
Objective: In 2010, Sainte Justine hospital took part in an international initiative of HSCT for CGD, based on a Reduced Toxicity Conditioning (RTC) and a HLA matched donor, either related or unrelated. Seven children were included in this study, followed by 12 others transplanted after the completion of the study. The objective of this study was to report the outcomes of the whole group.
Design/Method: Data were retrospectively extracted from medical charts for 19 consecutive children transplanted from 2010 to 2016. Donors were matched related (4/19), or matched unrelated (15/19). The RTC consisted of Fludarabine (180mg/m2), targeted Busulfan (55% to 75% of standard dose) and rabbit Antithymoglobulin (7.5mg/kg) or Alemtuzumab (0.5mg/kg). Graft versus host disease (GVHD) prophylaxis relied on Ciclosporin and Mycophenolate associated with Prednisone for patients with colitis.
Results: The median age at HSCT was 10 years (1-21). Previous history of severe infections included abscesses located in lymph nodes (5/19), skin (11/19), liver (7/19) or lung (12/19), with pulmonary aspergillosis proven for 5 patients. Inflammation mainly presented as Crohn like colitis (8/19) and chronic lung inflammation (8/19). Three patients had received granulocytes transfusions previously. None patient had active infection or inflammation at the time of transplantation.
All 19 patients engrafted. Acute toxicities before day 100 were very limited without any case of veino-occlusive disease or severe infection. Severe (grade 3-4) acute graft versus host disease (GVHD) and chronic extensive GVHD were not observed. Three patients experienced immune haemolytic anemia (3/19) and nephrotic syndrome (1/19).
The main complication was secondary graft failure for 4/19 patients occurring at 6 months. All 4 patients engrafted durably after a second HSCT. With a median follow-up of 50 months (3-82), 18 patients are alive and cured from CGD. One patient suddenly died at 3 months post HSCT. The cause of death has not been established. All 13 patients more than 12 months after HSCT are free from immunosuppressive drugs.
Conclusion: HSCT with a RTC and a matched donor either related or unrelated is safe and effective for children with CGD. Acute and chronic GVHD are uncommon. Secondary graft rejection is the main complication, but can be successfully cured by a second HSCT.

(PBMTC Poster Platform 1003)

EX VIVO EXPANDED MULTI-ANTIGEN SPECIFIC LYMPHOCYTES FOR THE TREATMENT OF SOLID TUMORS

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Background: Patients with solid tumors refractory to standard therapies have poor prognoses and limited therapeutic options. Most salvage therapies are toxic and ineffective. T cell therapies, which have been successful against hematologic malignancies, are a promising alternative that provide targeted therapy. Hence, we hypothesize that patient-derived tumor associated antigen-specific cytotoxic T cells (TAA-T) targeting WT1, PRAME, and survivin expressed by solid tumors can be safely administered and can prevent or treat relapse or refractory disease.
Objective: The objective of this phase I clinical trial is to determine the safety of administering TAA-T to patients who have undergone allogeneic HSCT (Group A) or conventional therapy (Group B) for a high-risk solid tumor due to the presence of refractory, relapsed and/or residual detectable disease. Secondary objectives include determination of disease response and immune reconstitution following infusion.
Design/Methods: T cell products expanded from patient peripheral blood are stimulated weekly with antigen presenting cells (APCs) expressing an overlapping peptide library spanning the tumor antigens WT1, PRAME, and survivin. Following extensive tests to determine suitability of the product for infusion, patients are infused with T cells potentially every four weeks, initially at a dose of 1 x 107/m2, with dose escalation in subsequent patient groups to maximum dose of 4 x 107/m2. Clinical and immune reconstitution studies are performed at set intervals following infusion to monitor potential adverse effects of T cells and assess immune and disease response. These studies, performed on pre-infusion and post-infusion samples, include enzyme-linked immunospot (ELISPOT) to evaluate specificity, flow cytometry to evaluate persistence and expansion in vivo, and Luminex to evaluate functionality.
Results: Thus far, we have generated TAA-T from two patients enrolled on the protocol with high risk and refractory solid tumors (osteosarcoma, neuroblastoma). Products have passed release criteria: lack of autoreactivity with <10% cytotoxicity vs autologous blasts, <1% residual APC, culture negative. Thus far we have safely infused two patients with no product related adverse events post-infusion. We are currently enrolling additional patients and performing immune reconstitution studies to characterize the persistence and anti-tumor effects of the infused TAA-T-cell products in vivo.
Conclusion: While still early for data regarding disease response and immune reconstitution, we have had two successful infusions of T cells without concerns regarding safety.

(PBMTC Poster Platform 1004)

DIAGNOSIS OF HEPATIC VENO-OCCULSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME IN STEM CELL TRANSPLANT PATIENTS: PHOENIX CHILDREN'S HOSPITAL EXPERIENCE

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Background: VOD (veno-occlusive disease), or SOS (sinusoidal obstructive syndrome), is a complication of stem cell transplantation (SCT), resulting from hepatocyte injury, characterized by painful hepatomegaly, hyperbilirubinemia, ascites, and fluid retention. SOS incidence

amongst pediatric patients ranges from 10-25%. For severe SOS, mortality rates are as high as 80%. Defibrotide was FDA approved to treat SOS and has shown significant clinical benefit in pediatric patients.
Objective: This study assessed the yearly incidence of SOS among Phoenix Children's Hospital (PCH) patients, quantified the association between pre- and post-transplant factors and SOS, and quantified the relationship of SOS and overall outcomes.
Design/Method: Patients examined in this retrospective chart review were children who received SCT (autologous or allogeneic) at PCH between January 1, 2009 and December 31, 2014. The Pearson Chisquare and Fisher exact tests were used to examine the association of transplant factors with the development of SOS. Overall survival (OS) was estimated for patients with and without SOS using the Kaplan-Meier estimator and Log-rank test.
Results: Twenty-three (13.6%) cases of SOS were observed, with 96% of patients with severe or very severe SOS as per EBMT severity criteria. In 2013, the incidence of SOS was almost doubled (27%, p=0.27) compared to preceding years. The incidence of SOS was highest for AML (32%), JMML (33%), and immunodeficiency disorder (27%) SCT. Pre-transplant exposure to Gemtuzumab (p=0.03) and Acyclovir (p=0.09) had a significantly higher risk of developing SOS. The age of transplanted patients who developed SOS were younger than those who did not (6.6 years vs. 7.9 years; p=0.06). Patients with an elevated pre-transplant ferritin level (>750ng/mL) had a higher risk of developing SOS (p=0.34). The majority of SOS cases (n=21) had received myeloablative conditioning. Incidence of SOS was significantly higher with allogeneic vs. autologous SCT (p=0.06). Patients who received a Busulfan containing conditioning regimen had higher incidence (36%; p=0.0001) of SOS, followed by cyclophosphamide (20%; p=0.06) and melphalan (15%; p=0.74). SOS diagnoses did not affect SCT outcomes in this cohort (p=0.27). Defibrotide improved PCH's survival rate (74%) for SOS cases, which is significantly better than published data (40-50% at day +100 in severe SOS cases).
Conclusions: Pre-transplant exposure to Gemtuzumab and Acyclovir and elevated ferritin levels were associated with increased risk of SOS. Patients receiving Busulfan-based conditioning had an increased risk of developing SOS. Outcomes for PCH patients diagnosed with SOS after receiving defibrotide were significantly better than historical data, despite having severe SOS.

(PBMTC Poster Platform 1005)

PROTOCOL FOR A PHASE 3, RANDOMIZED, ADAPTIVE STUDY COMPARING THE EFFICACY AND SAFETY OF DEFIBROTIDE VS BEST SUPPORTIVE CARE TO PREVENT HEPATIC VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) IN ADULT AND PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT)

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Background: VOD/SOS is a potentially life-threatening complication of HSCT, with a ~14% incidence, and higher rates in specific populations. VOD/SOS with multi-organ dysfunction

(MOD)/failure (MOF) (renal/pulmonary) may be associated with >80% mortality. Defibrotide is approved in the US to treat hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT, and in the EU to treat severe hepatic VOD/SOS post-HSCT. There are no approved therapies for VOD/SOS prevention. In a prior study, defibrotide prophylaxis reduced the incidence of VOD/SOD vs standard care in high-risk pediatric patients (12% vs 20% at Day+30).
Objectives: A new randomized prevention study in adult and pediatric patients at risk for VOD/SOS post-HSCT is underway (NCT02851407).
Design/Method: Patients receive open-label defibrotide prophylaxis or best supportive care and are stratified by risk of VOD/SOS (high/very high) and age (>16/≤16 years). VOD/SOS diagnosis is adjudicated by blinded central review, and patients in either arm with VOD/SOS will receive defibrotide rescue therapy. Patients: A sample size of 400 is planned to provide 90% power to detect a hazard ratio of 0.46 for VOD/SOS-free survival by Day+30 post-HSCT. Inclusion criteria: age ≥1 month, scheduled for allogeneic/autologous HSCT, and high/very high risk of VOD/SOS. High-risk is myeloablative conditioning (MAC) and ≥1 of: transaminase >2.5× upper limit of normal (ULN), serum total bilirubin >1.5× ULN, cirrhosis, hepatic fibrosis on biopsy, viral hepatitis within 1 year, prior hepatic irradiation, iron overload, or advanced neuroblastoma. Very high-risk is defined by ≥1 of: primary hemophagocytic lymphohistiocytosis and predefined related disorders and MAC, prior gemtuzumab ozogamicin (dose ≥9 mg/m2) or inotuzumab ozogamicin (≥1.5 mg/m2 over 28 days), high-risk thalassemia, or osteopetrosis and MAC. Exclusion criteria include hemodynamic instability, clinically significant bleeding, use of medication <24 hours that increases bleeding risk (heparin ≤100 U/kg/day to keep catheters open is allowed), or bleeding from a site that is potentially life threatening. Recommended defibrotide dosage is 25 mg/kg/day (4 divided doses) for ≥21 days from the day before conditioning. VOD/SOS is diagnosed by modified Seattle criteria and/or liver biopsy. The primary endpoint is VOD/SOS-free survival by Day+30. The key secondary outcome is VOD/SOS-free survival by Day+100. Other assessments include VOD/SOS-free survival by Day+180, VOD/SOS, disease relapse, and MOD/MOF onset and resolution.
Conclusion: Despite advances in VOD/SOS treatment, there is an unmet need for patients at risk of developing VOD/SOS. This prevention trial includes adult and pediatric patients at high/very high risk of VOD/SOS post-HSCT. Enrollment is ongoing.

(PBMTC Poster Platform 1006)

DAY +100 SURVIVAL AND SAFETY RESULTS FROM A DEFIBROTIDE EXPANDED-ACCESS PROGRAM FOR PATIENTS WITH HEPATIC VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME: FINAL RESULTS

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Background: Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of hematopoietic stem cell transplant (HSCT)

conditioning or chemotherapy, and VOD/SOS with multi-organ dysfunction (MOD) may be associated with >80% mortality. Traditionally, VOD/SOS has been diagnosed based on Baltimore or modified Seattle criteria, but the European Society for Blood and Marrow Transplantation recently proposed new criteria for adults. Defibrotide is approved for treating severe hepatic VOD/SOS post-HSCT in the European Union, and for hepatic VOD/SOS with renal/pulmonary dysfunction post-HSCT in the United States.
Objectives: The defibrotide expanded-access protocol was designed to provide access to defibrotide prior to United States' approval and collect Day+100 survival and safety results in patients with and without MOD following HSCT or chemotherapy.
Design/Method: The original expanded-access protocol required VOD/SOS diagnosis by Baltimore criteria or biopsy post-HSCT, with evidence of MOD (renal/pulmonary dysfunction). The study was amended to also include patients without MOD; with VOD/SOS per modified Seattle criteria; and/or with VOD/SOS post-chemotherapy. Patients received defibrotide 25 mg/kg/d (6.25 mg/kg q6h) for a recommended ≥21 days.
Results: This final analysis is based on 1154 patients enrolled from 2007–2016 who received ≥1 defibrotide dose. Of these patients, 571 (49.5%) had MOD. Median age was 12 years (range 0.0–77.0), with 15.8% <1–23 months, 33.3% 2–11 years, 10.8% 12–16 years, and 40.1% >16 years. Most common primary diseases were acute leukemias (48.4%). In 1137 patients with a confirmed VOD/SOS diagnosis, 88% received HSCT (84.3% allograft, 15.5% autograft, 0.2% unknown) and 12.0% had chemotherapy. Kaplan-Meier estimated Day+100 survival was 61.1% (95% CI, 58.2%–63.9%) for all patients; 51.9% (47.6%–55.9%) for the MOD subgroup. Overall, 810 patients (70.2%) reported ≥1 treatment-emergent adverse event (AE). Of these, 248 (21.5%) had investigator-assessed treatment-related AEs, with pulmonary hemorrhage (4.3%), gastrointestinal hemorrhage (3.0%), epistaxis (2.3%), and hypotension (2.1%) occurring in >2.0%. Serious AEs were reported by 598 patients (51.8%), of which 133 (22.2%) were considered related. Related AEs lead to discontinuation in 12% and death in 2.7% (pulmonary hemorrhage, 1.0%, was most common).
Conclusion: This final analysis of the defibrotide expanded-access protocol demonstrates favorable Day+100 survival (61.1%) in a diverse population with VOD/SOS, and 51.9% in those with MOD, a complication typically associated with dismal outcomes. Survival and safety findings, consistent with prior clinical trials, provide supportive evidence for the clinical utility of defibrotide for treatment of VOD/SOS in patients with and without MOD.

(PBMTC Poster Platform 1007)

AN EXPLORATORY POST HOC ANALYSIS OF SURVIVAL BY AGE AND TIME TO DEFIBROTIDE INITIATION AFTER DIAGNOSIS OF HEPATIC VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) IN PATIENTS RECEIVING HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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Background: Hepatic VOD/SOS is an unpredictable, potentially life-threatening complication of HSCT conditioning. VOD/SOS with multi-organ dysfunction (MOD) may be associated with >80% mortality. In the US, defibrotide is approved to treat hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT; in the EU, it is approved to treat severe hepatic VOD/SOS post-HSCT.
Objectives: The optimal time to initiate defibrotide for VOD/SOS was investigated using interim data from a large expanded-access program.
Design/Method: Patients with VOD/SOS (Baltimore/modified Seattle criteria or biopsy) with or without renal/pulmonary MOD post-HSCT or post-chemotherapy received defibrotide 25 mg/kg/d for a recommended ≥21 days. Day +100 survival rates in pediatric (age ≤16 years) and adult patients were examined post-hoc by time to start of defibrotide post-diagnosis for (1) all patients before/after Days 1, 2, 3, 4, 7, and 14, using Fisher's exact test and (2) patients starting defibrotide on a particular day: 0, 1, 2, 3, 4, 5, 6, 7, 8–14, and ≥15 (Cochran-Armitage test for trend across days). Causes of treatment delay were not assessed.
Results: Of 755 post-HSCT patients through April 18, 2015, 423 were pediatric (232 with MOD), and 332 were adults (194 with MOD). Defibrotide was started on the day of diagnosis in 33% of pediatric and 30% of adult patients; 94% and 92%, respectively, started defibrotide by Day 7 post-diagnosis. In the analysis of treatment initiation before or after Days 1, 2, 3, 4, 7, and 14 across each age group, earlier defibrotide start resulted in numerically higher survival rates for all cutoffs except Day 14 in adults, with only 4% of adult patients beginning treatment post-Day 14. Differences were statistically significant ($P<0.05$) at Days 1, 2, 3, 4, and 7 in pediatric patients, and at Days 2 and 3 in adults. The trend test also was statistically significant over time for higher Day +100 survival with earlier initiation in pediatric patients ($P<0.001$) and adults ($P=0.028$).
Conclusion: Decreased Day +100 survival in pediatric and adult groups was associated with longer treatment delays post-VOD/SOS diagnosis, confirmed by Cochran-Armitage testing. These results suggest that, irrespective of age, early defibrotide initiation post-VOD/SOS diagnosis may improve Day +100 survival outcomes, although no specific day post-diagnosis seemed to provide a clinically meaningful cutoff for better outcome, suggesting that later intervention still retains value if therapy is not initiated sooner.

(PBMTC Poster Platform 1008)

A PILOT TRIAL OF UNRELATED DONOR HUMAN PLACENTA-DERIVED STEM CELLS IN CONJUNCTION WITH SINGLE UNRELATED CORD BLOOD TRANSPLANTATION IN CHILDREN WITH MALIGNANT AND NON-MALIGNANT DISEASES (IND 14949)

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Background: Myeloablative (MAC) or reduced toxicity conditioning (RTC) followed by UCBT in children with malignant and non-malignant diseases is safe and effective. However,

concentration of CD34+ HPCs in UCB is low, leading to delayed hematopoietic reconstitution and higher incidence of engraftment failure. HPDSCs are rich in HPCs, low in HLA Class I/II expression and T-cells, and have regenerative, anti-inflammatory, and immunosuppressive properties.
Objective: To determine the safety and efficacy of HPDSC with UCBT in children with malignant and non-malignant diseases.
Design/Method: Four-six/six HLA matched UCB with TNC â‰¥ 5 x 107/kg (4/6 HLA match) or â‰¥ 3.5x 107/kg (5-6/6 HLA match) were included. Patients received MAC or RTC followed by UCB plus HPDSC infusion.
Results: Sixteen patients â‰¤18 years have been enrolled, 10 males and 6 females. The mean age was 5.8 (0.3-15.7) years. Pre B-cell ALL (n=4), AML (n=2), T-cell ALL (n=1), and T-cell LL (n=1), ALD (n=2), CGD (n=1), CAT (n=1), SCID (n=2), CN (n=1) and DC (n=1). Eight patients received MAC and eight patients received RTC. Five, three, and eight patients received 4/6, 5/6, and 6/6 HLA matched UCB, respectively. There were no severe adverse events associated with HPDSC infusions. The probability of neutrophil engraftment was 87.5 %, median day 23 (13-53) post UCBT. Two incidences of engraftment failure occurred in patients with non-malignant disease who received RTC using alemtuzumab. Of evaluable patients at day 100, the probability of platelet engraftment was 100%, median day 46 (20-98) post UCBT. At days 30, 60, 100 and 180, mean percent of whole blood donor chimerism were 88, 98, 99, and 99%, respectively. Average percent of whole blood HPDSC chimerism was 1% at day 30 and <1% at beyond day 60. Normalization of CD3+, CD19+, and CD56+ cells occurred by day 100, CD8+ cells by day 180, and CD4+cells by day 270. At median follow-up of 649 (51-1338) days, the probability of Grade II-IV aGVHD and cGVHD were 12.5% and 0%, respectively. Three deaths occurred due to systemic adenovirus infection (1) and multi-organ system failure (2). None of the patients with malignant disease have relapsed. 12 month overall survival was 81.2%.
Conclusions: These results suggest that UCBT with HPDSC is safe, well tolerated, and has a lower than expected probability of Grade II-IV aGVHD. A larger cohort and longer follow-up is required to determine the clinical significance of these findings.

Supported by a grant from Celgene Cellular Therapeutics.

(PBMTC Poster Platform 1009)

NEONATAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A MULTI-CENTER CASE SERIES HIGHLIGHTING THE CHALLENGES IN DIAGNOSIS AND MANAGEMENT INCLUDING THE UTILITY OF HEMATOPOIETIC STEM CELL TRANSPLANT

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by excessive inflammation and immune dysregulation. Very little is known about HLH presenting in the neonatal period.
Objectives: Thus, we aim to describe the most common phenotype, etiology, and efficacy of therapy, including utility of hematopoietic stem cell transplant (HSCT).
Design/Method: A multi-center retrospective case series describing neonatal HLH was performed with cases collected from 8 different tertiary care centers using a standardized data form. General descriptive statistics were completed. Review of the literature identified 16 additional cases.
Results: Symptoms were non-specific and difficult to distinguish between other common causes of critical illness in the neonate. Genetic causes of immune dysregulation were found in a minority of cases but specific etiologies were commonly unable to be identified. The most common mutation was in the gene encoding MUNC13-4. Mortality was high in this age group with survivorship highly dependent upon early therapy and transition to HSCT. Survival was significantly associated with initial and peak ferritin levels and initial platelet levels.
Conclusion: Overall, neonatal HLH is a difficult to diagnose condition causing severe illness in the neonate, which requires prompt identification in order to institute life-saving therapy early. Transfer to a tertiary care center early in the illness is important in addition to prompt institution of HLH directed therapy bridging to hematopoietic stem cell transplant when appropriate.

(PBMTC Poster Platform 1010)

INFLAMMATION IMPACTS FUNCTIONAL OUTCOMES OF HEMATOPOIETIC STEM CELL SUBPOPULATIONS FOLLOWING TRANSPLANTATION

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Background: Although hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for many diseases, engraftment failure remains a challenging clinical limitation and better understanding of the biology of hematopoietic stem cells (HSC) in this context is needed. Emerging evidence suggests pathologic environmental conditions such as inflammation can severely impair HSC function. Indeed, our lab previously showed that the pro-inflammatory cytokine, IL-1, directly increases cell cycling and enhances myeloid proliferation through induction of the PU.1 transcription program that ultimately leads to restricted lineage output and decreased long-term engraftment following HSCT.
Objectives: To identify whether one or more distinct HSC subsets retain their self-renewal and multilineage reconstitution capacity following chronic exposure to inflammatory signals such as IL-1.
Design/Method: We used the mouse as a highly conserved model of human hematopoiesis to understand the impact of chronic inflammation, induced via daily injection of IL-1, on HSC function. HSC fractions in the bone marrow (BM) of control and IL-1-treated mice were isolated, analyzed and purified using flow cytometry and subjected to molecular and functional analysis via RNA-seq and transplantation into conditioned syngeneic recipients, respectively.

Results: Regardless of IL-1 exposure, HSC subpopulations with low PU.1 expression demonstrated higher levels of post-transplantation donor engraftment and multilineage reconstitution, indicating that elevated PU.1 levels antagonize HSC function. RNA-seq and subsequent flow cytometry analysis of the HSC compartment identified a significant upregulation of surface markers including integrin alpha 2b (CD41), which is expressed in megakaryocyte (Mk) lineage-primed HSCs and integrin alpha M (Mac-1), a myeloid lineage marker. Notably, subsequent flow cytometry analysis demonstrates that IL-1 exposure results expansion of HSC sub-populations expressing high PU.1, CD41 and Mac-1, with Mac-1 expression specifically enriched in PU.1hi HSCs.
Conclusion: Collectively, our analyses demonstrate functional heterogeneity within the HSC compartment in the context of chronic inflammation, with some HSCs still retaining the capacity for hematopoietic regeneration and long-term donor engraftment when forced to undergo a subsequent replicative challenge such as HSCT. Moreover, our data suggest this fraction may be prospectively identified via low expression of Mac-1 and CD41, potentially reflecting a dormant or otherwise refractory HSC subpopulation. Altogether, our results suggest that identification and transplantation of such HSC subsets, particularly in the context of autologous transplant for treatment of diseases with an inflammatory component, may improve long-term engraftment and patient outcomes following HSCT. Further studies aimed at understanding the distinct molecular and cellular features of these HSC fractions are ongoing.

(PBMTC Poster Platform 1011)

FEMALE GENDER AND MALIGNANCY ARE ASSOCIATED WITH LOW PEDSQL SCORES AT 12 MONTHS POST-HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Hematopoietic cell transplantation (HCT) is a curative option for many malignant and non-malignant diseases. As survival rates continue to improve, post-transplantation quality of life (QoL), including patient-reported outcomes (PRO), is increasingly the focus of attention. Studies specifically addressing the importance of PRO in pediatric patients are limited.
Objective: To describe the temporal trends of PedsQL scores in pediatric HCT recipients
Design/Method: HCT recipients aged 2-18 years were prospectively enrolled at 6 participating institutions from 2011-2013. PRO were collected using the PedsQL measurement model at baseline (within 30 days prior to transplantation), day 100, 6 months and 12 months post-transplantation. Clinical data was gathered for Center for International Blood and Marrow Transplant Research (CIBMTR) at identical routine time-points. Means and standard deviations (SD) were obtained for the PedsQL measure (total score) and subscale scores: about feelings (FEEL), health and activities (HEALTH), school and studies (STUDY), and getting along with others (OTHERS). Scores were further stratified using patient, and disease related factors. Cut-off for ill health for total and subscale scores is derived from general population (69.7).

Results: Enrolled recipients (n=83) had a median age at HCT of 7 years. Fifty four percent were male and 53% received transplantation for non-malignant conditions. Among patients surviving to each time-point, PedsQL measures were completed by 77 (92.8%) at baseline, 45 (60.8%) at day 100, 49 (69%), at 6 months and 41 (58.6%) at 12 months post-HCT. Twelve (16%) died and 4 withdrew/ were lost to follow-up. The mean±SD PedsQL score at the 4 time-points were 67.3±17.7, 71.6±16.7, 73.4±17.8, and 76.6±20.3. Subscale scores about FEEL (66.4±18.9, 71.3±20, 76.4±21.2, 75.7±25.2), HEALTH (70.1±23.6, 70.1±23.7, 72.3±22.3, 78.5±22.7), STUDY (52.9±28, 66.5±24.5, 66.1±20, 72.4±19.8), and OTHERS (77.8±19.8, 76.6±15.1, 79.4±17, 80.2±19) were documented. Females vs. Males (71.4±20 vs. 80.7±20.3) and patients with malignant vs. non-malignant disease (71.6±21.6 vs. 81.2±18.5) had lower 12-month scores that represent lower QoL.
Conclusions: We reported temporal trends of PedsQL and subscale scores in a pediatric HCT population. We found the subscale score pattern differed from the overall score, especially 'about STUDY' which was below the cut-off for all of the first three time-points and 'about OTHERS' which did not drop below the cut-off throughout. Although the group overall had a continual improvement in scores with the highest scores being at 12-months post-transplantation, females and patients with malignancy had lower scores at 12 months post-HCT and suggest a target group for an early intervention.

(PBMTC Poster Platform 1012)

MALGLYCEMIA IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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Background: Malglycemia, defined as hypoglycemia, hyperglycemia, or glycemic variability, is common in adult hematopoietic stem cell transplant (HSCT) recipients and is associated with increased rates of nosocomial infection, acute graft-versus-host disease (GVHD), organ dysfunction, time to engraftment, and mortality. Similar research in the pediatric HSCT population is lacking.
Objectives: To identify the incidence and risk factors for malglycemia, during the primary HSCT admission for pediatric patients and to characterize associated outcomes.
Design/Method: Medical records for 351 pediatric and young adult patients, age 0-26 years (9.6±6.7 y/o, 59.5% male), who underwent first HSCT from 2007–2016 at Children's Hospital Colorado were retrospectively reviewed. The primary outcome was a clinically significant infection in the first 100 days after HSCT. Malglycemia was determined from mean and standard deviation of blood glucose for each patient.
Results: On preliminary analysis, malglycemia occurred in 45.9% of patients overall with 27.5% experiencing malglycemia in the week prior to transplant, 22.2% in the first 30 days post-transplant, and 23.7% in the first 100 days post-transplant. The rate of malglycemia was higher among patients who underwent allogeneic than autologous transplant (pre-transplant 36.9% vs 9.9%, $p<0.001$; days 0-30 26.7% vs 14.0%, $p=0.007$; days 0-100 29.3% vs 13.2%, $p=0.007$).

Patients who had any type of infection had significantly higher mean blood glucose in all time periods (p=0.012-0.037). Patients who had infections had a higher incidence of malglycemia in all time periods (pre-transplant 31.3% vs 14.1%, p=0.003; days 0-30 24.6% vs 14.1%, p=0.049; days 0-100 26.9% vs 12.8%, p=0.010). The impact of malglycemia appeared larger in recipients of allogeneic transplant in all time periods, with a difference in mean glucose of 9.33-9.99 mg/dL between allogenic recipients with and without infection (p=0.012-0.022). In a sub-analysis by infection type, serious bacterial illness (SBI), fungal infection and viremia/viruria were associated with increased mean blood glucose and rate of malglycemia. In patients who died within the first year post-transplant, mean glucose was higher during days 0-30 and 0-100; similarly, mortality was associated with malglycemia for days 0-100.
Conclusion: Malglycemia occurs frequently in the pediatric/young adult HSCT population and is more common in patients who undergo allogeneic transplant. Malglycemia is associated with increased rates of SBI, fungal infection, and viremia/viruria. Furthermore, mortality in the first year is associated with higher mean blood glucose. Analyses of additional outcomes and potential cofactors, as well as a prospective trial of these associations, is the focus of our ongoing research.

(PBMTC Poster Platform 1013)

A RETROSPECTIVE REPORT OF CHILDREN WITH VERY HIGH-RISK ACUTE MYELOID LEUKEMIA AND MYELODYSPLASIA UNDERGOING ALLOGENEIC TRANSPLANTATION IN BONE MARROW APLASIA

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Background: Children with very high-risk myeloid malignancies (MM)—relapsed/refractory acute myeloid leukemia (AML) or therapy-related AML/myelodysplasia (t-AML/MDS)—require allogeneic hematopoietic cell transplantation (alloHCT) for cure. When morphologic complete remission (CR) cannot be achieved, treatment options are limited, and the benefit of alloHCT is controversial. Proceeding with alloHCT during bone marrow aplasia after intensive pre-transplant chemotherapy can allow for alloHCT with curative intent when the leukemic burden is minimized; however, concerns exist regarding transplant-related mortality (TRM) and relapse risk.
Objectives: We report single institution outcomes of alloHCT in aplasia for children with very high-risk MM at Johns Hopkins All Children's Hospital.
Design/Method: We retrospectively reviewed the records of children (age<21 years) with high-risk MM (AML unable to achieve CR or t-AML/MDS, excluding myeloproliferative neoplasms) undergoing first alloHCT between January 2010 and April 2016.
Results: Six patients met criteria: three had t-AML/MDS (two with 11q23; one with monosomy 7), and three had primary AML, one with primary refractory disease and two with relapsed disease. Clofaribine- or high-dose cytarabine-based regimens were used to induce aplasia; all patients received fludarabine/melphalan/thiotepa as transplant conditioning, initiated at a mean of 29 days from start of last chemotherapy. Four patients received 10/10 matched unrelated

donor grafts; one received haploidentical unmanipulated bone marrow with post-transplant cyclophosphamide, and one received unrelated cord blood, 5/6. All patients engrafted neutrophils; one patient failed to engraft platelets, later dying in remission after developing serositis and multiple thrombotic complications. The remaining five patients are alive without disease relapse (overall survival 83%), with a median follow up of 21 months (range 8- 36). Three patients received post-transplant preventative azacitidine. Of the surviving patients, 3 developed graft-versus-host disease, 1 with severe disease who is alive on immunosuppression 18 months post-transplant. There was no sinusoidal obstructive syndrome.
Conclusions: AlloHCT in children with high-risk MM is challenging, particularly when CR cannot be achieved. Undergoing alloHCT during aplasia minimizes active disease burden. Concerns regarding high TRM and relapse risk have limited its use. We describe 6 patients undergoing alloHCT using this approach, with excellent disease control and minimal TRM. While more experience is required to reproduce this experience, transplant in aplasia should be considered for children with very-high risk MM and limited curative treatment options.

(PBMTC Poster Platform 1014)

HIGH DOSE CORTICOSTEROID THERAPY FOR TREATMENT OF LATE PULMONARY DISEASE POST-HSCT IN CHILDREN AND ADOLESCENTS

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Background: Hematopoietic stem cell transplantation (HSCT) is used to treat a variety of pediatric disorders, including malignancies, marrow failure syndromes and a variety of hematologic and metabolic disorders. Pulmonary complications continue to be a leading cause of post-transplant morbidity and mortality, with an incidence of 25-50% and mortality rate of 50% in patients with allo-HSCT. The most common late pulmonary complications are Bronchiolitis Obliterans (BOS), which has an incidence of 1.7 to 26%, and Bronchiolitis Obliterans Organizing Pneumonia (BOOP), which has an incidence of 1.6 to 10.3%.
Objective: There is currently no universally accepted treatment of sub-acute late pulmonary complications post-HSCT. The use of high-dose corticosteroid, pulse therapy for 3 consecutive days repeated on a 21-day or monthly cycle, is one treatment strategy that has been uniformly implemented in our institution. This method has also been reported for the treatment of infection-induced BOS, with pulse therapy repeated on a monthly basis.
Design/Method: We conducted a single-center retrospective case series to describe the clinical course and treatment outcomes of eight patients (4 male, 4 female) (age 9 mo-22 yr) who underwent HSCT (UCB (n=3), Haplo (n=3) URD (n=2)), with myeloablative conditioning regimens and diagnosed with late (>3 months) pulmonary complications post-HSCT. Patients were diagnosed with BOS or BOOP using standard international criteria (ISHLT) based on imaging, clinical symptoms, and PFTs and exclusion of other causes. All patients were treated with high-dose corticosteroid pulse therapy (methylprednisone 30mg/kg/day for three days) repeated on a 21-day or monthly cycle. The total amount of treatment cycles with pulse therapy ranged from 1 to 52 cycles (median 3 cycles).

Results: Treatment led to stabilization of lung function in six patients. Two patients died of progressive respiratory failure. Of the six surviving patients, median survival post transplant is 6.75 years (range 3-9 years). At the most recent follow-up, three patients are asymptomatic. One patient currently requires daily supplemental oxygen with activity, but also required treatment for a coexisting MAI infection. Oxygen saturation above 92% was achieved in all patients at one-month post therapy, and above 96% in all patients one-year post therapy.
Conclusion: Our preliminary data suggest high dose corticosteroid pulse therapy shows promise as an effective treatment for BOS and BOOP occurring as a late complication post-HSCT. Future prospective clinical trials are needed to further evaluate this treatment strategy.

(PBMTC Poster Platform 1015)

CLINICAL OUTCOME AND IMMUNE CELL RECOVERY AFTER C45RA-DEPLETED HAPLODENTICAL TRANSPLANTATION IN PAEDIATRIC PATIENTS WITH HIGH RISK ACUTE LEUKEMIA

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Background: Allogeneic hematopoietic stem-cell transplantation (HSCT) is the only alternative for many patients with high-risk leukemia. Haploidentical donors give the chance to transplant on time most of patients that need a HSCT. Haplo-HSCT requires T-cell depletion in order to minimize graft versus host disease (GvHD). However T cell depletion associates delayed immune recovery. Naïve T-cells identified by CD45RA+ expression are believed to cause graft-versus-host-disease (GvHD), while CD45RA- T-cells are memory cells that provide anti-infection and anti-tumoral effects. Depleting CD45RA+ naïve cells and retaining memory T-cells in the graft is a novel approach to haplo-HSCT for children.
Design/Methods: 19 children with high risk leukemia (7 AML, 12 ALL) received CD45RA-depleted haplo-HSCT following TLI-based reduced intensity conditioning. Cell-selection performed on G-CSF-mobilized peripheral blood. Two cellular products obtained using CliniMACS device, and infused to each patient: a CD34+ selection and a CD45RA+ depletion from the CD34-negative fraction.
Results. Product infused contained a median of 6.45 (range 4.04-9,93) $x10^6$/Kg CD34+ cells and a median of 3.59 (range 0.13-49) $x10^4$/Kg of CD3+ cells in the CD34-selected graft. The second product was the CD45RA depletion, CD45RA+/Kg was a median of 5.5 x103/Kg (range 0.3-$13x10^4$/Kg) and a median 4.52 (range 2.21-6.37) depletion log of CD45RA+ cells. Median dose of CD45RO+ cells (memory T-cells) infused was 9.98 (range 3.8-42) $x10^7$/Kg.

Eighteen patients achieved neutrophil engraftment at median of 10 days (range 8-12) post-transplant. One patient could not achieve engraftment, died at day +8 due to sepsis. Two patients presented secondary graft failure (day +18 and +20), one because AML-M7 relapse and one with the development of anti-HLA antibodies. Both received a second HSCT and engrafted. Three

patients developed aGvHD>grade II with gastrointestinal tract involvement, all steroids responsive. Three patients presented clinical features of cGvHD. Patients have an extensive skin involvement, with hepatic findings in one and pulmonary affection in other, at day +315, +130 and +330 posttransplantation.
Eleven of 19 patients (57.85%) remain alive in remission with median follow-up 211 (range 8-640) days post-transplant. Eight patients died, 3 due progression at day +128, +117, +162 (2 presented positive minimal residual disease at HSCT), 5 due to infectious complications (days +8, +44, +50, +55, +253).
T-cells led immune recovery, achieved values higher than 500, 600, 1500 and 2400 cells/mcL at day 30, 60, 90 and 210 respectively. Most of T cells were CD8+CD45RA- (median of 288, 370 and 2334 x106/mm^3 respectively on day +30, +60 and +90) and CD4+CD45RA- T cells (median of 129, 161 and 767 x106/mm^3 respectively on day +30, +60 and +90), while CD8+45RA+ and CD4+45RA+ cells remained low recapitulating the CD45RA depleted graft composition.
Six patients presented cytomegalovirus reactivation, one progressed to CMV disease. Five patients developed Human-Herpes virus 6 encephalitis during engraftment, 3 of them recovered without sequales.
Conclusion. CD45RA-depleted haplo-HCT showed acceptable tolerability with rapid and sustained engraftment as well as a full donor chimerism, minimal risk of acute GvHD and accelerated inmunologic reconstitution.

(PBMTC Poster Platform 1016)

DIAMOND BLACKFAN ANEMIA: SUCCESSFUL APPROACH TO ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANT USING UNRELATED CORD BLOOD AND OTHER DONOR SOURCES

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Background: Allogeneic hematopoietic stem cell transplant (HSCT) has been used successfully as curative therapy in steroid-refractory or transfusion-dependent patients with Diamond Blackfan Anemia (DBA). Unrelated umbilical cord blood (UCB)-HSCT using myeloablative cyclophosphamide-based conditioning has had poor outcomes with high graft rejection and mortality rates.
Objectives: We present the outcomes of our single-institution experience with allogeneic HSCT in seven patients with DBA using a consistent myeloablative, reduced toxicity preparative regimen across several donor types.
Design/Method: An IRB approved, retrospective chart review was performed of all patients with DBA undergoing allogeneic HSCT at the Children's Hospital Colorado between 2008 and 2016. Patients received myeloablative, reduced toxicity conditioning with Thiotepa (10 mg/kg), Busulfan (9.6 mg/kg), Fludarabine (160 mg/m2), and serotherapy with equine ATG (6) or alemtuzumab (1). GVHD prophylaxis consisted of cyclosporine A and mycophenolate mofetil.
Results: Seven patients with DBA underwent curative allogeneic HSCT for the following indications: steroid refractoriness/transfusion dependence (3), partial steroid response/progressive trilineage cytopenias (3) or steroid intolerance (1). Genetic mutations were

identified in 5/7 patients (RPS19[2], RPS24, RPL5 and RPL35a). Three patients had hepatic iron overload prior to HSCT. Four patients received 8/8 (High Resolution Typing HLA-A, B, C, DRB1) unrelated UCB-HSCT (including one double-UCB) with a mean cell dose of 5.6x107 TNC/kg (range: 2.5-12). The stem cell source for the remaining three patients was a matched-related marrow (2 siblings, 1 father). All patients engrafted with full donor chimerism and are alive with a median follow up time of 31 months (range 8-96 months). Median time to neutrophil engraftment was 19.5 days (range 15-26 days) in the unrelated-UCB cohort and 24 days (range 22-30 days) in the matched-related donor cohort. Following UCB, 2/4 patients had Grade II acute GVHD (skin, gut) and one patient had limited chronic GVHD (skin). Viral reactivation was the primary transplant complication in these patients with CMV reactivation in 2/4 patients and severe BK hemorrhagic cystitis in one patient. In the matched-related donor cohort, no GVHD was noted in any patient and one patient had post-HSCT autoimmune hemolytic anemia and severe CMV meningitis and retinitis requiring therapy with donor-derived, anti-viral cytotoxic T-lymphocytes.
Conclusion: At our institution, HSCT curative therapy for DBA using a myeloablative, reduced toxicity regimen consisting of thiotepa, busulfan, fludarabine and ATG has been associated with excellent engraftment rates and overall survival without severe (grade III/IV) GVHD in patients receiving both unrelated umbilical cord blood and matched-related marrow.

(PBMTC Poster Platform 1017)

STABILIZATION OF PULMONARY FUNCTION IN PEDIATRIC AND YOUNG ADULT SICKLE CELL DISEASE (SCD) RECIPIENTS UNDERGOING MYELO-IMMUNESUPPRESSIVE (MIC) AND FAMILIAL HAPLOIDENTICAL (FHI) TRANSPLANTATION ENRICHED CD34 SELECTION AND T-CELL ADD-BACK

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Background: SCD is characterized by chronic vaso-occlusion leading to organ dysfunction and premature death. Sickle cell lung disease is a common cause of death in SCD patients. Hematopoietic stem cell transplant (HCT) is a curative option for patients with SCD and can halt progression of lung disease1. However, most patients do not have unaffected, HLA-matched siblings2. Initial studies using unrelated donors have been limited by chronic graft-versus-host disease (GVHD) and lack of available donors3. To combat these challenges, we designed a multi-institutional study of MIC followed by FHI transplantation, enriched by CD34 selection and T-cell add-back.
Objective: We hypothesize that using MIC followed by FHI stem cell transplant will limit SCD related organ damage leading to stable pulmonary function.
Design/Method: Children and young adults with high risk SCD without a matched sibling donor were eligible. High risk disease was defined as a history of stroke or silent infarcts, â‰¥2 episodes of acute chest syndrome or â‰¥3 vaso-occlusive crises in the preceding 2 years, or abnormal transcranial doppler. Patients received MIC that included Hydroxyurea and Azathioprine, Fludarabine (150mg/m2), Busulfan (12.8mg/kg), Thiotepa (10mg/kg),

Cyclophosphamide (200mg/kg), ATG (10mg/kg), and a single dose of TLI (500cGy) followed by FHI AlloHCT with CD34 selections (10x106 CD34/kg, CliniMacsÂ®) and 2x105 CD3/kg add-back. Tacrolimus was used for GVHD prophylaxis. Pulmonary function tests (PFTs) were performed prior to the start of conditioning (FVC, FEV1, FEF25-75, TLC, DLCO) and repeated yearly post-HCT.
Results: Seventeen patients have been transplanted (median age:12y, range 3-20y; 12M/7F). Fourteen patients remain alive at a median of 643 days post-transplant (range 43-1499). Baseline PFTs were performed on 15 patients (2 patients unable to cooperate with testing) and did not show any significant deficits. In 8 evaluable patients at 1 year there was mild, non-significant decrease in lung volumes compared to baseline (median decrease in FEV1 by 11% and FVC by 13.7%). There was no sign of obstructive defect and DLCO remained stable. Four patients have been followed for 2 years post-HCT; in these patients, the restrictive decrease seen at 1 year resolved, with FEV1 and FVC returning to baseline. Lung function and DLCO was similar to baseline. Follow-up is ongoing.
Conclusion: Preliminary results are encouraging and suggest that patients with SCD stabilize their lung function after AlloHCT with MIC followed by FHI with CD34 enrichment and CD3 add-back. (Supported by R01FD004090-01A1)

1.Talano, Eur J Haematol, 2015 2.Shenoy , Blood,2016 3.Bhatia, Bone Marrow Transplant, 2014.

(PBMTC Poster Platform 1018)

ANTIBIOTIC-INDUCED DEPLETION OF ANTI-INFLAMMATORY CLOSTRIDIA IS ASSOCIATED WITH THE DEVELOPMENT OF GVHD IN PEDIATRIC STEM CELL TRANSPLANT PATIENTS

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Background: Adult stem cell transplantation (SCT) patients with graft-versus-host-disease (GVHD) exhibit significant disruptions in gut microbial communities. These changes are associated with higher overall mortality and appear to be driven by specific antibiotic therapies. It is unclear whether pediatric SCT patients who develop GVHD exhibit similar antibiotic-induced gut microbiota community changes.
Objectives: Demonstrate that pediatric SCT patients who develop GVHD have a significant and specific changes in their gut microbiota compared to those without GVHD.
Design/Methods: Using metagenomic shotgun sequencing analysis, we were able to identify fourteen specific commensal bacterial species, including eight AIC, that were significantly depleted in GVHD patients. We then used a preclinical GVHD model to verify our clinical

observations. Clindamycin depleted AIC and exacerbated GVHD in mice, whereas oral AIC supplementation increased gut AIC levels and mitigated GVHD in mice.
Results: Here, we show that pediatric SCT patients (from Children's Medical Center Dallas and Cincinnati Children's Hospital) who develop GVHD show a significant decline, up to 10-log fold, in gut anti-inflammatory Clostridia (AIC) prior to GVHD diagnosis compared to those without GVHD. In fact, the development of GVHD is significantly associated with this AIC decline and with cumulative antibiotic exposure, particularly antibiotics effective against anaerobic bacteria ($p= 5.6 \times 10^{-5}$, Firth logistic regression analysis).
Conclusions: This data demonstrates that an antibiotic-induced AIC depletion in the gut microbiota is associated with the development of GVHD in pediatric SCT patients.

(PBMTC Poster Platform 1019)

A PILOT STUDY OF THE SAFETY AND EFFICACY OF EXTRACORPOREAL PHOTOPHERESIS (ECP) IN THE TREATMENT OF CHILDREN, ADOLESCENTS AND YOUNG ADULTS (CAYA) WITH STEROID REFRACTORY ACUTE GRAFT-VERSUS-HOST DISEASE (AGVHD)

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Background: Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is in large part limited by severe aGVHD. Calcineurin inhibitors (tacrolimus) in combination with mycophenolate mofetil are commonly used in the prophylaxis of aGVHD, but the risk of development of aGVHD still remains 20-70%.1 Although treatment with steroids is the gold standard for new onset aGVHD, remission occurs only in about half of the patients, with more severe cases less likely to respond.2 ECP results in immune cell apoptosis and anti-inflammatory effects in various organ systems, minimizing systemic exposure and sparing generalized immunosuppression, and has been safe and effective in steroid resistant aGVHD3 and chronic graft-versus-host disease (cGVHD).4
Objective: To evaluate the safety and efficacy of ECP in treatment of CAYA with aGVHD after Allo-HSCT and Donor lymphocyte infusion (DLI).
Design/Method: We determined the safety and efficacy of ECP in CAYA under the age of 30 who developed aGVHD after Allo-HSCT/DLI. Response was classified as complete response, partial response, mixed response, stable disease, progression or no response, as previously reported.5 Kaplan- Meier survival curves were utilized to determine probability of overall survival (OS).
Results: A total of 6 patients (3 males and 3 females) received ECP for steroid refractory aGVHD: 5 after Allo-HSCT, 1 after DLI. The median age was 13 years (range 6 to 24 years), with 83.3% (5 of 6) having an underlying malignant disease. Reduced intensity conditioning regimens were used in 66.7 % (4 of 6) patients. All 6 patients had steroid refractory grade 2 (50%), grade 3 (33.3%) or grade 4 (16.7%) aGVHD. Complete response was achieved in 66.7% (4 of 6), mixed response in 16.7% (1 of 6) and stable disease was observed in 16.7% (1 of 6) patients. No side effects, probably or directly secondary to ECP, were reported during the

combined 236 ECP treatments, except nausea, vomiting and headache on 2 occasions. EBV reactivation occurred in 16.7% (1 of 6) patients. Two patients died: one from secondary sepsis, the other from cGVHD. The probability of survival at 1 year is 83.3% and at 2 years is 62.6%. **Conclusion**: This preliminary study suggests that ECP is safe and induces durable responses in CAYA Allo-HSCT recipients with steroid refractory aGVHD. Larger cohort and longer follow-up is needed to confirm these findings.

Bhatia/Cairo, BBMT, 2010; Ferrara, Lancet, 2009; Perotti, Transfusion, 2010; Greinix, Biol; Blood Marrow Transplant, 2011; Alousi, Blood, 2009

(PBMTC Poster Platform 1020)

IMPROVING KINETIC EXPANSION OF HUMAN NATURAL KILLER CELLS USED FOR ADOPTIVE IMMUNOTHERAPY

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Background: Ex vivo expansion of natural killer (NK) cells from peripheral blood is necessary in order to obtain a large number of cells for immunotherapy. NK cell expansion protocols are required to optimize immunotherapy on a clinical scale.
Design/Methods:The procedure is based on a current expansion process: 21 days of coculture with leukemia cell line k562 modified to express a membrane-bound form of interleukin 15 and 4-1BB ligand (k562-mb15-41BBL) kindly provided by Professor Dr. D Campana (NUH Hospital, Singapore). Thirty-four expansion processes were evaluated using 4 various growth culture media: RPMI-1640 medium (Lonza, Belgium); SCGM GMP grade medium (Cellgenix, Germany); NkMACS medium (Miltenyi Biotec, Germany); and TexMACS GMP medium (Miltenyi Biotec, Germany) . Peripheral blood mononuclear cells were obtained from 9 healthy adult donors. Lymphocyte subpopulations were determined by flow cytometry. The K562-mb15-41BBL cell line was used to expand the NK subpopulation after 3 weeks of coculture. Fresh medium supplemented with 10% human AB serum and IL-2 10 IU/mL during the first week and 100 IU/mL thereafter was added every 2 days. The percentage of NK cells was monitored every week. The cytotoxic activity and degranulation capacity of the final product was evaluated by 4-hour europium-TDA release assays and by flow cytometry. Cytokine production was measured in supernatant culture at various expansion times (0, 7, 14 and 21 days) by cytokine bead assay, according to the manufacturer's instructions.
Results: After analyzing the process of expansion (21 days) in the various culture media, the ratios of increase in the NK subset were the following: RPMI-1640 medium yielded a 389-fold increase, range 37–1557; SCGM medium a 642-fold increase, range 52–2218; NkMACS medium a 902-fold increase, range 122–3170; and TexMACS GMP medium a 841-fold increase, range 114–3513. All the processes resulted in a highly pure NK cell product (CD56+CD3- >80%). The effector functions of NK cell products on stimulation with k562 target cells revealed no differences in the production of proinflammatory cytokines (TNFa, IL10, IL6, IL-1β, IL8), as well as similar levels of degranulation and cytolytic activity. Three procedures were performed

with the CliniMacs Prodigy (automated expansion system) using TexMACS medium (best choice in GMP grade), with results similar to those obtained in the manual expansion processes.
Conclusions: Our results demonstrate that NkMACs and TexMACs media are the most effective options for improving the cell expansion process. However, despite having a similar capacity, the only medium available in GMP conditions is TExMacs. All the NK cell products had similar phenotypic and functional profiles; hence, this culture medium can be used to improve the clinical expansion procedure in a fully automated system (CliniMacs Prodigy) and in manual expansion procedures under Good Manufacturing Practices

(PBMTC Poster Platform 1021)

HLA-HAPLOIDENTICAL HEMATOPOIETIC CELL TRANSPLANTATION FOR TREATEMENT OF NON-MALIGNANT DISEASE USING NONMYELOABLATIVE CONDITIONING AND POST-TRANSPLANT CYCLOPHOSPHAMIDE

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Background: Allogeneic hematopoietic cell transplant (HCT) is often the only curative therapy for patients with non-malignant diseases (NMDs); however, many patients do not have fully matched related or unrelated donors. Historically, HLA-haploidentical donors have been used; however inferior survivals have been reported due to increased infections, poor immune reconstitution, GVHD, and graft failure. Previous nonmyeloablative HLA-haploidentical approaches using T-replete grafts have post-HCT cyclophosphamide (CY) in patients with hematologic malignancies and demonstrated effective engraftment with a low transplant related mortality (TRM). Here we report on a similar approach for patients with NMDs.
Objective: To evaluate engraftment and overall survival following HLA-haploidentical HCT using nonmyeloablative conditioning for patients with NMDs.
Design/Method: Twenty-one patients with NMDs [severe aplastic anemia (n=7), sickle cell disease (n=5), primary immunodeficiency diseases (n=4), hemophagocytic lymphohistiocytosis (n=3), Dyskeratosis Congenita (n=1), and Glanzmann's Thrombasthenia (n=1)] underwent HLA-haploidentical HCT between 2006 to 2016. Three patients had failed prior transplant, and the median augmented HCT-comorbidity index score was 4 (range 0-10). Patients were given bone marrow (n=16) or G-CSF mobilized peripheral blood stem cell (PBSC; n=5) grafts following nonmyeloablative conditioning with CY (25 mg/kg; days -6 and -5), fludarabine (30 mg/m2; days -6 through -2), and 2-4 Gy TBI (day -1). Postgrafting immunosuppression consisted of CY (50 mg/kg; day +3 and +4), then MMF, tacrolimus, and sirolimus beginning on day +5, except for the first 7 patients who received just MMF and tacrolimus.
Results: The median age at HCT was 11.4 years (range 0.6-47.3 years). Full donor (CD3>95%, n=17) or high-level mixed (CD3 50-94%, n=2) was achieved in 19 patients, whereas graft rejection occurred in 2. With a median follow-up of 1.3 years, the 2-year estimated overall and event free survival were 86% (95% CI, 53-97%) and 73% (95% CI, 46-88%), respectively. Day 100 TRM was 0%. Two patients died, 1 from intracranial hemorrhage/disseminated fungal

infection in the setting of graft failure and 1 from infection/GVHD. The estimated probabilities of grades IIâ€“IV and IIIâ€“IV acute GVHD at day 100 and 2-year NIH chronic GVHD were 81%, 29% and 27%, respectively.
Conclusion: These results are encouraging and demonstrate the ability to establish donor engraftment in patients with NMDs using nonmyeloablative conditioning followed by HLA-haploidentical grafts. Excellent overall survival and low TRM were seen; however, additional strategies are needed for GVHD prevention.

(PBMTC Poster Platform 1022)

NEUROCOGNITIVE AND NEUROLOGICAL OUTCOMES IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH HIGH RISK SICKLE CELL DISEASE (SCD) WHO HAVE UNDERGONE FAMILIAL HAPLOIDENTIAL (FHI) ALLOGENEIC STEM CELL TRANSPLANTATION UTILIZING CD34 ENRICHMENT AND T CELL ADDBACK FOLLOWING MYELOIMMUNOABLATIVE CONDITIONING (MIC)

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Background: The cognitive and neurological impairments associated with SCD due to cerebral vascular injury are devastating; over 40% of children with SCD have below normal IQ by 21 years of age.1 Brain abnormalities are evident on neuroimaging and associated deficits in attention, memory, processing speed, executive functioning, and intellectual functioning. Following reduced toxicity conditioning and matched sibling BMT in patients with SCD have stable to improved neurological functioning.2
Objectives: We aim to determine the changes in neuroimaging and neurocognitive sequelae in individuals with high-risk SCD prior to and following MIC and FHI AlloSCT utilizing CD34 selection and T cell addback.
Design/Method: MIC and FHI with CD34 enrichment and T cell addback was performed as previously described.3 High risk eligibility includes stroke, silent infarct, recurrent acute chest syndrome, recurrent pain and elevated Transcranial Doppler. Participants received neuroimaging (MRI/MRA), neurocognitive screening4 and abbreviated, standardized test battery measuring IQ, memory, attention, language, motor, processing speed and executive functioning. Three time points were evaluated: pre-transplant (baseline-T1), 1 year (Day +365-T2) and 2 years (Day +730-T3) post-transplant. Neurocognitive domain scores were calculated for each area of functioning in patients at baseline and Day +365.
Results: Nineteen patients have been enrolled in the study to date (Median age 12.5 years old, 56% prior history of stroke). Of the 14 who have undergone baseline evaluation, 9 of 14 patients had evidence of cerebral infarcts on baseline MRI/MRA, none had CNS hemorrhage, and 2 had evidence of cerebral atrophy. Patients were stable at follow up with only 1 patient developing new cerebral atrophy at 1 year. Seven males and 7 females received neurocognitive evaluations. Preliminary results are consistent with cognitive patterns seen in SCD patients. Intellectual

functioning improved over time (low average [T1M=7.8±2.5] to average [T2M=8.6±1.9]), processing speed remained stable (low average [T1M=84.2±16.8 and T2M=89.2±15.4]), memory and language improved (low average ([T1M=8.6±11.5; T1M=84.2±24.5] to average [T2M=9.5±5.9; T2M=102.4±20.8]), but fine motor skills decreased (borderline [T1M=74.5±19] to low range [T2M=63.4±8.4]). Attention and emotional/behavioral functioning (parent/self-report) was within normal limits and stable over time.
Conclusion: Preliminary results are encouraging and demonstrate stability of neurological imaging and neurocognitive functioning in patients who undergo FHI AlloSCT utilizing CD34 enrichment and T cell addback following MIC.

DeBaun et al (2016). Blood; 127 (7): 829-38; Bhatia/Cairo et al (2014). BMT, 49 (7): 913-20; Talano/Cairo et al (2015). EJH, May; 94 (5): 391-9; Krull et al (2008). JCO, 26 (25); 4138-43

(PBMTC Poster Platform 1023)

ROR1-SPECIFIC CHIMERIC ANTIGEN RECEPTOR (CAR) NK CELLS AS A POTENTIAL THERAPY FOR HIGH RISK SARCOMAS AND NEUROBLASTOMAS

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Background: Neuroblastoma and Sarcoma are the most common extracranial pediatric solid tumors. Patients with Neuroblastoma and Sarcoma who fail chemoradiotherapy have a dismal prognosis and poor long-term survival (≤30% OS). Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is highly expressed on the majority of Neuroblastoma and Sarcoma. NK cells can be expanded by co-culture with genetically engineered K562 cells with membrane bound IL-21 1, and CAR can be transfected into NK cells by mRNA electroporation methodology 2.
Objectives: We hypothesize that ROR1 CAR NK cells by mRNA transfection will be highly effective against Neuroblastoma and Sarcoma expressing ROR1.
Design/Method: Peripheral blood NK (PBNK) were expanded with lethally irradiated K562 Cl9.mb-IL21, and ex-vivo expanded PBNK cells (aNK) were electroporated with anti-ROR1-CAR mRNA with a 4-1BB signaling domain which is synthesized in vitro (ROR1-CAR was generously provided by Riddell S, MD, Fred Hutch, WA). Functional cytotoxic activity of anti-ROR1 CAR aNK cells against Neuroblastoma and Sarcoma cell lines was examined via 7-AAD/5-(6)-carboxyfluorescein diacetate succinimidyl ester (CFSE) cell-mediated cytotoxicity assay at different E:T ratios. Anti-ROR1 specificity of CAR aNK cells was demonstrated using ROR1 negative Neuroblastoma cells (by shRNA knock down) and ROR1 negative MCF-7 cells. Expression of CD107a, IFN-□□□ granzyme b, and perforin□were examined using MACSQuant flow cytometer.
Results: Flow cytometry demonstrated ROR1 is highly expressed in most of neuroblastoma and sarcoma cell lines including Ewing sarcoma, osteosarcoma and fibrosarcoma. $CD56^{+}CD3^{-}$ PBNK cells were significantly propagated to large numbers by co-culture with irradiated K562-derived mbIL21-expressing aAPC at 14 days (2000 fold) (p=0.002), and expanded NK cells were isolated with more than 95% purity. Anti-ROR1-CAR was expressed on up to 70% of anti-

ROR1 mRNA-transfected aNK cells at 24 hrs. aNK *in vitro* cytotoxicity was significantly enhanced by anti-ROR1-CAR-aNK compared to Mock-aNK against ROR1 positive SHSY5Y, SKNBE(2)N, and SKNFI neuroblastoma cells and U2OS, SaOS2, and HOS sarcoma cells at different E:T ratios. However, ROR1-CAR aNK cells were not cytotoxic against ROR1 negative MCF-7 cells or SHSY5Y neuroblastoma cells when ROR1 was knocked down by shRNA. Expression of CD107a, IFN-g, granzyme b, and perforin were significantly increased in ROR1-CAR aNK cells compared to Mock-aNK against ROR1 positive neuroblastoma and sarcoma cells ($p<0.01$).
Conclusion: These data demonstrated that electroporation with ROR1-CAR significantly increases in vitro cytotoxicity of aNK cells against ROR1 positive solid tumor cells. Future studies will investigate that approach in Xenografts and PDX in vivo models.

Lee D, PLoS ONE, 2012; Chu/Cairo, Can Imm Res, 2015

(PBMTC Poster Platform 1024)

REGULATION OF CYTOKINE RELEASE AND ANTI-TUMOR EFFECTS OF EXPANDED NK AND CAR NK BY ALT-803, AN IL-15 SUPERAGONIST

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Background: NK cells play a major role in the rejection of tumors. However, NK therapy is limited by several factors, including small numbers of active NK cells in unmodified peripheral blood, lack of tumor targeting specificity, and multiple mechanisms of tumor escape of NK cell immunosurveillance. Our group has successfully expanded peripheral blood natural killer cells (exPBNK) and modified exPBNK cells with chimerical antigen receptor (CAR) to redirect NK targeting specificity. ALT-803 is a superagonist of an IL-15 variant bound to an IL-15RαSu-Fc fusion with enhanced IL-15 biological activity.
Objective: To determine the cytokines/chemokines released and anti-tumor effects of exPBNK and CAR modified exPBNK cells stimulated by ALT-803 against hematological malignancies and solid tumors
Method: PBMCs were expanded with lethally irradiated K562-mbIL21-41BBL cells. ExPBNK cells were isolated using Miltenyi NK cell isolation kits. Anti-CD20-4-1BB-CD3ζ (CAR) mRNA was produced in-vitro and nucleofected into exPBNK as we previously described. ExPBNK were cultured with 0.35 or 3.5ng/ml ALT-803 (generously provided by Altor BioScience Corporation). NK proliferation, NK receptors expression and cytotoxicity were examined. Burkitt Lymphoma (BL) (Raji, Daudi) and osteosarcoma (OS) (SaoS-2, U2-OS, HOS) cells were used as target cells. Cytokines/chemokines released were measured by cytokine arrays.
Results: ALT-803 significantly promoted exPBNK in-vitro proliferation by increasing the phosphorylation of Akt, Stat3/5 and p38 MAPK. ALT-803 increased NK activating receptors expression: NKG2D, NKp30, NKp44, and NKp46. ALT-803 significantly enhanced exPBNK in-vitro cytotoxicity against BL and OS tumor cells ($p<0.001$) and augmented the ADCC of

exPBNK cells when combined with a type II anti-CD20 monoclonal antibody, obinutuzumab, against BL cells ($p<0.01$) or when combined with anti-GD2 antibody, dinutuximab, against OS cells ($p<0.001$). ALT-803 also significantly enhanced the in-vitro cytotoxicity of anti-CD20 CAR exPBNK against CD20+ BL cells ($p<0.001$). Additionally, we observed that the combination of anti-CD20 CAR NK and ALT-803 reduced tumor burden in Raji xenografted mice. In-vitro cytokines/chemokines studies demonstrated ALT-803 induced granzyme B, IFN-□, GM-CSF, MIP-1a, RANTES, TNF-alpha release from CAR exPBNK but did not induce IL-2, IL-6, IL-10, IL-12, IL-13, MCP-1, MIP-1b, MMP-9.
Conclusions: ALT-803 significantly enhanced exPBNK in vitro persistence and cytotoxicity against both BL and OS. It also significantly enhanced ADCC of exPBNK. CAR exPBNK cells cultured with ALT-803 do not release CAR T cell induced inflammatory cytokines associated with cytokine release syndrome. In-vivo cytokine release using BL and OS xenografts are under investigation.

Pical-Izard, BBMT 2015; Chu Can Imm Res 2015; Zhu J Immunol 2009; Lee, PLoS One, 2012

(PBMTC Poster Platform 1025)

SIGNIFICANT SUPPRESSIVE EFFECTS OF HUMAN UMBILICAL CORD BLOOD (CB) DERIVED UNRESTRICTED SOMATIC STEM CELLS (USSCS) ON HUMAN T-CELL FUNCTION AND IN A HUMAN (HU) NSG ACUTE GRAFT VERSUS HOST DISEASE (AGVHD) MODEL

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Background: aGVHD is a major limitation to the success of AlloHSCT and glucocorticoids remain as the mainstay of therapy for aGVHD, however the overall response rates are only 30-50%. Recently mesenchymal stem cells (MSCs) have been demonstrated to induce responses in AlloHSCT recipients with steroid refractory aGVHD. Human CB- derived USSCs are non-hematopoietic stem cells presumed to be precursors of MSCs and are conditionally immunosuppressive1. We have demonstrated that these USSCs promote wound healing and ameliorate the blistering phenotype in a recessive dystrophic epidermolysis bullosa animal model2.
Objectives: To determine the effect of USSCs' on human T-cell function and on the prevention and treatment of aGVHD in a Hu-NSG model.
Design/Method: T cells were isolated from human peripheral blood mononuclear cells (PBMC) using a T cell isolation kit, labeled with CFSE intracellular dye and stimulated either by irradiated allogeneic human PBMC in a mixed leukocyte reaction (MLR) or by phytohemagglutinin (PHA), with or without pre-seeded irradiated USSCs (unlicensed or pre-licensed with IFNγ and TNFα) at a USSC:T cell ratio of 1:3.5-4. Flow cytometry was performed at select days to determine the cell numbers and division peaks based on the intensity of CFSE fluorescence. In vivo, NSG mice were sub-lethally radiated followed by retro-orbital infusion of

human PBMCs. USSCs (1.5x106cells/mouse) were then infused on days 2, 5 and 9 in one group to prevent aGVHD or on days 12 and 15 in another group to treat aGVHD.
Results: Exponential expansion of T cells was observed in both MLR and PHA stimulated conditions. In contrast, there was no significant increase in T cell divisions or in T-cell numbers in either condition when PBMCs were co-cultured with licensed or unlicensed USSCs ($p<0.05$). In addition, USSC coculture decreased the percentage of CD8 T cells from 25% to 10% of total PBMC. In vivo, NSG mice injected with human PBMC developed aGVHD symptoms including weight loss and slow locomotor function. Preventative ($P<0.05$) and treatment USSC injections increased the median life span of mice from 16 days to 22 and 20 days, respectively, but only preventative USSC injections significantly decreased the hazard rate[HR] (Preventative/PBMC HR=0.21, P=0.023 and Treatment/PBMC HR=0.76, P=0.827). Immunohistochemical analysis further suggested that USSC injections diminished human CD45+ cell infiltration in target organs.
Conclusion: CB-derived USSCs significantly suppress in-vitro T cell proliferation and prolong in-vivo survival in a Hu-NSG murine mouse model.

Winter/Kögler,J.Cellular and Molecular Medicine, 2008; Liao/Cairo, Stem Cells, 2011

(PBMTC Poster Platform 1026)

END OF LIFE CHARACTERISTICS AND SYMPTOMS OF HOSPITALIZED ADOLESCENT AND YOUNG ADULT PATIENTS THAT HAVE RECEIVED HEMATOPOIETIC CELL TRANSPLANT

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Background: Adolescent and young adult (AYA) oncology patients experience a significant number of physical and psychological symptoms at the end of life (EOL). Many of these symptoms are persistent, not addressed, or refractory to treatments. Hematopoietic cell transplantation (HCT), an intensive therapy that comes with the risk of serious complications and death, has been associated with both an increased intensity of treatment and number of symptoms at the EOL.
Objectives: To investigate the characteristics of AYA patients aged 15 to 25 who received HCT and died while inpatient at our pediatric hematology/oncology institution between the years 2008 and 2014, with a focus on identifying symptoms present during the last month of life (LMOL). To compare the EOL characteristics of AYA patients that did and did not receive HCT.
Design/Method: A standardized data extraction tool was used to collect information about demographics, treatment, EOL characteristics, and symptoms during the LMOL. Symptom data included 17 physical symptoms and 7 psychological symptoms.
Results: Thirty-four AYA patients received HCT and died at our institution during this time frame. The majority of these patients (68%) died of treatment-related complications. Patients experienced a median of 11.5 symptoms during the LMOL; the most common symptoms were pain (97%), fatigue (91%), and edema/lymphedema (82%). Compared to AYA oncology patients

that did not undergo HCT (n=35), patients that received HCT were more likely to die in the intensive care unit (ICU) (71% vs. 23%, p<0.0001) and to receive mechanical ventilation (68% vs. 17%, p<0.0001), hemodialysis (53% vs 0%, p<0.0001), and cardiopulmonary resuscitation (CPR) (21% vs. 3%, p=0.028) in the LMOL. Patients that underwent HCT were less likely to receive chemotherapy (29% vs. 69%, p=0.001) in the LMOL, but experienced a greater number of medical procedures (median 3 vs. 1, p<0.001).
Conclusion: AYA patients that receive HCT as a part of therapy and die in the hospital receive intensive therapy and require significant medical interventions and support at the EOL. These patients experience a large number of symptoms throughout the LMOL. Compared to AYA oncology patients that do not receive HCT, they are more likely to die in the ICU, receive mechanical ventilation and hemodialysis, and undergo CPR at the EOL. This high risk patient population may benefit from early integration of palliative care practices and/or multidisciplinary team involvement to help with the prospective assessment and management of distressful symptoms, as well as advanced care planning.

(PBMTC Poster Platform 1027)

FAMILIES ARE NOT THE BARRIER: EVALUATING ATTITUDES TOWARD EARLY INTEGRATION OF PALLIATIVE CARE IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT

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Background: The benefits of early integration of palliative care (PC) in oncology have been well established yet, there remain significant barriers to PC integration, especially in the setting of pediatric hematopoietic stem cell transplant (HSCT). HSCT patients are prone to a great degree of treatment related toxicity and are at high risk for morbidity and mortality and, while ideally suited to benefit, inherent factors in this cure oriented field preclude the integration of PC services. Most notably, family receptivity to PC is often perceived as a barrier in HSCT yet there is no data on family attitudes toward PC in this setting.
Objectives: This study aimed to evaluate perceived symptom burden in the first month of pediatric HSCT, as well as patient and parent attitudes toward early PC integration in pediatric HSCT.
Design/Method: After IRB approval, development and pre-testing, novel survey tools were administered to HSCT patients and parents. Eligibility criteria included parent of an HSCT recipient < age 10 or patient/parent dyad for patients aged10 years or older, time from HSCT >1 month and <1 year, English-speaking, and consent/assent. Data was assessed for trends in response content frequencies, percentages and parent/child concordance.
Results: 81 total participants were enrolled, including 60 parents and 21 patients. Analysis revealed high levels of perceived symptom related suffering in the first month of HSCT with suffering from: nausea 98.3%, loss of appetite 93.3%, pain 90%, diarrhea 88.3%, depression 75%, anxiety 70%, and constipation 41.7%. 85.7% of patients and 73.4% parents expressed that a great deal or a lot of attention should be paid to quality of life from the start of HSCT. The

majority of patient and parent respondents (52.4/50%) indicated they would likely want to meet with PC early in HSCT and very few reported definite opposition (0% children, 3.3% parents). **Conclusion**: Pediatric HSCT patients experience a high degree of symptom related suffering, perceive quality of life as a high priority, and are largely in favor of early PC involvement. Our findings suggest that family receptivity should not be a barrier to early PC in pediatric HSCT and that aggressive cure directed therapy can and should be accompanied by aggressive quality of life directed care through early PC integration.

(PBMTC Poster Platform 1028)

IRON OVERLOAD SURVEILLANCE AND MANAGEMENT PRACTICES IN PEDIATRIC BONE MARROW TRANSPLANT PROGRAMS IN NORTH AMERICA

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Background: Owing to improved strategies in pediatric bone marrow transplantation, a larger number of transplanted children are now becoming long term survivors. These post-transplant patients remain at risk for late complications including iron overload that has the potential to impair quality of life and adversely affect later outcomes. To date, there is scant literature that addresses routine evaluation and management of iron overload in the pediatric bone marrow transplant population.
Objectives: 1) To determine most commonly used diagnostic tests and treatment modalities for iron overload among PBMTC centers.
2) To assess variation in hemoglobin thresholds for routine red cell transfusions in BMT patients among the different PBMTC centers.
Design/Methods: A 25-question survey was distributed to PBMTC centers in North America via Survey Monkey. All questions were validated by the PBMTC Supportive Care Committee prior to survey dissemination. There was a total of 78 answered surveys. Of those, there were 55 unique evaluable surveys available for review.
Results: Only 48% of North American PBMTC centers have existing practice guidelines for surveillance and management of iron overload. 42.9% of PBMTC centers use a conservative Hgb threshold of 8 g/dL. The following populations were identified by the majority of PBMTC centers to be most at risk for iron overload: 1) Thalassemia and Sickle Cell patients pre-transplant, 2) ALL/AML patients post-transplant, 3) Bone marrow failure patients pre-transplant, and 4) patients receiving a 2nd (or more) transplant pre-transplant. All centers follow serial ferritin measurements. 90% of PBMTC centers utilize ferriscan/T2* magnetic resonance imaging for iron overload surveillance. Of those, 85% intervene at a cutoff of 7g/g dry tissue. Only 56.1% of centers utilize liver biopsies to guide management. 87.5% of PBMTC centers utilize oral chelation to treat iron overload whereas 82.5% perform routine phlebotomy. Only 52.5% of PBMTC centers utilize a combination of chelation plus phlebotomy.
Conclusion: There exists a significant practice variation in surveillance and management of iron overload as well as red cell transfusion thresholds among PBMTC centers North America. There remains a need for the development of clinical practice guidelines to address this.

(PBMTC Poster Platform 1029)

NEUTROPHIL EXTRACELLULAR TRAPS, ENDOTHELIAL INJURY, AND COMPLEMENT ACTIVATION IN THROMBOTIC MICROANGIOPATHY AND GRAFT VERSUS HOST DISEASE

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Background: Transplant–associated thrombotic microangiopathy (TA-TMA) is caused by excessive complement activation via the alternative pathway, likely triggered by endothelial injury, and clinically, TA-TMA is improved by complement blockade. An important missing piece is the link between endothelial injury and complement activation. We hypothesized that neutrophil extracellular traps (NETs) mechanistically link endothelial damage with complement activation and subsequent TA-TMA. Neutrophil activation releases granule proteins together with chromatin, to form extracellular fibers known as NETs. NETs have been shown to activate complement through the alternative pathway. NETs can be assessed in humans by quantification of double stranded DNA (dsDNA) in serum (Takaori-Kondo, BBMT, 2015).
Objective: Explore the mechanistic link between endothelial damage and microangiopathy.
Design/Method: Longitudinal analysis of NETS in serum from 103 consecutive allogeneic pediatric transplant patients at Days 0, +30, +60, and +100. A second cohort consisted of serum from an additional 18 pediatric patients with TA-TMA at four time points: prior to initiation of therapy with complement blockade using eculizumab, 2 and 4 weeks into treatment, and following discontinuation of therapy. Serum NETs were quantified using the Quant-iT PicoGreen dsDNA Reagent and Kit (Molecular Probes).
Results: Elevated levels of NETs at Days 30, 60, and 100 were significantly associated with overall survival ($p=0.04$, <0.0001, 0.0002, respectively), TA-TMA ($p=0.002$, 0.02, <0.001, respectively), and gastrointestinal GVHD ($p=0.02$, <0.001, 0.006, respectively). In patients with TA-TMA, serum NET levels were significantly elevated at 4 weeks after initiation of therapy with eculizumab when compared to levels prior to therapy ($p=0.006$) and 2 weeks into therapy ($p=0.0006$). There was a significant decrease in NETs after termination of therapy due to resolution of TMA compared to levels at 4 weeks ($p=<0.0001$) and prior to therapy ($p=0.04$), supporting our hypothesis that NET formation contributed to complement activation in TA-TMA. In addition, we looked at NET formation in children with TA-TMA both with and without GVHD. NET levels were higher in children with GVHD compared to those without prior to initiation of complement blockade ($p=0.01$) and remained elevated following resolution of TA-TMA ($p=0.02$).
Conclusion: Increased levels of NETs 30, 60 and 100 days post-HSCT were associated with decreased overall survival, TA-TMA, and gastrointestinal GVHD. NETs decrease with resolution of TA-TMA in patients without GVHD, but persist in those with GVHD. NETs may serve as a mechanistic link and indicator between endothelial injury and complement activation, and NET formation may explain the overlap between GVHD and TA-TMA.

(PBMTC Poster Platform 1030)

EVOLUTION OF SELECTIVE T CELL DEPLETED PAEDIATRIC HAPLOIDENTICAL STEM CELL TRANSPLANT IN MALIGNANT AND NON MALIGNANT DISEASES IN A SINGLE SOUTH EAST ASIAN INSTITUTION

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Background: A major barrier to urgent paediatric stem cell transplant in Southeast Asia has been the difficulty of finding appropriate HLA matched donor and also the significant cost of procurement. Haploidentical transplantation has allowed us to proceed to a transplant with comparable outcome to unrelated donor transplant.
Objective: To report our early experience and rapid evolution of methods of paediatric haplo-transplants
Methods: This is a retrospective study looking at details of Haploidentical transplants performed from 2014-2016. KIR genotyping and donor specific antibody measurement were done in all to select the better haploidentical donor. Disease indication, conditioning chemotherapy, graft details, engraftment, viral reactivations, chimerism, GVHD and overall outcome were noted.
Results: Six T depleted haplo-identical transplants were performed in 5 patients for bone marrow failure syndromes (n=3) and leukaemia (n=2, 1 JMML and 1 undifferentiated leukaemia). Cell processing evolved with increasing experience - CD3 depletion in our first, TCR αβ/CD19 depletion in the next three, and subsequently TCR αβ depletion alone. Graft source was GCSF-primed peripheral blood stem cells. Target cell doses were a minimum CD 34 cell dose of 5 x 10^6/kg and a maximum CD3/TCR αβ cell dose of 5 x 10^4/kg. GvHD prophylaxis was not routinely prescribed if we met the T cell targets, otherwise cyclosporine was used. Conditioning regimens were myeloablative in 2 malignant and reduced intensity in 3 non malignant patients. Distal Rabbit ATG (Thymoglobulin) 5 to 7.5 mg/kg was given for in vivo lympho-depletion. A single dose of Rituximab was given on day -1.
Haplo-identical transplant was used as the second transplant in 2 cases of graft failure post MUD transplant (FA, JMML). All patients are alive, at 6 months to 2 years post-transplant. 4/6 procedures achieved full donor chimerism. 1 patient (JMML) is alive with mixed chimerism 6 months post-BMT. One patient (SAA) underwent 2 TCR αβ depleted HSCT with early graft rejection and eventually salvaged with a T-replete haploidentical bone marrow transplant using a different parent.
Mean time to neutrophil engraftment was 14 days (9-18 days), and to platelet engraftment 22 days (7-55 days). Cyclosporine was used in 2 patients. Viral reactivation was common with CMV reactivation in 3/5 children. Skin GvHD developed in one and graft rejection (twice in same patient) in one patient.
Conclusion: T cell depleted haplo-transplantation is a viable option for alternative donor transplantation in children, with good donor engraftment and little risk of GvHD and excellent overall survival. Viral infections remain an important source of post-transplant morbidity.

(PBMTC Poster Platform 1031)

HEMOPTYSIS AND RESPIRATORY FAILURE AS A PRESENTATION OF PULMONARY TA-TMA

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Background: Hematopoietic stem cell transplantation (HSCT)- associated thrombotic microangiopathy (TA-TMA) is a complication of HSCT that carries a significantly high risk of nonrelapse mortality. Given its often insidious presentation in complex transplant patients, early recognition and treatment are often difficult. Although TA-TMA most commonly affects the kidneys, the endothelial damage causing organ dysfunction has also been seen in the lungs, gut, liver and brain.

Objective: We present a 7-year-old male with a history of acute lymphoblastic leukemia (ALL) in CR2 who is status post 8/8 matched unrelated donor HSCT complicated by increased intracranial pressure of unknown etiology, skin graft versus host disease (GVHD), GVHD myositis, and stage IV gut GVHD. While hospitalized for the treatment of stage IV gut GVHD, the patient developed culture negative sepsis, TA-TMA, and respiratory failure requiring intubation originally thought to be secondary to diffuse alveolar hemorrhage, but pathology later was consistent with severe acute and chronic TA-TMA. The patient clinically worsened despite withdrawal of calcineurin inhibitors (CN-I) and initiation of eculizumab. Despite normal transthoracic echocardiograms, the patient's respiratory status worsened to include high flow oxygen, prompting initiation of sildenafil with rapid clinical improvement to room air. After 13 weeks of treatment with eculizumab, the patient showed signs of recovery from TA-TMA.

Method: Diagnosis of TA-TMA made by evaluating urine protein, LDH, ADAMST13, and SC5b-9. Bronchoscopy performed to obtain cytology as well as infectious studies. Diagnosis of pulmonary TA-TMA made through apical wedge biopsy, and diagnosis of pulmonary hypertension based on clinical status and lung pathology.

Results: Laboratory results consistent with TA-TMA. Bronchoscopy cytology revealed fresh blood with moderately increased lipid-laden and hemosiderin-laden macrophages. Infectious studies from bronchoscopy negative. Lung biopsy revealed intra-alveolar hemorrhage with focal organization. Biopsy forwarded to Cincinnati for expert consultation; findings consistent with severe acute and chronic TA-TMA with significant interstitial bleeding. Patient recovered with treatment including withdrawing CN-I, eculizumab, diuresis, and sildenafil.

Conclusion: This case highlights the importance of early diagnosis and treatment of TA-TMA as well as the importance of keeping a high index of suspicion for multi-organ involvement of TA-TMA. TA-TMA should be considered in post HSCT patients that develop unexplained pulmonary hemorrhage. The case also highlights how slowly hematologic dysfunction can correct after the initiation of eculizumab and the importance of continuing treatment until hematologic parameters correct.

(PBMTC Poster Platform 1032)

DEVELOPMENT OF A LONG-TERM FOLLOW-UP PROGRAM IN THE BLOOD AND MARROW TRANSPLANT DIVISION AT CHILDREN'S NATIONAL HEALTH SYSTEM IN WASHINGTON, DC

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Background: As outcomes for hematopoietic stem cell transplants (HSCT) continue to improve, the number of long-term survivors is increasing. These survivors are at risk for developing late complications secondary to exposures incurred during pre-transplant and their preparative regimen, as well as underlying organ dysfunction and any post-transplant sequelae. Our team launched the Long-Term Follow-Up (LTFU) Program in June of 2015. This program is both unique and comprehensive in that it utilizes a variety of lifesaving guidelines from leading organizations such as Children's Oncology Group (COG), the National Marrow Donor Program (NMDP), and working groups that include the Center for International Blood and Marrow Transplant Research (CIBMTR), the European Group for Blood and Marrow Transplant (EBMT), and the American Society of Blood and Marrow Transplantation (ASBMT). One key component to our LTFU Program is our annual follow-ups schedule for all patients post HSCT, one year or greater, using standardized testing and organ evaluations based on their primary diagnosis and preparative regimen.
Methods: In order to accommodate a weekly schedule (every Tuesday), the LTFU program is divided into four separate clinics: Non-Malignant, Sickle Cell, Malignant and Chronic Graft Versus Host Disease (cGvHD). Each clinic has a HSCT Team consisting of an attending physician, advanced practice provider and clinical program coordinator in addition to an interdisciplinary team with core a group in Endocrinology, Gynecology, Nutrition, and Social Work. Each clinic may have additional team support. For example, our Malignant clinic includes Cardiology, our Sickle Cell clinic includes Neurology, and our cGVHD clinic has input from Dermatology, Physical Medicine & Rehab. The patients complete their organ evaluation (Echocardiogram, EKG, Pulmonary Function Testing, Dexa Scan and Bone Age, with Brain MRI/MRV for Sickle Cell patients) and blood work at least one week prior to their LTFU visit. The LTFU program assessments and plans are provided by consulting services, referrals are made to additional services as needed, and nurse education is provided regarding long-term self-care along with resources and support groups for families.
Results: The LTFU clinic has seen 150 patients in the past year. Interdisciplinary collaboration has contributed to the program's success. Most common findings among these patients were ovarian failure, hyper/hypothyroidism, delayed bone age, osteopenia and adequate immune reconstitution. One unanticipated finding has been the lack of adherence to the reimmunization schedule.
Conclusion: As HSCT patient's survivorship evolves, a focus on long term effects will be essential in achieving quality care for patients. Continuing a multidisciplinary approach is vital to having a successful LTFU clinic.

(PBMTC Poster Platform 1033)

IN VITRO EVIDENCE OF COMPLEMENT ACTIVATION IN TRANSPLANT ASSOCIATED-THROMBOTIC MICROANGIOPATHY

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Background: Hematopoietic stem cell transplantat (HSCT)-associated thrombotic microangiopathy (TA-TMA) significantly affects transplant-related morbidity and mortality. Over the past several decades, the cause of TA-TMA has remained unknown, limiting treatment options to non-specific therapies adapted from other diseases. Recent data demonstrating remission of TA-TMA after use of the anti-C5 monoclonal antibody eculizumab suggests a central pathophysiologic role of the complement cascade. The modified Ham test utilizes PIGA null TF-1 cells, which lack expression of the complement regulatory proteins CD55 and CD59, rendering them increasingly vulnerable to complement mediated cell death. This test may be used to distinguish microangiopathic diseases based upon the degree of complement activation.
Objectives: We aimed to determine if TA-TMA is associated with complement activation in vitro using a modified Ham test.
Methods: We assayed five samples of pooled normal human serum (NHS), six samples of patients diagnosed with TA-TMA, and five samples of patients' post-HSCT without TA-TMA. We incubated PIGA null TF1 cells (generously provided by Dr. R. Brodsky, Johns Hopkins University) with serum for 30 minutes and then assessed cell viability using the cell proliferation reagent WST-1. Serum from each sample was also separately heat treated for 30 minutes at 560 C to serve as a negative control. Cells were incubated with WST-1 for two hours then absorbance measured at 440nm. Cell non-viability was determined using the equation [100%-(sample absorbance/heat inactivated sample absorbance)]. Groups were compared using a Wilcoxon rank sum test.
Results: Samples were obtained a mean of 39.6 days post-HSCT. Patients with TA-TMA had higher levels of Lactate Dehydrogenase (408 U/L vs. 218 U/L $p=0.02$) at the time of sample procurement. Patients with TA-TMA had a mean of 2.7 antihypertensive in use at the time samples were obtained, whereas those without TA-TMA had 1.0 antihypertensives. Four of five patients with TA-TMA were eventually treated with eculizumab (after sample procurement). Serum from patients with TA-TMA had a greater percentage of non-viable cells than patients post-HSCT without TA-TMA (median 52.3% vs. 34.5% $p=0.03$) or pooled normal human serum (median 52.3% vs. 9.9% $p<0.01$). Patients without TA-TMA did not significantly differ from pooled NHS (median 34.5% vs. 9.9%, $p=0.31$).
Conclusions: Transplant associated thrombotic microangiopathy is associated with complement activation in vitro. Further investigation into the genetic underpinnings and clinical causes of complement activation post-HSCT may improve risk stratification for TA-TMA.

(PBMTC Poster Platform 1034)

SYSTOLIC FUNCTION IN LONG-TERM SURVIVORS OF PEDIATRIC HSCT

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Background: Congestive heart failure and subclinical left ventricular systolic dysfunction (LVSD) affect long-term survivors of hematopoietic stem cell transplant (HSCT). Echocardiographic measurements of global longitudinal and circumferential strain have shown promise in identifying subclinical systolic dysfunction in cancer survivors.
Objectives: We sought to understand changes in systolic function in long-term survivors of pediatric HSCT. Additionally, we aimed to determine if the biomarkers soluble suppression of tumorigenicity 2 (sST-2), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and cardiac troponin-I (cTn-I) measured during HSCT could predict LVSD in long-term survivors.
Design/Methods: We analyzed echocardiograms performed prior to HSCT and one to six years post-HSCT in children and young adults with malignancies or bone marrow failure syndromes. Echocardiographic measurements included shortening fraction (SF), ejection fraction (EF), left ventricular end diastolic dimension (LVEDD), septal thickness, and posterior wall thickness, as well as global longitudinal and global circumferential strain. We measured sST-2, NT-proBNP, and cTn-I in the same children using prospectively stored samples at clinical baseline, at HSCT day 0, 7, 14, 28, and 49. Changes in echocardiograms and biomarkers were compared using a paired t-test, and correlation between biomarkers and echocardiographic measurements were analyzed using linear regression.
Results: 95 patients had echocardiograms obtained before, and at a mean of 2.3 years post-HSCT. Ejection fraction post-HSCT was unchanged from baseline (baseline: z-score -0.73 vs. long term follow up: -0.44, $p=0.11$). Left ventricular end diastolic dimension decreased post-HSCT (z-score 0.04 vs. -0.81, $p<0.01$) and septal thickness increased post-HSCT (z-score -1.27 vs. -0.92, $p<0.01$). No significant difference was observed for SF or posterior wall thickness. Global longitudinal strain was unchanged from baseline (-20.66% vs. -20.74%, $p=0.90$) as was global circumferential strain (-24.3% vs. -23.5%, $p=0.32$). Levels of sST-2 were elevated ($p<0.05$) at all time points compared to baseline samples. Compared to baseline samples, NT-proBNP was elevated at days zero, seven, and 14, and cTn-I was elevated at days 14 and 28. Levels of cardiac biomarkers at any time point did not correlate with long-term ejection fraction, shortening fraction, or measurements of global strain.
Conclusions: In children and young adult survivors of HSCT, systolic function as measured by EF was not worse 2.3 years post-HSCT. Further, changes in LVEDD and septal thickness suggest a decrease in dilation of the left ventricle, perhaps as patients with chronic anemia achieve normalization of hemoglobin post-HSCT. Elevation in cardiac biomarkers occurring post-HSCT suggest subclinical cardiac injury occurs in many patients undergoing HSCT, and long term monitoring for LVSD should continue.

(PBMTC Poster Platform 1035)

CD45RA- MEMORY T CELLS EXPRESSING A CHIMERIC ANTIGEN RECEPTOR WITH NKG2D SPECIFICITY TARGET PEDIATRIC ACUTE LEUKEMIA

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Background: Lymphoid and myeloid acute leukemia are the most frequent cause of cancer related death in children. Relapse and refractory disease are the main clinical problems that current therapies are unable to solve. One of the main NK cell activating receptors is NK cell group 2D (NKG2D). NKG2D receptor recognizes human MICA/ULBP1-6 ligands. NKG2D ligands (NKG2DL) are expressed in leukemia cells and constitute suitable targets for immunotherapy.
Objectives: To evaluate the efficacy and safety of an NKG2D-CAR T cell therapy for Leukemia treatment.
Design/Method: The expression of NKG2DL (MICA, MICAB, ULBP-1, ULBP-2, ULBP-3 and ULBP-4), was analyzed by flow cytometry and quantitative PCR in Peripheral Blood Mononuclear Cells from 61 pediatric patients suffering from acute leukemia (21 Acute Myeloid Leukemia, 25 B cell Acute Lymphoid Leukemia and 15 T cell Acute Lymphoid Leukemia), as well as in 7 leukemia cell lines (K562, RS4-11, Jurkat, NALM-6, MOLT-3, REH and CEM). Peripheral blood mononuclear cells from healthy donors were labeled with CD45RA microbeads and depleted using AutoMACS device. The HL20i4r-MNDantiCD19bbz lentiviral vector was derived from the clinical vector CL20i4r-EF1a-hgcOPT27 but contained the extracellular domain of NKG2D, the hinge region of CD8a and the signaling domains of 4-1BB and CD3-z. The cassette was driven by MND promoter. Viral supernatant was produced by transient transfection of HEK293T cells with the vector genome plasmid and lentiviral packaging helper plasmids pCAGG-HIVgpco, pCAGG-VSVG and pCAG4-RTR2. Cytogenetic studies and array Comparative Genomic Hybridization were performed to analyze the genetic stability of lentiviral-transduced CD45RA- memory T cells. The in vitro cytotoxicity of CD45RA- T cells against leukemia cells, healthy PBMC and Mesenchymal Stem cells (MSC) was evaluated by performing conventional 4-hour europium-TDA release assays or by flow cytometry using CFSE and 7AAD labeling of target cells.
Results: NKG2DL were heterogeneously expressed in leukemia cells. For B cell ALL primary samples, we found expression of MICA/B, MICA and ULBP1 decreased in refractory disease compared to remission ($p=0.01$, $p=0.03$ and $p=0.02$ respectively). Lentiviral transduction of NKG2D-4-1BB-CD3z markedly increased NKG2D surface expression in CD45RA- memory T cells, which became consistently more cytotoxic than untransduced cells against leukemia cells. Additionally, no chromosomal aberrations nor cytotoxic activity against healthy PBMC or Mesenchymal Stem cells was observed in NKG2D CAR expressing T cells.
Conclusion: Our results demonstrate NKG2D-CAR redirected CD45RA- memory T cells target NKG2DL expressing leukemia cells in vitro and could be a promising and safe immunotherapeutic approach for acute leukemia patients.

(PBMTC Poster Platform 1036)

CARDIOVASCULAR RISK IN SEVERE MUCOPOLYSACCHARIDOSIS TYPE I AFTER HEMATOPOIETIC CELL TRANSPLANTATION

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Background: Long term survivors (LTS) of hematopoietic cell transplantation (HCT) are at increased risk for development of metabolic syndrome (MetS), a precursor of early cardiovascular disease. The presence of at least 3 of the 5 following components: increased body mass index (BMI), hypertension, low HDL-cholesterol, hypertriglyceridemia, elevated fasting blood glucose is consistent with the diagnosis of MetS. International guidelines recommend screening for MetS after HCT. Most studies of MetS after HCT involve LTS of childhood cancer where the prevalence may be as high as 39%. The prevalence of MetS in patients with severe mucopolysaccharidosis (MPS IH) who are LTS of HCT has not been reported.
Design/Methods: We performed a chart review of LTS after HCT for MPS IH to determine adult height, weight, BMI, blood pressure, HDL-cholesterol, triglycerides and fasting blood glucose. Total body irradiation (TBI) as part of the preparative phase and the current percentage donor chimerism were noted.
Results: We identified 11 adults (8 male), average age 21.1 (range 17-29) years, followed for a mean of 20.4 (range 15.5-28.4) years after HCT. TBI had been administered in 6/11; full engraftment (more than 90%) was present in 7/11, partial engraftment (10-89%) in 4/11 pts. Only 2/11 (18.2%) patients fulfilled criteria for MetS – (both female; one with TBI; both with partial donor chimerism). For the remaining patients (all with previous TBI), 4 (36%) had dyslipidemia: low HDL-cholesterol (2 pts; 18.2%) and elevated triglycerides (2 pts; 18.2%).
Conclusions: Although dyslipidemia is present in more than one-third of this small group of LTS of HCT for MPS IH, the incidence of MetS is low in comparison to LTS of childhood cancer who received HCT. Further investigation into factors, such as absence of chemotherapy prior to HCT and percentage donor chimerism, is warranted.