2014 ASPHO/PBMTC Abstract Index

Leukemia Platform Sessions (presenting Thursday, May 15 from 4-5:00pm) .........................2-5
Hematology Platform Sessions (presenting Thursday, May 15 from 4-5:00pm) ......................6-9
Plenary Platform Sessions (presenting Thursday, May 15 from 5:15-5:45pm) .......................10-11
Solid Tumor Platform Sessions (presenting Friday, May 16 from 4:45-5:45pm) ....................12-15
Clinical/Translational Research/Quality Improvement Platform Sessions .........................16-19
(presenting Friday, May 16 from 4:45-5:45pm)
Young Investigator Awards (presenting Friday, May 16 at 6:00pm) .................................20-21
Posters (1000s) Presented Thursday, May 15.................................................................22-132
Posters (2000s) Presented Friday, May 16.................................................................133-239
Posters (3000s) Presented Saturday, May 17...............................................................240-348
Pediatric Blood and Marrow Transplant Consortium Abstracts ........................................349-367
ANTI-CD33 CHIMERIC ANTIGEN RECEPTOR THERAPY FOR ACUTE MYELOID LEUKEMIA

Carol O'Hear, Joshua Heiber, Terrence Geiger. St. Jude Children's Research Hospital, Memphis, Tennessee, United States of America

Background: There has been great interest in the identification of surface molecules expressed by AML cells in order to selectively target tumor cells for destruction. One potential therapeutic target is CD33, a myeloid-specific receptor that is overexpressed on nearly 90% of AML blasts.

Objectives: To show that CD33-positive cells can be specifically targeted for destruction through the use of a chimeric antigen receptor (CAR) expressed on cytotoxic T-lymphocytes (CTL).

Design/Method: We developed a CAR that links a humanized CD33-specific single chain Fv to a 41BB-TCRζ signaling tail and expressed this on human CTL by retroviral transduction. We assessed the specific lytic ability of the anti-CD33 CAR-modified CTL (CD33-CTL) using murine cell lines transduced with human CD33, parent CD33-negative lines, AML cell lines, and patient samples. CD33-CTL were co-cultured with target cells at a 2:1 effector to target cell (E:T) ratio for 24 hours. Mock-transduced CTL served as a control. Residual living tumor cells were quantified by flow cytometry. T-cell activation in the presence of CD33 was verified by ELISA of the supernatants from the co-culture experiments. In addition, we tested the CD33-CTL in vivo. On day 0, Molm-13 AML cells were injected into immune-compromised NSG mice at a 10:1 E:T ratio with either CD33-CTL, non-transduced CTL, or PBS mock-injection control. At day 20, mice were sacrificed and tumor cell number in the bone marrow, liver, spleen, and blood was assessed by flow cytometry.

Results: Our results show that CD33-CTL kill CD33-transduced cell lines with greater than 90% lysis at 24 hours. CD33-CTL does not kill CD33-negative cells. Similar results were seen across seven different CD33-positive human AML cell lines and seven primary AML patient bone marrow samples. ELISAs showed release of interferon-γ and granzyme B from CD33-CTL after incubation with CD33-positive tumor cells, but no cytokine release from mock-transduced T-cells in these experiments. In vivo, CD33-CTL nearly eradicated the tumor cells in 13 of 15 treated mice. In contrast, a high tumor burden was observed in mice treated with either PBS or non-transduced CTL.

Conclusion: These results show that this anti-CD33 CAR is effective and specific, and support its further development for clinical use.
TARGETING CD19-POSITIVE MALIGNANCIES WITH ENGAGER T CELLS
Mireya Velasquez, Kota Iwahori, Sunitha Kakarla, David Torres, Caroline Arber, Tania Rodriguez-Cruz, Claudia Gerken, Xiao-Tong Song, Stephen Gottschalk. Baylor College of Medicine/Texas Children's Hospital, Houston, Texas, United States of America

Background: Immunotherapy with CD19-specific T cells has shown promise for the immunotherapy of CD19+ malignancies, but infused T cells do not redirect the vast reservoir of resident T cells to attack tumor cells, potentially limiting antitumor effects. While the infusion of bispecific T-cell engagers is one strategy to recruit bystander T cells, these molecules have short half-lives and do not accumulate at tumor sites. We have recently developed a strategy to overcome these obstacles by genetically modifying T cells with secretable, bispecific T-cell engagers.

Objectives: To evaluate in preclinical models the antitumor activity of T cells expressing CD19-specific T-cell engagers (CD19-ENG T cells).

Design/Method: CD19-ENG T cells were generated by transducing T cells with a retroviral vector encoding a CD19-specific T-cell engager and mOrange separated by an IRES. The effector function of CD19-ENG T cells was evaluated in vitro and in two xenograft models.

Results: After transduction, 50-60% of T-cells were positive for transgene expression. In coculture assay CD19-ENG T cells recognized CD19+ lymphoma (Daudi, Raji) and acute leukemia (BV173) cells as judged by IFN-γ and IL-2 secretion in contrast to negative controls. None of the targets were recognized by T cells secreting engagers specific for an irrelevant antigen (EphA2-ENG T cells). Antigen-dependent recognition was confirmed in cytotoxicity assays. In transwell assays containing inserts preventing T-cell migration, only CD19-ENG T cells redirected NT T cells in the bottom well to CD19+ tumor cells. To assess in vivo anti-tumor activity of CD19-ENG T cells we used BV173 or Daudi cells modified with firefly luciferase (ffLuc-BV173 or ffLuc-Daudi) to allow for serial bioluminescence imaging. NSG mice received ffLuc-BV173 or ffLuc-Daudi cells iv, and were treated with 3 iv doses of CD19-ENG or control T cells (EphA2-ENG or NT). Untreated mice served as controls. CD19-ENG-T-cells had potent anti-leukemia activity in contrast to EphA2-ENG or NT T cells, resulting in a significant survival advantage of treated animals.

Conclusion: We have generated CD19-ENG T cells with the ability to direct bystander T cells to CD19+ malignancies. CD19-ENG T cells had potent anti-leukemia activity and may present a promising alternative to current CD19-targeted immunotherapies.
Marrow Stromal Support for Acute Lymphoblastic Leukemia: Seeking New Targets for Maintenance Chemotherapy

Craig Mullen, Lauren Patrick, Olena Tkachenko, Urmila Sivagnanalingam. University of Rochester, Rochester, New York, United States of America

**Background:** Acute lymphoblastic leukemia is the most common childhood malignancy. While nearly all children enter remission about 25% relapse and most who relapse die. ALL is unique in that its successful treatment requires two years of low dose maintenance chemotherapy. Curiously, the serum levels of the drugs used in maintenance chemotherapy are not highly cytotoxic for ALL cells. The biology of maintenance chemotherapy is poorly understood and it is not known what triggers the transition from leukemia cell quiescence or dormancy to cause relapse. Our work tests this hypothesis: During remission maintenance therapy B-precursor ALL cells occupy a supportive microenvironmental bone marrow stromal cell niche. Stromal cells provide anti-apoptotic signals to ALL cells and contribute to leukemia cell dormancy and relapse.

**Objectives:** The objectives of our work are to identify stromal cell derived molecules that support ALL cell dormancy and survival in the setting of clinically relevant concentrations of maintenance chemotherapy drugs.

**Design/Method:** We have developed a robust in vitro assay in which primary human ALL cells remain viable in serum free media when cocultured with human stromal cells. We have developed techniques for siRNA mediated knockdown of candidate genes in stromal cells, and quantitative flow cytometry based techniques for measuring changes in ALL cell viability.

**Results:** (1) ALL maintained in a viable state by stromal cells in this assay include leukemia initiating cells as defined by xenografting. (2) Noncytotoxic interference with global stromal gene transcription/translation increases ALL cell apoptosis. (3) Knockdown of candidate stromal genes by siRNA leads to increased apoptosis of primary ALL cells. (a) Knockdown of the chemokine CXCL12 increases apoptosis of primary ALL cells by 53% (p = 0.05). (b) Knockdown of VCAM1 increases apoptosis of primary ALL cells by 38% (p < 0.05).

**Conclusion:** The results demonstrate that this approach can identify potentially "drugable" stromal cell derived molecules that maintain ALL viability. The system is now being scaled to assess potential synergism with conventional chemotherapy drugs and to facilitate high throughput screening of large numbers of stromal cell candidate genes selected by RNASeq based analysis of stromal cells that efficiently maintain ALL cell viability.
TARGETING NOTCH AND PLK1 IN HUMAN B-ALL: A NOVEL TUMOR SUPPRESSING MECHANISM AND A THERAPEUTIC TARGET.
Sankar Kannan, Leonard Golfman, Mandy Hall, Patrick Zweidler-McKay. UT MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Notch is a well-known oncogene in T-ALL, yet appears to have tumor suppressor effects in B-ALL. These cell type-specific effects of Notch signaling mirror consequences seen in early lymphocyte development and raise the question of how Notch leads to such divergent consequences in closely related cell types. In exploring these Notch mechanisms we discovered a B-ALL specific Notch-mediated reduction in the cell cycle regulator Polo-like kinase-1 (PLK1), revealing a novel targetable kinase in B-ALL.

Objectives: To explore the consequences of Notch-mediated down regulation of cell cycle regulator kinase PLK1.

Design/Method: Co-culture with Notch ligand DLL1 expressing human bone marrow stroma (HS-5) was used to induce endogenous Notch receptor-based signaling. Effects on protein expression, PARylation and ubiquitination were measured by immunoprecipitation and immunoblot. PLK1 inhibitors poloxin and BI2536 were used in vitro and in vivo in human B-ALL lines (SB, JM1, Nalm6) and two primary B-ALL patient samples.

Results: Notch activation in B-ALL down-regulates PLK1 in our panel of human B-ALL. Similarly PLK1 inhibitors poloxin and BI2536 induced G2/M growth arrest and decreased cell number by >80%, and increased apoptosis in B-ALL cells (>75% AnnexinV binding). Importantly, PLK1 inhibition led to MDM2 degradation and stabilization of p53, revealing >5-fold increase in total p53 protein levels within 48 hours. Mechanistically, Notch target gene HES1 induces PARP1 PARylation resulting in CHFR E3 ligase-mediated ubiquitination and destruction of PLK1. In three xenografts (human SB line and two human B-ALL patient samples), PLK1 inhibitors lead to significant reduction in leukemia burden in peripheral blood, spleen and bone marrow (50% vs. 5%, p=0.001).

Conclusion: While exploring the mechanisms of cell type-specific effects of Notch signaling in B-ALL, we have revealed a novel therapeutic target, the cell cycle regulator PLK1. Indeed, targeting Notch and PLK1 drives p53-dependent growth arrest and apoptosis in B-ALL.
RN-1, A NEW AND POTENT LSD-1 INHIBITOR, INCREASES γ-GLOBIN EXPRESSION IN A HUMANIZED SICKLE CELL MOUSE MODEL

Angela Rivers, Maria Ruiz, Kestis Vaitkus, Tatiana Kouznetsova, Vinzon Ibanez, Joseph DeSimone, Donald Lavelle. University of Illinois, Chicago, Chicago, Illinois

Background: Increased levels of fetal hemoglobin (HbF) in a pancellular distribution (high F-cells) decrease symptoms and increase life expectancy in Sickle Cell Disease (SCD). DNA Methyltransferase 1 (DNMT1) and Lysine Specific Demethylase-1, (LSD-1), a mono- and dimethyl-histone H3 K4 demethylating enzyme, are components of the DRED multiprotein complex (Cui Mol Cell Biol 31:3298, 2011). While DNMT1 inhibitors such as decitabine(DAC) are well known to induce high levels of HbF in non-human primates and SCD patients, LSD1 inhibitor tranylcypromine (TCP) have only recently been shown to increase γ-globin expression in cultured human erythroid progenitors and human βYAC mice (Shi Nat Med 19:291, 2013. RN-1 is a more potent inhibitor of LSD-1 than TCP (IC50 of 0.01-0.07 compared to 2-100).

Objectives: To determine if LSD-1 inhibitor, RN-1, will be more effective than TCP or the DNMT-1 inhibitors DAC and hydroxyurea on F cell and γ-globin mRNA in the sickle cell mouse B6; 129-Hbatm1 (HBA) Tow Hbbtm2 (HBG1, HBB*) Tow/J model.

Design/Method: Mice were injected for 10 days with RN-1(2.5mg/kg and 5mg/kg), TC (6mg/kg), DAC (0.25mg/kg) and hydroxyurea (100mg/kg). F-cells and γ-globin mRNA blood samples were drawn at Day 5 and Day 11. Mice were sacrificed at Day 11 and quantitative analysis of murine terminal erythroid differentiation was performed on bone marrow and spleen per Jing Liu (Blood 121(8): e43 2013)

Results: At days 5 and 11 TCP showed no changes in F-cells or γ mRNA. Day 11 Hydroxyurea and RN-1 (2.5mg/kg) showed a small but significant increase in F-cells with a doubling in γ mRNA. At days 5 and 11 DAC and RN-1 (5 mg/kg) showed a doubling in F-cells and 5 fold increase in γ mRNA levels. F cells and γ-mRNA in mice treated with RN-1 (5mg/kg) were significantly higher than hydroxyurea and TCP at day 11.

Conclusion: These results demonstrate that RN-1, a recently developed LSD-1 inhibitor with increased potency and selectivity compared to TCP, increases γ-globin expression in γ-globin expression to higher levels than hydroxyurea and comparable levels to decitabine with no measurable effect on erythroid differentiation.
GROWTH FACTOR INDEPENDENCE (GFI)-1 POST-TRANSLATIONAL MODIFICATION IN HEMATOPOIETIC DIFFERENTIATION

Luke Maese, Matthew Velinder, Daniel Andrade, Diana Bareyan, Jason Singer, Helena Lucente, David McClellan, Michael Engel. University of Utah, Huntsman Cancer Institute, Salt Lake City, Utah, United States of America

**Background:** GFI proteins are master regulators of multi-lineage fate specification. The GFI family has two members, GFI1 and GFI1B. Despite similar structures, they control distinct hematopoietic outcomes. Erythropoiesis and megakaryopoiesis require GFI1B. GFI1 is required for neutrophil differentiation and stem cell maintenance. Gfi1 -/- mice are profoundly neutropenic. Mutations in GFI1 cause congenital neutropenia yet enforced GFI1B expression in a Gfi1 -/- background fails to completely complement the null phenotype. This suggests differing roles for these proteins, yet how they direct lineage allocation in hematopoiesis is incompletely understood. We identified SUMOylation as a post-translational modification that regulates GFI1-mediated transcriptional repression. We have identified lysine (K)-239 as a SUMOylation site in GFI1 and shown its impact on GFI1 function in transcription.

**Objectives:** Determine contributions of GFI1 SUMOylation to neutrophil development in cells committed to a myeloid fate.

**Design/Method:** HL-60 cells express GFI1, display commitment along a myeloid lineage, and differentiate into neutrophils when treated with all-trans retinoic acid (ATRA). Using RNA interference techniques, we will leverage ATRA-mediated differentiation of HL-60 cells to assess the role of GFI1 and its derivatives in late stage myeloid differentiation.

**Results:** We show GFI1 represses transcription, and this can be reversed by the E3-SUMO ligase, PIAS3. GFI1 is SUMOylated on K239. K239R mutant GFI retains transcriptional repression, but is insensitive to reversal by PIAS3. Using a zebrafish model of developmental hematopoiesis, we show that GFI1-K239R fails to complement the hematopoietic defect resulting from Gfi1aa depletion. This suggests GFI1 SUMOylation is essential during hematopoietic development. Extending these observations, we show Gfi1 depletion in HL60 cells blocks neutrophilic maturation beyond the promyelocyte stage. The need for SUMOylation of GFI1 in neutrophil fate specification is being actively explored.

**Conclusion:** Our findings in zebrafish suggest SUMOylation of GFI1 within its linker is a critical determinant of successful hematopoietic development within the myelo-erythroid compartment, and intimate an essential contribution to late stages of neutrophil specification as well. Understanding the regulatory events that control GFI1 function is fundamental to correcting constitutional and acquired neutropenias.
NOVEL RIBOSOMAL AND AUTOSOMAL RECESSIVE NON-RIBOSOMAL PROTEIN GENE CANDIDATES IN DIAMOND BLACKFAN ANEMIA (DBA)

Jason Farrar, Ross Fisher, Kelly O'Brien, Robert Arceci, Steven Ellis, Jeffrey Lipton, David Bodine, Adrianna Vlachos. Univ Arkansas Medical Sciences/Arkansas Children's Hosp, Little Rock, Arkansas, United States of America

**Background:** DBA is a congenital bone marrow failure syndrome characterized by anemia, congenital anomalies and predisposition to cancer. Approximately 65% of DBA patients have heterozygous mutations or deletions in ribosomal protein (RP) genes encoding components of the large or small ribosomal subunit. Current data suggests that most abnormalities in the remaining 35% of patients are not caused by RP gene abnormalities.

**Objectives:** To identify novel DBA genes in patients lacking mutations in the DBA-associated RP genes, we performed a sequential molecular characterization in a cohort of DBA patients from the Diamond Blackfan Anemia Registry (DBAR).

**Design/Method:** We evaluated these patients for copy number variation (CNV) at RP loci by SNP and comparative genomic hybridization microarray. We subsequently used whole exome sequencing (WES) to identify candidate gene mutations in 4 DBA kindreds who lacked both RP gene mutations and copy variation. After filtering common variants, we prioritized candidates within each pedigree based on inheritance pattern, degree and pattern of erythroid lineage expression and computationally-predicted functional impact. We also tested the importance of novel candidate genes in erythroid differentiation assays of normal CD34+ progenitors after shRNA-mediated knockdown.

**Results:** We identified one subject in CNV analysis with a de novo 3.2 Mb deletion on chromosome 2 that includes RPL31, a large ribosomal subunit protein not previously implicated in DBA. We identified an average of 3-5 high priority variants per kindred in the WES studies that were consistent with either a sporadic autosomal dominant mutations or with an autosomal recessive pattern of inheritance. No candidate genes were commonly affected among more than 1 DBA family in this cohort. We prioritized 2 genes, MCM2 and FLNB, for further study. Compared to controls, lentiviral-mediated shRNA knockdown of RPL31, MCM2 and FLNB markedly skews differentiation of CD34+ hematopoietic progenitors from erythroid to megakaryocyte differentiation and significantly reduces BFU-E compared to CFU-GM colony formation.

**Conclusion:** These results suggest RPL31 is a rare DBA-associated large subunit RP gene. Additionally, these data suggest the first putative autosomal recessive mutations in DBA involving non-ribosomal protein genes and demonstrate an important role for these genes in erythropoiesis.
A MICRO-RNA MEDIATED SIGNALING PATHWAY CONSTRAINS THE HEMATOPOIETIC STEM CELL POOL IN FANCONI ANEMIA
Kelsie Storm, Ashley Kamimae-Lanning, Katy Lawson, Natalya Goloviznina, Peter Kurre. Oregon Health and Science University, Portland, Oregon, United States of America

Background: Fanconi anemia (FA) is a recessively inherited DNA repair disorder that leads to bone marrow failure in 90% of affected individuals. Despite characterization of the FA pathway in DNA crosslink repair, its role in hematopoietic stem and progenitor cell (HSPC) maintenance remains elusive. While most FA mouse models reveal loss of self-renewal only after HSPC transplantation, we previously reported unprovoked, in utero hematopoietic deficits in Fancc mice. These results suggest that rapid, self-renewing divisions in the hematopoietic stem cells (HSC) of the fetal liver require the integrity of the FA pathway and present a previously unrecognized opportunity for the study of FA HSPCs without experimental induction. The enhanced self-renewal capacity of the fetal HSC pool was recently shown to involve Lin28, let-7 family microRNA, and HMGA2.

Objectives: Here, we hypothesize that the Lin28/let-7/HMGA2 axis and upstream regulator mir125b orchestrate a signaling pathway that compromises fetal liver HSC pool expansion in FA.

Design/Method: We harvested fetal livers from mice with Fancc and Fancd2 disruption at embryonic day 14.5 and determined quantitative and qualitative progenitor cell content and expression of candidate messenger and microRNA.

Results: Liver HSPCs from Fancd2-/- fetuses recapitulate the phenotype we previously described in Fancc-/- fetuses, demonstrating 50% less total cellularity with a 25% decrease in progenitor cell population and characteristic sensitivity to a DNA crosslinking agent. Within the enriched hematopoietic progenitor population, mir125b and let7b transcription was decreased by half in Fancc-/- and Fancd2-/- fetuses and transcription of Lin28 and Hmga2 was concomitantly increased. Further, we found evidence of DNA damage in FA fetal liver progenitors via increased transcription of DNA repair genes Prkdc, Xrcc5, Xrcc6, Rad51, and Xrcc2.

Conclusion: A key developmental pathway governing self-renewal is dysregulated in FA fetal liver HSPCs. Downregulation of mir125b in FA progenitors is consistent with its previously reported response to DNA damage. Hmga2 overexpression favors a self-renewing phenotype dependent on efficient cellular replication. Ongoing experiments now investigate the role of replication stress induced DNA damage in constraining fetal FA progenitor expansion.
Plenary Session # 4009

EVENT FREE (EFS) AND OVERALL SURVIVAL (OS) FOR CHILDREN WITH DOWN SYNDROME (DS) and B-LYMPHOBLASTIC LEUKEMIA (B-ALL) IN CHILDREN'S ONCOLOGY GROUP (COG) CLINICAL TRIALS AALL0232 and AALL0331

Kelly Maloney, Eric Larsen, Meenakshi Devidas, Len Mattano, Alison Friedmann, Jule M. Gastier-Foster, Drew Carroll, Nyla Heerema, Michael Borowitz, Brent Wood, James Whitlock, Mignon Loh, Elizabeth Raetz, Naomi Winick, Stephen Hunger, William Carroll. Children's Hospital Colorado, Aurora, Colorado, United States of America

Background: Children with DS-ALL have an increased risk of toxicity and mortality. Recent COG B-ALL trials AALL0232 (high risk; HR) and AALL0331 (standard risk; SR) encountered excess early mortality leading to protocol modifications.

Objectives: To determine EFS and OS for DS-ALL on AALL0331 and AALL0232.

Design/Method: AALL0232 used an augmented BFM backbone with randomized comparisons of 28 days of prednisone vs. 14 days of dexamethasone (DXM) during induction (IND), and high dose methotrexate (MTX) with leucovorin rescue vs. escalating IV MTX without rescue plus PEG asparaginase using the Capizzi schedule (CMTX) in interim maintenance (IM). DS-ALL patients participated in the induction steroid randomization, but were non-randomly assigned to CMTX. COG AALL0331 utilized a 3-drug induction with DXM for 28 days, vincristine and PEG asparaginase. Post-IND therapy included a randomization between intensified vs. standard consolidation, with CMTX in IM. DS-ALL participated in the randomization. Both studies experienced excessive induction mortality for children with DS initially and were modified with expanded supportive care guidelines and leucovorin rescue after intrathecal MTX. These modifications successfully eliminated excessive mortality on AALL0331; however, excessive mortality persisted in HR DS-ALL on AALL0232 and enrollment to this protocol was halted in 2008.

Results: AALL0232 (2003-2011) enrolled 3084 (39 DS-ALL) patients and AALL0331 (2005-2010) enrolled 5311 patients (140 DS-ALL). The combined 5-yr event-free (EFS) and overall survival (OS) for DS-ALL patients on both studies was 80±4% and 82.8±3.8% as compared to 84.3±0.6% (p=0.059) and 92.2±0.4% (p<0.001) for nonDS patients (NDS). On AALL0232, the 5-yr EFS for DS vs. NDS was 57.8±8.4% vs. 75.3±1.1% (p=0.007), and 5-yr OS was 60.3±8.3% vs. 85.4±0.9% (p<0.001). Interestingly, there were no events in DS patients after 3 years. For AALL0331, the 5-yr EFS for DS vs. NDS was 86.1±4.2% vs. 89.5±0.6% (p=0.102) and 5-yr OS was 89.2±3.8% vs. 96.1±0.4% (p<0.001).

Conclusion: DS patients on AALL0232 had inferior EFS and OS, largely due to increased toxic mortality rates. To address this problem, the current COG HR B-ALL study AALL1131 uses a modified 3-drug induction for DS-ALL patients. AALL0331 therapy was safe for DS patients, with similar EFS to NDS but significantly inferior OS.
BONE MARROW STROMAL CELLS FROM ACUTE MYELOID LEUKEMIA PATIENTS RELEASE EXOSOMES THAT RESCUE LEUKEMIA CELLS FROM KINASE INHIBITOR CHEMOTHERAPY
Shelton Viola, Jeff Tyner, Marcel Betsch, Brian Johnstone, Rajani Kaimal, Noah Nornick, Jianya Huan, Peter Kurre. Oregon Health & Science University, Portland, Oregon, United States of America

**Background:** Relapse in pediatric Acute Myeloid Leukemia (AML) remains unacceptably high. The leukemic bone marrow microenvironment has emerged as a setting where altered stromal cell function provides a sanctuary for leukemia cells through extrinsic drug resistance. The mechanism by which altered stromal cell function provides that protection is unclear. The release of cell membrane derived vesicles, including exosomes, is a constitutive cellular function, and we recently reported that exosomes transfer protein and RNA between cells in the AML niche (1). Stromal cell exosome trafficking as a mechanism for chemoresistance has not yet been studied.

**Objectives:** Here we hypothesize that AML patient bone marrow stromal cell exosomes (AML-BMSC’s) differ from those of healthy individuals (N-BMSC’s), and that the differences contribute to extrinsic drug resistance.

**Design/Method:** Bone marrow stromal cells were obtained from AML patients and healthy individuals. Exosomes were purified by differential ultra-centrifugation and analyzed for candidate mi-RNA and mRNA. Viability of MOLM-14 AML cells (Flt3-ITD+) exposed to the selective Flt3 tyrosine kinase inhibitor Quizartinib +/- exosomes from AML-BMSC’s or N-BMSC’s was measured using MTS assay.

**Results:** Stromal cells were selected by adherence, fibroblastic morphology, stromal transcript expression, CD90 positivity and CD45/CD34 negativity. Of the AML patient stromal cell exosome preparations assessed thus far (N=9), 88% (8/9) have shown a protective effect on the viability of MOLM-14 cells in the presence of Quizartinib, while normal controls (N=3) showed no protective effect, relative to exosome-free media. In examining the content of patient stromal exosomes (N=5 to date), all samples showed a significant increase in miR-155 content, as well as significant decreases in CXCL-1 and CXCL-12, relative to controls.

**Conclusion:** This is the first report of bone marrow stromal cell exosomes from AML patients and our results show consistent chemoprotection of AML cells by patient, but not control, exosome preparations. Ongoing analysis of exosome content demonstrates differences between patient and control exosomes in factors relevant to maintenance of residual hematopoietic function (CXCL-12, CXCL-1) and oncogenesis (miR-155), suggesting that the stromal component of the leukemic microenvironment is a potential therapeutic target. 1. Huang et al, Cancer Research, 2013.
ENHANCEMENT OF ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY TOWARDS NEUROBLASTOMA CELLS THROUGH COMBINATION OF GD2 MONOCLONAL ANTIBODY WITH ALLOGENEIC NK CELLS

Susanne Wendt, Wing Leung. St.Jude Children's Research Hospital, Memphis, Tennessee, United States of America

**Background:** Neuroblastoma cells almost uniformly express GD2, a disialoganglioside facilitating attachment of tumor cells to extracellular matrix proteins. GD2 is an ideal target for antibody-based immunotherapy via antibody-dependent cellular cytotoxicity (ADCC) as part of cancer-directed treatment. ADCC is mediated by T lymphocytes and NK cells. Current standard of care in neuroblastoma treatment allots immunotherapy after cytotoxic and immunosuppressive therapy.

**Objectives:** To study if transfer of allogeneic NK cells may enhance ADCC and improve tumor regression in a neuroblastoma mouse model.

**Design/Method:** Flow cytometry was performed to evaluate multiple neuroblastoma cell lines for GD2 expression. Cytotoxicity assays were used in vitro to compare specific lysis of neuroblastoma cells through NK cells with and without prior incubation with a GD2 monoclonal antibody (GD2 mAB). In an in-vivo model, neuroblastoma mice received either monotherapy with cyclophosphamide, or NK cells, or GD2 mAB versus a combination of these modalities in a defined order and schedule. Tumor progression was measured through bioluminescence of luciferase-expressing tumor cells.

**Results:** In-vitro, combination of GD2 mAB and NK cells lead to an appr. 5-fold increased specific lysis of neuroblastoma cells in a dose-dependent manner. In vivo, mice who received combination therapy, showed slower tumor growth and longer survival than mice after monotherapy. No increase in treatment-related deaths was observed in the mice with combination therapy.

**Conclusion:** Allogeneic NK cell transfer to enhance ADCC during immunotherapy is safe and effective in a neuroblastoma mouse model. Further investigation is needed to determine the optimal order of application as well as the minimal effective dose of both NK cells and mAB to achieve the best possible efficacy.
DFMO REVERSES THE LIN28/LET-7 AXIS AND INHIBITS GLYCOLYTIC METABOLISM IN NEUROBLASTOMA

Giselle Sholler, Ann Lozier, Maria Rich, Akshita Dutta, Anderson Peck, Ping Zhao, Anthony Chang. Helen DeVos Children's Hospital, Grand Rapids, Michigan, United States of America

**Background:** Overexpression of LIN28 correlates with poor outcome in neuroblastoma (NB). Recent studies have shown that ornithine decarboxylase (ODC) inhibition decreases LIN28 levels, thereby reversing the LIN28/Let-7 axis. The LIN28/Let-7 axis affects many cellular processes including cell differentiation and glycolytic metabolism. The LIN28/Let-7 axis also affects MYCN, often overexpressed in high risk NB.

**Objectives:** We propose that therapy targeting ODC will reverse the LIN28B/Let-7 axis in NB, thus suppressing tumor glycolytic metabolism and decreasing MYCN protein expression. We also propose that cells overexpressing LIN28B will have greater sensitivity to difluoromethylornithine (DFMO) treatment which inhibits ODC and decreases cellular polyamines.

**Design/Method:** Experiments were conducted using two MYCN high-expression NB cell lines, BE (2)-C and SMS-KCNR, and one MYCN low-expression cell line, CHLA90. Calcein AM measured cell viability. Western blot measured changes in LIN28 and MYCN, qRT-PCR showed changes in Let-7 miRNA. Cell Titer GLO assay, which measures total ATP levels, combined with the CyQuant DNA assay to measure ATP level/cell. Xenograft models with SMSKCNR cells were evaluated using PET scan.

**Results:** NB cells overexpressing LIN28B are more sensitive to treatment with DFMO. Gene expression profiling revealed elevated levels of LIN28B and MYCN in BE(2)-C and SMS-KCNR, but not in CHLA90. Cell viability testing indicated that sensitivity to DFMO treatment correlated with LIN28B overexpression. Reversal in the LIN28/Let-7 axis after treatment with DFMO was seen, as well as a decrease in cellular metabolic activity. DFMO treatment reduces LIN28B and MYCN protein levels and qRT-PCR showed increased Let-7 miRNA levels in BE(2)-C and SMS-KCNR cell lines with DFMO. Metabolic activity was seen to decrease with DFMO treatment as indicated by ATP/cell analysis. Patient data and in vivo studies further validated the findings that DFMO treatment reduces glycolytic metabolism as observed by a decrease in PET activity.

**Conclusion:** DFMO targets the LIN28/Let-7 and MYCN pathways in NB. Both Phase I patient and in vivo PET scans showed decreased glucose uptake and glycolytic metabolism in NB. These pathways are involved in cancer stem cell targeting. These studies demonstrate the potential for using DFMO to target glycolytic metabolism in NB and potentially may target cancer stem cells.
EGFR AND MTORC1 SIGNALING PATHWAYS ARE NOVEL TARGETS IN PEDIATRIC GERM CELL TUMORS
Dinesh Rakheja, Kenneth Chen, Nicholas Fustino, Abhay Shukla, Jonathan Wickiser, Theodore Laetsch, James Amatruda. University of Texas Southwestern Medical Center, Dallas, Texas, United States of America

Background: Germ cell tumors (GCTs) affect children and young adults, and testicular germ cell tumor is the most common cancer in young men. While cisplatin treatment has been successful for many GCTs, patients whose GCTs are refractory to cisplatin have a poor prognosis. Further, even patients who are cured suffer long-term side effects including hearing loss, kidney damage and secondary malignancies. GCTs can occur as undifferentiated seminomas, or non-seminomas, which exhibit differentiation. The genes and pathways that contribute to the development of GCTs are incompletely understood, which is a serious impediment to the development of targeted therapy.

Objectives: Determine targetable pathways that are activated in germ cell tumors.

Design/Method: We used quantitative RT-PCR to measure the expression of growth factor receptors in pediatric GCTs, immunohistochemistry (IHC) on a panel of clinically annotated germ cell tumors, and resazurin cell viability assays on GCT cell lines (NCCIT and Ntera-2) to determine the effect of inhibition of these pathways on cell viability.

Results: By RT-PCR, we found that multiple members of the EGF and FGF receptor families are more highly expressed in non-seminomas than seminomas. Further, EGF and FGF2 stimulate both the Ras-MAPK and PI3K/mTOR signaling in GCT cell lines. We determined that both the Ras-MAPK and PI3K-mTOR pathways are highly active in non-seminomas based on IHC staining of phosphorylated ERK1/2, mTOR, and S6 ribosomal protein. Based on these results, we tested the effect of small-molecule inhibitors of EGFR and mTORC1 on growth and survival of GCT cell lines in vitro. While mTOR inhibition with rapamycin decreased cell viability, the IC50 was >10uM in cell lines, a concentration that is not clinically achievable. However, we found that the combination of the EGFR inhibitor erlotinib and rapamycin potently and synergistically (>1000-fold sensitization) inhibited the growth of two GCT cell lines and that cells were sensitive to the combination of these agents at clinically achievable concentrations (1uM and 10nM respectively).

Conclusion: Non-seminomatous germ cell tumors are dependent on EGFR and mTOR signaling in vitro. Based on these results we have developed a Phase II trial using targeted therapy for the treatment of recurrent, chemoresistant GCTs in children and young adults.
EPITOPE RECOGNITION AND IMMUNE RESPONSE TO EXTRACELLULAR DOMAIN OF HER-2/NEU ONCOPROTEIN IN MICE
Girmay Tekle-Yohannes, Gregory Plautz, Li-Xin Wang. Cleveland Clinic, Cleveland, Ohio, United States of America

**Background:** Background: Her-2/Neu gene is amplified in certain childhood and adult cancers. Natural immunity against Her-2/Neu is low magnitude or negative due to immune tolerance in cancer microenvironment.

**Objectives:** Objective: Characterize immune response and identify epitope regions of Her-2/Neu oncoprotein.

**Design/Method:** Methods: Wild type (WT) and neu-N transgenic mice were vaccinated subcutaneously with irradiated HER-2+ mammary carcinoma (MMC-10) cell line (dose = 20 million). Nine days later tumor draining lymph nodes (TDLNs) were harvested. From the TDLNs vaccine-primed CD62L(low) lymphocytes, and subsets of CD4+ and CD8+ T-cells were purified using magnetic-activated cell sorting (MACS) beads. The lymphocytes were then expanded in vitro using anti-CD3/IL-2/IL-7 stimulation. The T-cells were cultured with peptides and splenocytes. The splenocytes were harvested from naïve WT mice. The peptides were derived from extra-cellular domain (ECD) of Her-2 protein (constructed as 20 mer with 10 mer overlapping segment). Control lymphocytes were incubated without peptides. Immune response was measured using ELISA for IFN-γ and IL-2 levels in the supernatants.

**Results:** Results: TDLN-derived CD62L(low) T-cell showed immune response to one peptide (p411-430) in the WT mice. The IFN-γ response of lymphocytes against this peptide was 3.5-fold higher than the control. IFN-γ response of purified CD8+ cell to peptide p411-430 was 40-fold higher than the control. However, CD4+ cell response was similar or lower than the controls. Lack of Th-cell response was confirmed using IL-2 assay on a separate experiment. Fluorescence-activated cell sorting (FACS) analysis for T-Cell receptor (TCR) repertoire usage showed oligoclonal response to whole cell vaccine. In vitro re-stimulation with the peptide p411-430 showed similar TCR repertoire usage. Lymphocytes from transgenic mice did not exhibit immune response to any of the peptides as determined by IFN-γ or IL-2 assays.

**Conclusion:** Conclusions: One dominant CTL epitope region (p411-430) of Her-2/neu oncoprotein was identified in the WT mice using our method. This peptide contains previously reported MHC-1 restricted epitope p420-429. However, transgenic mice were tolerant to the ECD-Her-2/Neu protein. Novel mechanisms to circumvent immune tolerance are needed for successful Her-2/neu-based immunotherapy. Other epitopes reported in previous studies were not detected in our study, underscoring the importance of vaccination strategies in cancer immunotherapy.
INDUCTION MORTALITY AND ITS ASSOCIATION WITH INVASIVE FUNGAL INFECTIONS (IFI) IN CHILDREN AND YOUNG ADULTS WITH HIGH RISK (HR) B-LYMPHOBLASTIC LEUKEMIA (B-ALL): EARLY RESULTS FROM CHILDREN’S ONCOLOGY GROUP STUDY AALL1131

Salzer, Wanda Salzer, Mike Burke, Meenakshi Devidas, Lia Gore, Eric Larsen, Theoklis Zaoutis, Brian Fisher, William Steinbach, Joanne Hilden, Mignon Loh, Naomi Winick, William Carroll, Elizabeth Raetz, Lillian Sung, Stephen Hunger. U.S. Army Medical Research and Materiel Command, Frederick, Maryland, United States of America

Background: Children and young adults with HR B-ALL are at risk of death during Induction (1.5-3%), mostly due to infection.

Objectives: To assess the Induction mortality rate and patterns of death on AALL1131.

Design/Method: AALL1131 is a Phase III trial for patients 1-30.99 years (yrs) old with newly diagnosed HR B-ALL. Induction consists of vincristine, daunorubicin, dexamethasone (<10 yrs) or prednisone (>10 yrs), PEG-asparaginase, and age-adjusted intrathecal therapy. Induction regimens are identical to the prior HR B-ALL study AALL0232, with the exception of intravenous vs. intramuscular PEG-asparaginase.

Results: Early data (11/8/2012), revealed a higher than expected Induction mortality rate of 3.1% (9/286) compared to 1.98% (dexamethasone arm) and 1.8% (prednisone arm) on AALL0232. IFI were identified in six of the nine deaths (two definitely and three possibly/probably related to the death). In evaluating infectious deaths, no clear patterns emerged related to clustering at institutional/regional level, age or body surface area, inpatient/outpatient status, hyperglycemia, or antimicrobial prophylaxis. Five subjects were exposed to active construction. Investigators and families were notified and AALL1131 was amended to include monitoring rules for both Induction mortality rate and deaths attributed to IFI. As of 12/02/2013 the Induction death rate is a stable 2.05% (20/975): <10 yrs - 10/356 (2.8%); 10-14.99 yrs - 5/353 (1.4%); and >15 yrs - 5/266 (1.9%). Deaths resulted from: infection (n=16), respiratory arrest (n=1), multi-organ failure/cardiac arrest (n=1), pancreatitis (n=1), and hepatic failure (n=1). Infections, often mixed, included Gram-positive (n=6), Gram-negative (n=5), and fungal (n=9) organisms. IFIs included: Aspergillus (n=3), mucormycosis (n=2), mucormycosis and Aspergillus (n=1), Trichosporon ashii (n=1), Candida krusei (n=1), and Candida parapsilosis (n=1).

Conclusion: Early data raised concern for increased Induction mortality and IFI related deaths on AALL1131 but continued follow-up demonstrates mortality rates consistent with past studies. This highlights the need for caution when interpreting analysis of small sample sizes with few events. IFI were identified in about half of those with infectious deaths. However, IFI related deaths were still relatively rare and the identified fungal pathogens widely variable, limiting a recommendation for routine prophylaxis with a single antifungal agent. Continued follow-up with a focus on IFI is warranted.
CORTICOSTEROID PRETREATMENT IS NOT AN INDEPENDENT RISK FACTOR IN PEDIATRIC PATIENTS WITH NEWLY DIAGNOSED B-LYMPHOBLASTIC LEUKEMIA (B-ALL): RESULTS FROM CHILDREN’S ONCOLOGY GROUP (COG) STUDY AALL03B1

Elizabeth Raetz, Brent Wood, Michael Borowitz, Naomi Winick, Stephen Hunger, William Carroll, Mignon Loh, Meenakshi Devidas, Kelly Maloney, Len Mattano, Eric Larsen, Andrew Carroll, Nyla Heerema, Julie Gastier-Foster. University of Utah, Salt Lake City, Utah, United States of America

**Background:** Leukemic blasts are very sensitive to corticosteroids; exposure prior to ALL diagnosis may alter interpretation of the initial white blood cell count (WBC)/risk group and treatment response during Induction. Previously, Children’s Cancer Group and Pediatric Oncology Group B-ALL trials did not enroll patients with steroid pretreatment.

**Objectives:** To determine the prognostic impact of steroid pretreatment prior to B-ALL diagnosis.

**Design/Method:** Patients ages 1-31 years were enrolled on a uniform disease classification study, COG AALL03B1, at the time of B-ALL diagnosis and were risk stratified at the end of Induction therapy. Steroid pretreatment was assessed and used to modify risk group. Variables assessed included the duration and timing of steroid exposure before diagnosis and the availability of a pre-steroid WBC. Without a pre-steroid CBC, patients receiving steroid pretreatment in the week preceding diagnosis were assigned to a high risk (HR) treatment protocol (COG AALL0232). Patients who received >48 hours of corticosteroids were assigned to augmented treatment regimens.

**Results:** From 2003-2011, 8388 patients were enrolled on AALL03B1 and companion COG therapeutic trials for NCI standard or high risk B-ALL (SR; AALL0331, n=5304) (HR; AALL0232, n=3084); 284 (3.4%) received steroid pretreatment (82 on AALL0331, 202 on AALL0232). Analyzing all patients together, steroid pretreatment was significantly associated with age ≥ 10 years (P <0.0001); presenting WBC ≥ 50,000/µL (P <0.0001); Day 29 minimal residual disease (MRD) ≥ 0.1% (P=0.0003) and central nervous system (CNS) leukemia (CNS3) (P <0.0001). Five-year event-free (EFS) and overall survival (OS) rates were 84.3%±0.5% vs. 80.1%±3.6% .1 (P=0.0163) and 92%±0.4% vs. 87.4%±3.0% (P=0.0070) respectively, in non-steroid pretreated vs. steroid pretreated patients. In analyzing patients enrolled on AALL0331 and AALL0232 separately, there were no significant differences in end Induction remission rates, EFS or OS in non-steroid pretreated vs. steroid pretreated patients. Moreover, in multivariate analysis including NCI risk group and Day 29 MRD ≥ 0.1%, steroid pretreatment was not an adverse prognostic factor (Hazard Ratio 1.097; P=0.6584).

**Conclusion:** Steroid pretreatment is not an independent risk factor when patients with B-ALL receive risk adjusted therapy with modifications based on duration and timing of steroid exposure and ascertainment of a pre-steroid CBC.
PHARMACOGENETIC DIRECTED DOSING LEADS TO OPTIMIZED VORICONAZOLE LEVELS IN PEDIATRIC PATIENTS RECEIVING HEMATOPOIETIC STEM CELL TRANSPLANTS
Ashley Teusink, Alexander Vinks, Kejian Zhang, Stella Davies, Alexandra Filipovich, Tsuyoshi Fukuda, Parinda Mehta. Cincinnati Children's Hospital Medical Center and CIBMTR, Cincinnati, Ohio, United States of America

Background: Voriconazole, one of the commonly used antifungal agents, is known to have wide inter- and intra-patient variability in levels that are affected by a common CYP450-2C19 polymorphism. We have previously shown that voriconazole dosing of 5 mg/kg/dose every 12 hours is not sufficient to achieve target prophylactic goal levels.

Objectives: The aim of this follow-up study was to determine if genotype directed initial voriconazole dosing and subsequent adjustment based on our new algorithm will decrease time to desired target level for fungal prophylaxis.

Design/Method: Patients undergoing HSCT at Cincinnati Children’s Hospital Medical Center who received voriconazole fungal prophylaxis (June 2013 and September 2013) were followed prospectively. All were genotyped for CYP450-2C19; known to alter voriconazole metabolism (normal, fast or slow metabolizers). Initial voriconazole dose was decided based on the patient’s genotype and changes in dose were made to achieve concentrations within the target range of 1 mcg/mL to 5 mcg/mL.

Results: A total of 20 patients, aged 10 months to 26 years received voriconazole prophylaxis based on their CYP450-2C19 genotype and according to the predetermined algorithm. The median time to reach the target level was 8 days (range 2-47 days). This was significantly improved compared to time to target level in our pilot study (median 30 days range 3-67 days) (p < 0.001) (figure 1).

Conclusion: Our results show that CYP450-2C19 genotype directed initial dosing and subsequent dose adjustments as per our predetermined algorithm, can successfully achieve prophylactic voriconazole target levels in pediatric patients undergoing HSCT.

Time to Target Voriconazole Levels
Pharmacokinetic Range (1–5)

- Patients Started at 5 mg/kg/dose
- Dosing directed by CYP genotype and new dose escalation algorithm

Log Rank p-value ≤ 0.001
PROVIDER ADHERENCE TO ORAL CHEMOTHERAPY DOSE ADJUSTMENT GUIDELINES IN THE TREATMENT OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
Amy Fowler, David Leonard, Tamra Slone, Christian Tellinghuisen, Alexis Kennedy, Patrice Griffith, Naomi Winick. University of Texas Southwestern, Dallas, Texas, United States of America

Background: A maintenance phase with nightly oral 6-mercaptopurine (6MP) and weekly methotrexate (MTX) is a universal component of therapy for patients with ALL. Dosing guidelines are provided in standardized chemotherapy protocols. Both dose intensity of these agents and the degree of myelosuppression during maintenance have been correlated with risk of relapse. Many protocols target an absolute neutrophil count (ANC) of between 500/μL and 1,500/μL. A retrospective review of our patients with ALL demonstrated a median ANC of over 2100/μL during maintenance; higher than the target range. Further analysis demonstrated that providers adhered to protocol indicated dose escalations only 39% of the time.

Objectives: To improve provider adherence to guidelines for oral chemotherapy dose adjustments from 39% to > 75% during the six month study period (1/1/2011-6/30/2011).

Design/Method: Providers were surveyed to assess reasons for non-adherence. We initiated a campaign with providers and nursing regarding the importance of adherence and details of the guidelines. Process mapping was used to identify problems in clinic flow, and changes were made in the clinic visit process, to facilitate follow up of laboratory results. Flow sheets were designed to provide easy access to blood counts and dosing information. Provider adherence was defined as the percentage of time a dose escalation was made when indicated by guidelines. A trained set of providers evaluated each outpatient encounter during the study period to determine if the decision made was consistent with the dose delivery guidelines. During the intervention period we collected each patient’s median ANC and number of neutropenic episodes.

Results: Following the interventions, monthly adherence rates rose to >80% for each study month and the median ANC decreased from > 2100/μL to 1800/μL. There was no increase in number of neutropenic episodes (ANC <500/μL).

Conclusion: We achieved our goal improving adherence to dosing guidelines to >80% through increasing awareness and knowledge of the guidelines, creating easy access to relevant clinical information, and improving clinic flow to increase the likelihood of provider follow up. Larger trials are needed to assess the efficacy and risks associated with more aggressive dose modifications.
**Background:** T-cells can be genetically modified to target tumor antigens through the expression of a chimeric antigen receptor (CAR).

**Objectives:** Target the CD19 antigen using the CD19-specific CAR (19-28z) in patients with relapse B-ALL.

**Design/Method:** Phase I dose escalation clinical trial in pediatric/young adult patients utilizing 19-28z CAR T-cells (MSKCC IRB Protocol #13-052; NCT 01860937).

**Results:** Our center has treated 19 adult and pediatric patients with relapsed B-ALL using patient derived 19-28z CAR T-cells. Overall 15/19 patients (79%) had a complete response (complete remission + complete remission with incomplete count recovery) with 13/19 (68%) demonstrating a complete remission (MRD negative) as determined by flow cytometry or deep sequencing of IgH clonotype. To date, eight pediatric patients have been enrolled on study and five have been treated according to protocol. Age of patients enrolled for T-cell collection ranged from 2-23 years and ranged from 14-23 years for patients treated with 19-28z CAR T-cells. Severe cytokine release syndrome (sCRS) defined by fever for ≥3 consecutive days, elevated serum cytokine levels, and one clinical sign of toxicity (hypotension, hypoxia, neurologic disorder including altered mental status, obtundation, and/or seizure) occurred in 8/19 patients (42%) including 2/5 pediatric/young adult patients. Morphologic disease (≥5% bone marrow blasts) at time of treatment was present in all patients with sCRS and systemic immunosuppressants (corticosteroids or anti-IL6 receptor antibody tocilizumab) abrogated clinical symptoms of sCRS. Elevated serum cytokines of IFN-gamma (>20 fold), fractalkine (>25 fold), FLT-3 (>60 fold) and IL-6 (>160 fold) was demonstrated in one pediatric patient with sCRS. Monitoring of bone marrow demonstrated peak 19-28z CAR T-cell detection within 1-2 weeks following infusion with gradual contracture over 2-3 months.

**Conclusion:** These early results demonstrate the feasibility and significant clinical impact of this approach. To more rapidly generate statistically relevant data, demonstrate the “exportability” of this technology, and offer this therapeutic option to a broader number of patients our trial will expand into a phase I multicenter clinical trial with a collaborating institution. Subsequent cohorts of patients will receive dose escalation of modified T-cells and will be evaluated for toxicity, persistence of 19-28z CAR T-cells, and for anti-tumor efficacy.
GENETICALLY MODIFIED T CELLS SIMULTANEOUSLY TARGET HER2 AND GD2 TO ENHANCE THE CONTROL OF OSTEOSARCOMA
Meenakshi Hegde, Amanda Wakefield, Tiara Byrd, Kristen Fousek, Eric Yvon, Stephen Gottschalk, Helen Heslop, Gianpietro Dotti, Mathew Baker, Nabil Ahmed. Texas Children's Cancer Center, Baylor College of Medicine, Houston, Texas, United States of America

Background: Adoptive transfer of chimeric antigen receptor (CAR) T cells has shown remarkable efficacy against some resistant pediatric cancers. In preclinical models, HER2-specific CAR-T cells exhibited potent anti-osteosarcoma (OS) activity; however, tumor recurred in ~40% of treated animals after initial regression, in part due to the heterogeneous nature of the tumor, resulting in antigen escape.

Objectives: To develop a T-cell product that could offset antigen escape and enhance the control of OS by simultaneously targeting HER2 and GD2.

Design/Method: We studied the expression of HER2 and GD2 in 12 OS cell lines using flowcytometry. We created a novel bispecific CAR that incorporates two extracellular antigen-recognition domains; one for HER2 (derived from HER2 monoclonal antibody FRP5) and the other for GD2 (derived from GD2 monoclonal antibody 14g2a), in tandem (TanCAR). TanCAR was rationally designed by in silico modeling. The intracellular domain consisted of a CD28 and zeta-signaling chains that mediate T-cell activation upon antigen encounter. The TanCAR encoding DNA was then synthesized, sequence verified and force expressed on primary human T cells using a retroviral system. The functionality of HER2/GD2 bispecific TanCAR-T cells was evaluated using standard immunoassays.

Results: OS cell lines showed varying expression patterns of HER2 and GD2: LM7 was HER2/GD2 +/+ , HOS HER2/GD2 +/- and IOR/OS9 was HER2/GD2 -/+ . B-cell lymphoma cell line Raji, was used as a HER2/GD2 -/- control. The surface expression of extracellular domain of the TanCAR in its entirety was confirmed using HER2- and GD2- specific methods on flowcytometry. In cytotoxicity assays, TanCAR-T cells distinctly recognized and killed HER2 and GD2 expressing OS cells as well as those expressing either HER2 or GD2 only. Further, TanCAR-T cells released immunostimulatory cytokines upon encounter of HER2 and/or GD2 expressing tumor cells. Importantly, bispecific TanCAR-T cells sustained their anti-tumor activity at low T-cell to tumor cell ratios.

Conclusion: HER2/GD2 bispecific TanCAR-T cells can distinctly target HER2 or GD2 individually as well as both antigens simultaneously. In the absence of a universal OS-associated antigen to achieve complete tumor eradication with targeted therapy, simultaneous targeting of two or more antigens could potentially reduce the risk of recurrence.
A UNIQUE DESCRIPTION OF STAGE IV EXTRANODAL MARGINAL ZONE LYMPHOMA (EMZL) IN AN ADOLESCENT ASSOCIATED WITH GAMMA HEAVY CHAIN DISEASE SHOWING EXCELLENT RESPONSE TO BENDAMUSTINE-RITUXIMAB
Nupur Mittal, Bing Zhu, Sujata Gaitonde, Frederick Behm, Yang Lu, Mary Lou Schmidt. University of Illinois at Chicago, Chicago, Illinois, United States of America

**Background:** EMZL is an extremely rare diagnosis in children. Most are localized involving the eye, skin or stomach with excellent prognosis however advanced stage EMZL in adults (median age at diagnosis 60 years) is considered incurable, although prolonged remissions may occur after multi-agent chemotherapy. Gamma heavy chain disease (γHCD) is a rare disease of adults mostly associated with lympho-proliferative processes. There are no comparable reports or consensus recommendations for therapy in children.

**Objectives:** We report a case of Stage IV EMZL and γHCD in an adolescent.

**Design/Method:** Review of medical literature.

**Results:** 15 yr old African American male presented after 3 months of asymmetrical tonsillar enlargement, weight loss, cough, chest pain, significant nasal congestion and difficulty breathing during sleep and after recent tonsillar biopsy. Exam revealed 5 x 4 cm periauricular, 3 x 3 cm occipital, 2 x 2 cm inguinal masses. PET scan confirmed stage IV. Pt underwent tonsillectomy/uvulectomy then subsequent periauricular mass biopsy. EMZL with concurrent γHCD was confirmed on morphology, flow cytometry and immunohistochemistry. Pt received 5/6 cycles: Bendamustine (90 mg/m² days 1, 2) + Rituximab (375 mg/m² day 1) with complete remission on exam and PET after 4 cycles. There was no monoclonal spike on serum protein electrophoresis, day 3 of cycle 1. EMZL in adults demonstrates a 5yr OS- 90%, 10yr OS- 80% and 5yr PFS - 60-70%. No reports of advanced stage EMZL in children were found. 6 cycles of Bendamustine/ Rituximab demonstrated >/= efficacy with less toxicity compared to R-CHOP in a randomized multi-center European trial (n=300, median age 60)[Lancet:April 2013]. There are < 150 reported cases of γHCD including no pediatric cases with management directed at control of underlying disease. In the largest series (23 patients) the median survival was only 7.4 yrs.

**Conclusion:** The rare association of advanced stage EMZL and γHCD and the paucity of data in young patients makes it impossible to predict the ultimate prognosis for this patient. The indolent nature of the disease in adults characterized by multiple recurrences raises the question of need for prolonged maintenance therapy. The combination of Bendamustine and Rituximab is an excellent option for treatment of patients with advanced disease EMZL.
LOCALLY ADVANCED CLEAR CELL ADENOCARCINOMA (CCA) OF THE CERVIX/VAGINA IN AN ADOLESCENT WITH NO DIETHYLSTILBESTROL (DES) EXPOSURE WITH EXCELLENT RESPONSE TO NEOADJUVANT CHEMOTHERAPY WITH CARBOPLATIN/PACLITAXEL
Nupur Mittal, Paul Kent, Alaa Alsadi, Saman Ibrahim. Rush University Medical Center, Chicago, Illinois, United States of America

Background: CCA is rare in woman <18 yrs with < 10 published reports post DES era and few of advanced stage. CCA is a slow growing tumor that is often chemo- resistant. There is no guidance on optimal management.

Objectives: Highlight a case of locally advanced Cervico-vaginal CCA with excellent response to neoadjuvant chemotherapy in an adolescent.

Design/Method: Review of Medical literature

Results: 14 yr old without maternal DES exposure with painless vaginal bleeding refractory to OCPs for 1 yr along with 12 lb weight loss and fatigue. Ultrasonography and MRI showed a large mass confirmed on biopsy to be CCA. PET-CT confirmed FIGO stage IIIa with pelvic lymph node involvement. Upfront surgery or radiation would have left her infertile. Therefore we offered neoadjuvant chemotherapy (carboplatin + weekly paclitaxel every 3 weeks. After 3 cycles there is an excellent response by imaging and tumor markers (fig 1). She is receiving local control with concurrent Cisplatin-radiation after relocation of ovaries. We found 7 reports of CCA in adolescents since 1971 but none treated with neoadjuvant chemotherapy. In patients <18 yrs, 3-year survival for localized and metastatic adenocarcinoma are 80% and 33% respectively. Concurrent chemo-radiation is the standard of care for adults with non-CCA locally advanced cervical cancer. Initial surgery is preferred in adolescents because of effects of radiotherapy on growth and fertility.

Conclusion: Cervico-vaginal malignancies must be considered in diagnosis of adolescents with vaginal bleeding often attributed to dysfunctional uterine bleeding. Our initial results support platinum-taxane based neoadjuvant chemotherapy in young women with advanced cervico-vaginal CCA.
AN UNUSUAL CASE OF PATIENT WITH HEPATOBLASTOMA
Irina Pateva, Rachel Egler, Rolla Abu-Arja, Duncan Stearns. Rainbow Babies and Children's Hospital, Cleveland, Ohio, United States of America

**Background:** Hepatoblastoma is a rare malignancy; approximately 100 cases are diagnosed yearly in the US. The highest incidence is in the 0-4 years age group, cases in patients > 5 years are very rare.

**Objectives:** To describe a patient who was diagnosed with hepatoblastoma at an unusual age. We review the epidemiology and summarize case reports of patients with hepatoblastoma > 5 years.

**Design/Method:** Ovid MEDLINE was searched for hepatoblastoma case reports and epidemiology reports for children between the ages of 5 to 18 years

**Results:** Our patient is an 11 year old boy with stage IV hepatoblastoma with lung and omental metastases at diagnosis. He received 6 cycles of chemotherapy, per COG protocol AHEP 0731, followed by tumor resection and omentectomy and achieved complete remission, but later had disease recurrence. He continues to receive therapy. Review of SEER program data shows that the incidence of hepatoblastoma in children > 4 years is too infrequent to be calculated. Literature review revealed 13 cases of patients diagnosed at age > 5 years (table 1). Most cases were published due to unusual associations and/or complications. There are no obvious unifying characteristics for these cases, although there may be a slight male preponderance and many patients in this selected series presented with elevated alpha-fetoprotein.

**Conclusion:** The reported case is rare given the very low incidence of hepatoblastoma outside of infancy. Systematic review of characteristics and outcomes for subjects older than 5 years, enrolled in cooperative group hepatoblastoma trials may reveal important information about tumor biology in this rare patient population.

<table>
<thead>
<tr>
<th>Case#</th>
<th>Author, year of report and country</th>
<th>Association reported</th>
<th>Age at Dx</th>
<th>Sex</th>
<th>AFP at Dx</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pereira et al. 2012, USA</td>
<td>Mosaic trisomy 18</td>
<td>10 years</td>
<td>F</td>
<td>1040 ng/ml</td>
<td>Free of disease recurrence 2 years after definitive resection</td>
</tr>
<tr>
<td>2</td>
<td>Tumino et al. 2010, Italy</td>
<td>Kabuki syndrome</td>
<td>6 years</td>
<td>M</td>
<td>920 ng/ml</td>
<td>Free of disease recurrence 2 years after end of treatment</td>
</tr>
<tr>
<td>3</td>
<td>Cosson et al. 2008, France</td>
<td>Methylomalonic aciduria</td>
<td>11 years</td>
<td>M</td>
<td>73.16 ng/ml</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>Mukhopadhyay et al. 2007, India</td>
<td>Down syndrome</td>
<td>17 years</td>
<td>F</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>5</td>
<td>D'Angelo et al. 2006, Italy</td>
<td>Developed Reversible Posterior Leukoencephalopathy Syndrome during treatment</td>
<td>13 years</td>
<td>M</td>
<td>Elevated, not known</td>
<td>Alive 23 months after RPLS</td>
</tr>
<tr>
<td>6</td>
<td>Iida et al., 2004, Japan</td>
<td>Present with severe anemia and liver dysfunction</td>
<td>12 years</td>
<td>M</td>
<td>Elevated, not known</td>
<td>Free of disease recurrence 25 months after surgery</td>
</tr>
<tr>
<td>7</td>
<td>Inagaki et al. 2001, Japan</td>
<td>Carrier status for HBsAg, chronic active hepatitis B</td>
<td>18 years</td>
<td>M</td>
<td>1548 000 IU/ml</td>
<td>Free of disease recurrence 12 months after diagnosis</td>
</tr>
<tr>
<td>8</td>
<td>Yamazaki et al. 2000, Japan</td>
<td>Pulmonary embolism during injection of lipiodol</td>
<td>7 years</td>
<td>M</td>
<td>Not known</td>
<td>Recovered from pulmonary embolism, not known</td>
</tr>
<tr>
<td>9</td>
<td>Morita et al. 2000, Japan</td>
<td>High plasma renin activity</td>
<td>8 years</td>
<td>M</td>
<td>2619 ng/ml</td>
<td>Disease free and normotensive 12 months after BMT</td>
</tr>
<tr>
<td>10</td>
<td>Bhattacharya et al. 1999, India</td>
<td>Presenting symptoms, fever, and anemia</td>
<td>6 years</td>
<td>M</td>
<td>Not known</td>
<td>Died</td>
</tr>
<tr>
<td>11</td>
<td>Bhattacharya et al. 1998, India</td>
<td>Abdominal pain and ileus as presenting sign</td>
<td>9 years</td>
<td>F</td>
<td>Not known</td>
<td>Lost to follow up</td>
</tr>
<tr>
<td>12</td>
<td>Bernard et al. 1997, Australia</td>
<td>Tumor was T1-2,01 positive and Ga-67 negative-different nuclear medicine tracers</td>
<td>12 years</td>
<td>M</td>
<td>Normal</td>
<td>Disease free 12 months after diagnosis</td>
</tr>
<tr>
<td>13</td>
<td>Hillard et al. 1997, USA</td>
<td>Retinal and renal toxicity associated with aspirin and etoposide</td>
<td>7 years</td>
<td>F</td>
<td>656 000 ng/ml</td>
<td>Died</td>
</tr>
</tbody>
</table>
A RARE PRESENTATION OF BONE MARROW ANGIOMATOSIS YEARS AFTER SUCCESSFUL TREATMENT FOR KAPOSIFORM HEMANGIOENDOTHELIOMA (KHE)
Mansi Sachdev, Melanie Comito, Michael Bayerl, Xingcao Nie. Penn State Hershey Medical Center, Hershey, Pennsylvania, United States of America

**Background:** KHE is a rare locally aggressive vascular neoplasm reported mainly in newborns and infants. It is often complicated by Kasaback-Merritt phenomenon (KMP). Majority of the cases are localized though small percentage of cases do present with diffuse lesions.

**Objectives:** Numerous case reports have identified KHE in non-cutaneous locations, including bone, mediastinum and retroperitoneum, but minimal literature exists regarding the development of angiomatosis of the bone marrow years after successful treatment of localized KHE.

**Design/Method:** Here we describe an unusual case of angiomatosis of the bone marrow developing years later in a patient who had successfully completed therapy for retroperitoneal KHE (complicated by KMP).

**Results:** Our patient was a 4-month old female who was diagnosed with extensive chest and retroperitoneal KHE with KMP without marrow involvement. She successfully completed treatment consisting of steroids, Cyclophosphamide, Vincristine and interferon-IIA after which her tumor had regressed substantially. At 4 years off-therapy, she developed thrombocytopenia which was initially thought to be ITP. Since she did not respond to IVIg, a bone marrow aspiration was done which was unremarkable. Since she continued to have thrombocytopenia, a repeat bone marrow aspirate/biopsy was done 3 months later which revealed angiomatosis of the bone marrow. Re-staging imaging was negative for local recurrence. She was diagnosed with disease recurrence now presenting with angiomatosis of the bone marrow that was not present on her initial diagnosis. She started treatment with alpha-interferon which was gradually increased to 2.1 million units 3 times/week, with resolution of her thrombocytopenia in about 3 months after starting treatment. After 14 months of interferon, she was started on Celebrex for its anti-angiogenic properties. Currently she is on once a week low dose interferon without recurrence of her thrombocytopenia, though bone marrow continues to show diffuse infiltration with blood vessels and marked hypocellularity.

**Conclusion:** This case illustrates that isolated angiomatosis of the bone marrow can occur years after successful treatment of KHE and that long term follow up in these cases is essential. There are reports of KHE affecting the bone at initial presentation but there is minimal literature regarding relapse of KHE as isolated angiomatosis of the bone marrow.
A FULMINANT EPISODE OF CLOSTRIDIUM SEPTICUM BACTEREMIA IN A CHILD WITH RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA
Muaz Alrazzak, Martin Brecher, Denise Rokitka. Roswell Park Cancer Institute, Buffalo, New York, United States of America

Background: Clostridium septicemia is a rare but often fatal infection in children. Although, it may occur in otherwise healthy children, it is more common in children with underlying immunodeficiency; especially those with hematologic malignancy. The clinical presentation is non-specific, particularly in patients receiving chemotherapy. The symptoms may include abdominal pain, vomiting, diarrhea, fever and chills. Myonecrosis, which manifests as severe musculoskeletal pain may represent muscular destruction due to the invasion of the organism and its toxins. Patients frequently develop septic shock with or without disseminated intravascular coagulation (DIC). The prognosis of clostridium septicum bacteremia is generally poor. Successful therapy requires early recognition and intervention with antibiotics and sometimes surgical intervention.

Objectives: To report a case of fulminant clostridium septicum bacteremia in a patient treated for relapsed ALL. We will discuss the pathophysiology, clinical presentation, management and prognosis of Clostridium septicemia in pediatric oncology patients.

Design/Method: The medical record including clinical presentation and laboratory data were reviewed.

Results: A 12 years old girl being treated for relapsed Acute Lymphoblastic Leukemia (ALL), who presented with fever, muscle pain and abdominal pain, progressed into septic shock and died within 7 hours of her presenting symptoms. Her blood culture grew clostridium septicum.

Conclusion: Clostridium septicum bacteremia is rare but is associated with high mortality rate in immune-compromised patients. The presenting symptoms are often non-specific, and consequently require a high index of suspension with early treatment intervention including broad spectrum antibiotics and frequently surgical intervention.
A CONCEPTUAL MODEL FOR PHYSICIAN DECISION MAKING IN SELECTING SECOND LINE PEDIATRIC IMMUNE THROMBOCYTOPENIA (ITP) TREATMENT
Rachael Grace, Robert Klaassen, For the ITP Consortium of North America. Boston Children's Hospital, Boston, Massachusetts, United States of America

Background: Refractory ITP, requiring treatment beyond accepted first-line therapies, is uncommon, and published data comparing second-line treatments is limited.

Objectives: The ITP Consortium of North America (ICON) held a focus group in April 2013 to describe and rank the factors hematologists use when selecting second line ITP treatment.

Design/Method: 13 pediatric hematologists with ITP expertise participated in a moderator-led discussion to generate factors that physicians consider when selecting second line ITP treatment. These factors were prioritized and grouped. An additional 6 hematologists (total 19) joined the group to rank the factors and groupings. Using an interpretive description approach, top ranking factors in each group were used in the final conceptual model.

Results: We discerned 27 factors physicians use when selecting second line ITP treatment. The top ranking factors by mean ranking order included: efficacy, short-term toxicity, long-term toxicity, and sustainability of response. Each factor ranking had wide inter-rater variability; thus, physicians disagreed on the importance of each the factor. Groupings by ranking included: clinical patient factors, treatment specific factors, patient preference factors, physician factors, and health systems/external factors. The figure shows the final conceptual model.

Conclusion: Physicians consider a number of factors when selecting second line treatment in refractory pediatric ITP. In general, clinical patient and treatment specific factors were most important, but hematologists vary on which specific factors are most important in their own decision making. An open ICON study (ICON1, clinicaltrials.gov NCT01971684) will prospectively study the factors physicians use when determining second line treatment in individual ITP patients.

Figure. Conceptual Model for Physician Decisions Regarding Second Line Pediatric ITP Treatment
AN ASSESSMENT OF DISEASE KNOWLEDGE DIFFERENCES BETWEEN ADOLESCENTS WITH SICKLE CELL DISEASE AND THEIR PARENTS AND ITS CORRELATION TO QUALITY OF LIFE

Pillai Pallavi Madhusoodhan, Hemant Menghani, Ashish Gupta, Fernando Fireman, Aziza Sedrak, Swayam Sadanandan. The Brooklyn Hospital Center, Brooklyn, New York, United States of America

Background: As per the Health Belief model, health behavior is determined by personal beliefs or perceptions about a disease. This is more so in a chronic illness like Sickle Cell Disease {SCD}. In pediatrics, health education is mostly parent centred. Disease knowledge of caregivers affecting outcomes is well studied, but disease knowledge amongst pediatric patients of SCD themselves has been less explored. We believe this is important, especially in the age group of 12-21 yrs, as disease knowledge would be a fundamental skill for transition readiness.

Objectives: • To assess and compare disease knowledge amongst adolescents with sickle cell disease and their parents. • To examine if patient reported quality of life differs from the parents’ perception of the quality of life for their child. • To analyze if there is a correlation between level of disease knowledge and perceived quality of life.

Design/Method: We enrolled 40 patients with SCD, between 12-21 yrs of age and 1 parent of each patient. Patients and parents were administered two questionnaires each. The first pertained to disease knowledge and the second, was a standardised QoL questionnaire, PedsQLTM.

Results: We observed that caregiver knowledge scores were significantly (p=0.01) higher than patient’s scores, with a positive correlation (R=0.34). No significant difference between caregiver perceived Total QoL and patients reported Total QoL. But among patients with HbSS , patients’ perceived QoL was significantly higher than their parents’ perception (p=0.01). There was a positive correlation between patient and parents scores in both disease knowledge and QoL. Disease knowledge did not have an impact on QoL. Patient age correlates directly to higher disease knowledge scores (p=0.01, R=0.35). Caregiver education was also strongly associated with better knowledge (p=0.0002, R=0.46).

Conclusion: Our study demonstrates disparity in disease knowledge between adolescents with SCD and their caregivers. These findings underline the importance of patient focused health education as an essential component of transition preparation in adolescents with SCD. They also reflect the need for health communication within families of children with SCD. This would contribute to dissemination of knowledge and also to a more accurate caregiver perspective of how the disease affects their child.
EVOLUTION TO CLONAL HEMATOPOIESIS IN BONE MARROW OF INDIVIDUALS WITH FANCONI ANEMIA
Kasiani Myers, Gretchen Radloff, Parinda Mehta, Richard Harris, Stella Davies. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

Background: Individuals with Fanconi anemia (FA) have increased sensitivity to DNA damage resulting in a pronounced predisposition to bone marrow failure (BMF) and malignancy, particularly acute myeloid leukemia. Progression to BMF and malignant transformation remain poorly understood. Clonality of hematopoiesis can be assessed using the HUMARA assay, which is designed to detect skewing of X-inactivation using differential methylation of alleles in the human androgen-receptor gene (HUMARA). In patients without Fanconi anemia, significant changes in allele representation over time have been demonstrated in serial samples from children receiving intensive chemotherapy.

Objectives: The goal of the current study is to use the HUMARA assay to longitudinally screen for clonality in bone marrow from individuals with FA to better understand the changes in the hematopoietic stem cell compartment and how they may correlate with changes in clinical status.

Design/Method: DNA from bone marrow collected via an IRB approved repository was tested using HUMARA assays to quantify clonality of hematopoiesis, and these results were correlated with clinical status.

Results: Using X-linked clonality studies we examined bone marrow from 20 female patients with Fanconi anemia. Oligoclonal hematopoiesis (allelic ratio > 70:30) was present in 10 patients, while 6 patients demonstrated clonal hematopoiesis (allelic ratio >90:10). Serial samples collected over a period of 6 months to 7 years were available in 10 patients. Five of these patients revealed evolution to oligoclonal or clonal hematopoiesis over time. Progression towards clonality was associated with progression towards severe marrow failure in 2 patients and myelodysplastic syndrome in 3 patients. In two patients evolution to clonality occurred with reversion of previous moderate marrow failure.

Conclusion: These observations indicate that progression towards clonal hematopoiesis may herald increasing depletion of stem cell reserve or emergence of a pre-malignant clonal population. Further development of the HUMARA assay may allow for clinical use to assess progression of disease or acquired mosaicism. Identification of early genetic changes and biomarkers of marrow failure or leukemic transformation, such as clonality of hematopoiesis, may allow earlier diagnosis and lead to more timely therapy.
SHWACHMAN-DIAMOND SYNDROME IN ADULTS
Kasiani Myers, Audrey Anna Bolyard, Amanda Jones, Barbara Otto, Nicholas Dobbins, Joan Moore, Richard Harris, Stella Davies, David Dale, Akiko Shimamura. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

**Background:** Shwachman-Diamond syndrome (SDS) is a rare autosomal recessive marrow failure syndrome associated with exocrine pancreatic dysfunction. With the advent of genetic testing, diagnosis of patients with non-classical presentations of SDS is now possible, allowing for expansion of the clinical phenotype. Additionally, pediatric patients with SDS are now surviving into adulthood, and little is known regarding disease progression in adulthood.

**Objectives:** We investigated clinical presentation and phenotypic spectrum of adult individuals with SDS in order to better understand disease manifestations and/or progression with age,

**Design/Method:** using the North American Shwachman-Diamond Syndrome Registry.

**Results:** Genetic reports of biallelic SBDS mutations confirming diagnosis of SDS were available for 11 individual’s age ≥ 18 years. Current median age is 23.7 years (18.1-50.7). Ages at initial presentation ranged from 0.8-18, median 7.6yrs. Only five had the classic initial presentation of neutropenia and steatorrhea. Episodic neutropenia, anemia and thrombocytopenia were seen with varying severity in all subjects. Severity of episodic neutropenia was most significant, while persistent mild thrombocytopenia was seen most often in older individuals. Bone marrow evaluations were available in ten, all demonstrating marrow hypoplasia, and two progressing to morphologic marrow dysplasia. Five showed clonal abnormalities including del7q, trisomy 8, del20q and iso7q, with age at initial appearance ranging from 10-44 years (median 21 years). One individual developed acute myeloid leukemia at age 19.5 years. Evidence of pancreatic dysfunction was seen in seven with five currently requiring enzyme replacements. Seven had evidence of prior failure to thrive, but normal adult height and weight were achieved by eight and nine respectively. Abnormal bone density was seen in four of five evaluated. Three had neuropsychological diagnoses, including depression and bipolar disease. Nine have achieved secondary level education, and six some collegiate level education.

**Conclusion:** SDS patients are surviving into adulthood, and some are diagnosed in late adolescence or early adulthood. Timely diagnosis prior to development of life-threatening complications is essential for optimal medical management and outcomes, particularly as dose modifications are needed for AML or bone marrow transplantation. Referral of additional adult patients to the SDS registry will inform and improve clinical care of all SDS patients.
CONGENITAL VOLKMANN'S ISCHEMIA WITH CUTANEOUS NECROSIS AND NEURONAL INJURY IN A NEONATE
Sherif Badawy, Robert Liem, Molly Ball, Arun Gosain, Anjali Sharathkumar. Lurie Children's hospital, Northwestern University, Chicago, Illinois, United States of America

Background: Despite limited reports, in our experience, neonatal forearm compartment syndrome is not an uncommon event, however, poorly understood. Left untreated, it may progress to Volkmann’s ischemia, contracture and neuronal injury.

Objectives: We describe a neonate with right hand necrosis and clinical presentation suggestive of forearm compartment syndrome on the second day of life.

Design/Method: History: A 2-day-old term boy was transferred to our institution with progressive right upper extremity (RUE) swelling. He had a small blister on his right hand at birth that evolved into an area of necrosis. Physical Exam: His right hand and RUE were erythematous and markedly swollen. Pulses were absent below the level of the brachial artery, and neurological exam revealed isolated hypotonia of the extremity. A 3 cm purple/black, stellate eschar was present on the dorsum of his right hand with 2 smaller, adjacent purple lesions. Laboratory: His evaluation showed elevated AST/ALT and consumptive coagulopathy. Doppler-Ultrasound of the RUE showed a non-occlusive arterial thrombus of brachial and axillary arteries. Thrombophilia work-up negative. Clinical course: Upon transfer, he was started on unfractionated heparin with improvement in extremity perfusion. Antibiotics we administered for concerns of cellulitis. His right forearm compartment pressure was 20 mmHg while the unaffected forearm was 15 mmHg. Fasciotomy on day of life 7 revealed necrotic subcutaneous tissue but pink viable deep tissue and muscle. His nerve conduction study was consistent with right brachial plexopathy. Mobility of the right fingers, elbow, armand shoulder has shown significant improvement overtime with minimal contracture.

Results: Our patient had evidence of liver dysfunction and consumptive coagulopathy of unclear etiology associated with arterial thrombosis of the RUE. He had presumed forearm compartment syndrome based on clinical examination. Although he had comparable pressures in both forearms, there are no standard references in this age group. His coagulopathy improved soon after removal of necrotic subcutaneous tissue.

Conclusion: The diagnosis of forearm compartment syndrome and Volkmann’s ischemia requires a high index of suspicion. Any delay in the management may significantly affect the survival and functional outcome of the involved limb. Further studies are needed to evaluate the benefits of both anticoagulation and early fasciotomy.
STIMULATION OF ALPHA 7 NICOTINIC ACETYLCOLINE RECEPTOR REDUCES TRAUMATIC HEMORRHAGE VIA THROMBIN-DEPENDENT PLATELET PRIMING IN SPLEEN

Susmita Sarangi, Jason Fritz, Hannah Hoffman, Sara Valentino, Jared Huston, Kevin Tracey. North Shore LIJ, Feinstein Institute of Medical Research, New Hyde Park, New York, United States of America

Background: Trauma is the fifth leading cause of death in the United States, and uncontrolled hemorrhage is the leading cause of preventable death following traumatic injury. Vagus nerve stimulation reduces blood loss and accelerates local clot formation following tissue injury in swine. The cholinergic anti-inflammatory pathway reduces pro-inflammatory production and protects against lethal systemic inflammation. Activation of this brain-to-immune pathway requires vagus nerve signaling to splenic macrophages expressing the α7 subunit of the nicotinic acetylcholine receptor (α7nAChR). Currently, the molecular, cellular and anatomic components contributing to the hemostatic effects of cholinergic stimulation are unknown.

Objectives: Here we hypothesized that cholinergic stimulation via nicotine can reduce hemorrhage by priming platelets passing through the spleen via the α7 subunit of the nicotinic acetylcholine receptor (α7nAChR).

Design/Method: Male aged 8-12-week-old mice (C57BL/6J, α7 KO or wild-type littermates) were pretreated with nicotine (2 mg/kg, ip) or saline vehicle 60 min before 2 mm distal tail transection and bleeding time measurement. In separate experiments, systemic blood from nicotine or vehicle-treated mice was stimulated with thrombin or ADP ex vivo, and platelet activation was determined via FACS expression of P-selectin (CD62P) and glycoprotein IIb/IIIa (JON/A). To evaluate the role of spleen, animals underwent splenectomy or sham laparotomy five days prior to tail bleeding experiments. Circulating soluble P-selectin concentrations, which reflect systemic platelet activation, were measured by ELISA. Local and systemic platelet counts were determined as well.

Results: Administration of nicotine significantly reduces bleeding time and increases platelet activation as quantified by P-selectin and glycoprotein IIb/IIIa membrane expression. Nicotine enhances thrombin-dependent but not ADP-dependent platelet activation. Nicotine fails to reduce bleeding time or activate platelets following splenectomy or in mice genetically deficient in the α7 subunit. There are no differences in systemic platelet counts or soluble P-selectin concentrations following nicotine or vehicle treatment.

Conclusion: Cholinergic stimulation via nicotine specifically enhances hemostasis at the site of tissue trauma and reduces hemorrhage via thrombin- and α7nAChR-dependent platelet priming in spleen. Further studies are needed to evaluate cholinergic stimulation as a hemostatic therapy to safely prevent lethal traumatic hemorrhage or be useful in bleeding disorders.
WILMS' TUMOR GENE 1 (WT1) EXPRESSION IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

Mohamed Badr, Tamer Hassan, Asmaa Esh, Wesam Mokhtar. Zagazig University, Zagazig, Egypt

Background: Wilms' tumor 1 (WT1) gene encodes a zinc finger transcription factor that plays a crucial role in cell survival, differentiation and proliferation. It is expressed in normal CD34+ bone marrow cells and down regulated in more differentiated cells. Alterations of WT1 expression (both under- or overexpression) have been described in a number of malignancies and premalignant syndromes. Considering hematopoietic malignancies, it is over expressed in the majority of acute leukemia and has been suggested to represent a potential prognostic factor however, it has been least studied in ALL and its impact remains most controversial.

Objectives: We aimed to evaluate WT1 gene expression in children with acute lymphoblastic leukemia and to find out the relationship between it and the standard prognostic factors.

Design/Method: A case-control study was conducted in Pediatric Oncology Unit of Zagazig University Children's Hospital during the period from January 2011 to June 2013. We examined the level of expression of WT1 gene in 44 newly diagnosed children with acute lymphoblastic leukemia and 20 healthy control children. Fresh peripheral blood samples were collected from patients and controls and submitted to RNA extraction, reverse transcription of extracted RNA and quantitative real-time PCR.

Results: A wide range of WT1 gene expression levels was detected in our patients. WT1 gene expression level was significantly higher in patients than in controls. Moreover, WT1 gene expression was significantly higher in T-cell acute lymphoblastic leukemia (T-ALL) than in B-cell Precursor acute lymphoblastic leukemia (BCP-ALL) (P<0.001) and also higher in those with expression of some myeloid markers than those without expression of myeloid markers. As regards WT1 gene expression in relation to the standard prognostic factors, there were a significant positive correlation between WT1 expression and both age and total leukocytic count at time of diagnosis. In relation to outcome, WT1 was significantly higher in patients who failed to achieve complete remission after induction chemotherapy and in relapsed patients.

Conclusion: We concluded that WT1 gene expression was significantly higher in patients with acute lymphoblastic leukemia especially those with older age at time of diagnosis, higher total leukocytic count at time of diagnosis, T cell immunophenotype and relapse.
UNIQUE APOPTOTIC EFFECTS OF PANOBINOSTAT AND MARIZOMIB IN ACUTE MYELOID LEUKEMIA MODELS
Fernando Corrales-Medina, Blake Johnson, Christa Manton, Daniela Egas-Bejar, Mary Irwin, Joya Chandra. The University of Texas - MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Panobinostat, a potent pan-histone deacetylase inhibitor (HDACi) is emerging as a valuable therapeutic option for cancer treatment. Compared with the FDA-approved vorinostat, it displays a more potent and broader spectrum of inhibitory activity at clinically achievable concentrations. Combinatorial therapies with proteasome inhibitors (PI) have been recently evaluated. Recent work from our laboratory has shown that marizomib, a second-generation PI, is more effective inhibiting the activity of the proteasome and inducing higher caspase-8 and reactive oxygen species (ROS) dependent cell death than bortezomib.

Objectives: To (1) determine if a panobinostat+marizomib combination displays synergy in AML cells; and (2) whether cell death by this combination triggers a unique profile of caspase activation.

Design/Method: Human-derived AML cell lines, ML-1 and AML3, were exposed to increasing concentrations of HDACi, (panobinostat or vorinostat), and PI (bortezomib or marizomib) alone and in combination. Caspase-3 activity was measured. Caspase-8 and caspase-9 dependence, were evaluated using pre-treatment with specific caspase-8 (IETD-fmk) and caspase-9 (LEHD-fmk) inhibitors.

Results: Panobinostat had an IC50 within the nanomolar range at 24 hours of treatment; in contrast, an IC50 was not achievable with vorinostat until after 48 hours of treatment. Marizomib was found to have a much lower IC50, higher ROS levels induction and slightly higher DNA fragmentation capacity than bortezomib in both cell lines. Calcusyn software was used to determine synergistic combinations. Synergistic cytotoxicity was observed with the combination treatment of panobinostat with both PIs. No synergy was observed with combinations involving vorinostat. Interestingly, these combinations did not decrease cell viability of healthy-control peripheral blood mononuclear cells. Panobinostat+marizomib combination induced an earlier and 2.5x higher induction of caspase-3 activation than the combination of panobinostat+bortezomib. Caspase-8 inhibition decreased the cytotoxicity of the panobinostat+marizomib combination compared to control, whereas no difference was observed on cells treated with panobinostat+bortezomib. Western blotting for cleaved caspase-8 corroborated these data. Caspase-9 inhibitors did not significantly protect against DNA fragmentation in any of the combinations.

Conclusion: Panobinostat+marizomib combination displays synergism in AML cell lines. Caspase-8 has a role in sensitivity to synergistic combinations of HDACi and PI. Overall, these data support the use of these novel anticancer agents in hematological malignancies.
Background: Health related quality of life (HRQL) assessments provide information needed to better understand the patient experience. Recent studies of HRQL in pediatric oncology have had variable response rates of 58-98%. One method to improve response rates is to use a central patient-reported outcome (PRO) coordinator, to remind centers about upcoming HRQL assessments and follow-up in cases of delinquency.

Objectives: To determine the impact of a PRO coordinator on completion rates of HRQL assessments during a pediatric acute myeloid leukemia (AML) trial.

Design/Method: AAML1031 is a multicenter Children’s Oncology Group therapeutic study for de novo AML. One secondary aim of AAML1031 is to assess HRQL of children and adolescents treated with chemotherapy and hematopoietic stem cell transplantation (HSCT), using the PedsQL inventory. In order to improve the response rate for the HRQL aim, a central PRO coordinator was instituted. Responsibilities of the PRO coordinator included: contacting sites to remind them about upcoming completion deadlines; and to inform sites of delinquent HRQL data. The proportion of HRQL questionnaires completed by parent proxy were compared prior to, and following the institution of the central PRO coordinator.

Results: At the time of data collection 402 were patients eligible to enroll on the HRQL aim of AAML1031. Of these, 231 consented to participate. The overall response rates for the 3 assessments were 73-83% at the 5 time points. At time point 1 (within 14 days if Induction I) for 2 PedsQL assessments post-PRO coordinator completion rates were significantly higher (90% and 89%) compared with pre-PRO coordinator completion rates (78% and 75%, p=0.0166 and 0.0069, respectively). However, at time point 4 (one month from start Intensification II or HSCT), the proportion of all 3 completed assessments was significantly lower post-PRO coordinator (65%, 64%, 64%) compared to pre-PRO-coordinator (89%, 89% and 89%, p=0.0092, 0.0071 and 0.0071, respectively).

Conclusion: Addition of a central PRO coordinator did not result in a sustained improvement in completion rates for HRQL assessments on a pediatric AML therapeutic study. Other strategies, such as utilization of electronic PROs may be a potential mechanism to improve completion rates for pediatric oncology HRQL studies.
RARE PRESENTATIONS OF ORBITAL MASSES
Harini Rao, Farzana Pashankar. Yale University, New Haven, Connecticut, United States of America

Background: Orbital masses are rare in children. The common malignant causes for orbital tumors are metastases from solid tumors like neuroblastoma, LCH, and retinoblastoma. Leukemia and lymphoma rarely present primarily as orbital masses. We discuss two patients, who presented with orbital tumors and were diagnosed as having leukemia and lymphoma. These cases highlight the importance of keeping leukemia and Non Hodgkin's lymphoma (NHL) high in our differentials in patients presenting with orbital tumors.

Objectives: To describe the rare differential diagnosis associated with orbital mass presentations.

Design/Method: Case series of two patients.

Results: Case 1: 15 y/o female presented with a slowing enlarging eyebrow mass over six months. Complete blood count was normal. Biopsy was done which confirmed B Lymphoblastic Lymphoma. Staging workup including bone marrow and whole body PET CT were negative, and hence the patient was diagnosed with a localized Non Hodgkin's lymphoma. Case 2: 4 y/o female presented with a two week history of an enlarging eyelid lesion. Complete blood count was normal. MRI orbit showed a right orbital mass, with lesions in sphenoid, and right mandibular ramus. Pathology of right orbital mass showed sheets of intermediate-sized cells a high nuclear-cytoplasmic ratio, that were strongly positive for TdT and Pax 5, consistent with a diagnosis of pre-B ALL. Bone marrow biopsy showed cells that were CD19/CD10 positive with cytoplasmic mu positivity, consistent with marrow involvement by pre-B ALL.

Conclusion: Initial presentations of ALL and NHL as an orbital mass are extremely rare. Few case reports have been published for either. We describe 2 patients who presented with orbital masses with normal blood counts and were diagnosed with lymphoid malignancies. These cases highlight that we must consider ALL and NHL in patients who initially present with orbital masses.
BURKITT LYMPHOMA IN A PATIENT WITH HEREDITARY MULTIPLE EXOSTOSES
Andrew Walter, Sara Prince. A. I. duPont Hospital for Children, Wilmington, Delaware, United States of America

Background: Hereditary multiple exostosis (HME) is an autosomal dominant disorder consisting of multiple osteochondromas arising from germline mutations in the EXT family of tumor suppressor genes. HME can be considered a tumor predisposition syndrome since patients have an increased risk for both benign chondromas and sarcomas. Far less common in HME patients are non-sarcomatous malignancies. Leukemias and lymphomas are intriguing in HME since there may be an association between EXT genes and hematopoiesis in the pathogenesis of lymphoid malignancies. We report a case of a 10 year old boy with HME who developed a Burkitt’s lymphoma of the abdomen. To our knowledge there are no reported cases of high-grade lymphoma in the pediatric population outside of this case report.

Objectives: review and report recent case

Design/Method: case report

Results: A 10 year old male with HME presented with abdominal pain, distention, and vomiting for five days. His medical history was unremarkable except for several orthopedic procedures for benign osteochondromas. His family history was positive for HME. CT demonstrated abdominal neoplasm involving bowel wall, anterior peritoneum, and liver. Tissue biopsy confirmed Burkitt’s lymphoma. Bone marrow biopsies/aspirates and cerebrospinal fluids were negative for tumor, he was diagnosed with stage III Burkitt lymphoma. He was treated with COP-R/COPADM/CYM-RM combination chemotherapy without radiation therapy. He achieved a complete remission and remains disease free 8 years later after completion of therapy.

Conclusion: This is the first reported case of high-grade lymphoma in a pediatric patient with HME. This patient is also the only known HME patient cured of a lymphoid neoplasm. HME is a known cancer predisposition syndrome, normally associated with sarcomas and benign bone tumors. Most tumors and malignancies in HME patients are linked to mutations or epigenetic modifications in the EXT family of tumor suppressor genes. Silencing of the EXT genes by hypermethylation suggests that demethylating agents may have a therapeutic role in the treatment of HME related neoplasms.
CLASSICAL HODGKIN LYMPHOMA-LIKE PTLD: A LATE PRESENTATION OF PTLD FOLLOWING LIVER TRANSPLANTATION
Andrew Walter, Violet Fernandes, Stephen Dunn. A. I. duPont Hospital for Children, Wilmington, DE, United States of America

**Background:** Post transplant lymphoproliferative disease (PTLD) is a well-known complication of the long term immunosuppressive therapy required in solid organ or allogeneic stem cell transplant recipients, with the majority of cases being classified as non-Hodgkin lymphoma.

**Objectives:** Review and report recent case.

**Design/Method:** Case report

**Results:** 19-year-old male presented with back pain, 18 years after receiving a cadaveric liver transplant for biliary atresia. Complications post-transplant included an asymptomatic infection with hepatitis C, hypertension and intermittent compliance with medications. A CT scan demonstrated lytic lesions of the sacral and lumbar vertebrae as well as an epidural mass extending from L4 to S2 with cauda equine compression. Dexamethasone was initiated. Biopsy of the epidural mass showed classical Hodgkin lymphoma-like PTLD, stage IV disease. Immunosuppression was withdrawn without resolution of the lymphomatous mass. He was then treated with chemotherapy active against Hodgkin lymphoma, BEACOPP, with significant improvement. He required several significant chemotherapy dose reductions due to unacceptable toxicity. He eventually completed only five of eight planned cycles of BEACOPP. Due to his significant risk for relapse from insufficient therapy, he proceeded to stem cell harvest followed by high dose chemotherapy with peripheral blood stem cell rescue approximately seven months after his initial diagnosis. Unfortunately, he died from liver failure due to catastrophic reactivation of his hepatitis C disease one month after high dose chemotherapy.

**Conclusion:** Hodgkin Lymphoma-like PTLD is a rare and clinically aggressive form of PTLD that may present late after transplant. This case is unusual due to the latency of almost 20 years and that the preceding transplant was a liver transplant. Combined treatment with reduced immunosuppression, rituximab, chemotherapy, radiation, high dose chemotherapy with stem cell rescue and surgery should all be considered. Pre-existing morbidities, such as hepatitis C, complicate therapy and can even contribute to a fatal outcome, such as in this case.
CONTRASTING ROLES FOR NOTCH SIGNALING IN T-ALL, B-ALL AND AML
Mandy Hall, Sankar Kannan, Patrick Zweidler-McKay. UT MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Notch activation plays an oncogenic role in T cell leukemia. In contrast, Notch signaling has a tumor suppressing role in B-ALL and AML. The divergent roles are likely due to cell type-specific differences in downstream Notch signaling.

Objectives: To define the downstream consequences of Notch activation induced by Notch ligands JAG1 and DLL1 in leukemia subtypes.

Design/Method: Notch ligand-inducible expression of Notch target genes (HES1, HES4, HEY1, HEY2) was assessed by QRT-PCR in a panel of human B-ALL (SB, JM1, Nalm6), AML (THP1), and T-ALL (CEM, MOLT4) cell lines. Leukemia cells were co-cultured with a human bone marrow stromal cell line (HS5) expressing JAG1 or DLL1 ligands.

Results: In general B-ALL and AML lines express higher levels of Notch2 compared to Notch1. In contrast T-ALL lines express Notch1 over Notch2. Consistent with constitutive Notch activation, T-ALL lines express high levels of HES1 compared to B-ALL and AML (>100-fold). Both JAG1 and DLL1 increased transcription of multiple Notch target genes, however, DLL1 induced higher expression in most genes. Upon co-culture with DLL1, HES1 was significantly increased in B-ALL and AML lines compared to T-ALL (2.5-18-fold, 5.5-fold and <1.5-fold respectively). In contrast DLL1 induced greater increases in HEY2 expression in T-ALL than B-ALL and AML (4-fold, <1.5-fold and no change respectively). Interestingly, JAG1 induced greater response than DLL1 in HEY1 and HEY2 in the AML line THP1. Under these co-culture conditions, DLL1 but not JAG1, induced apoptosis (AnnexinV-binding) in all B-ALL and AML lines by 48-72 hours, while having no effect on T-ALL survival.

Conclusion: In this study we report differences in Notch target gene expression in leukemia subtypes following co-culture with Notch ligands. In the presence of Notch2 receptor, exposure to DLL1 induces high HES1 expression in B-ALL and AML which correlates with increased apoptosis. Thus, Notch agonists based on DLL1 may provide a therapeutic opportunity for B-ALL and AML. Further studies to determine cell fate consequences when Notch target genes are increased will also be important in understanding the tumor suppressor role of Notch signaling in B-ALL and AML.
LEAP (LEARNING, EDUCATION, AWARENESS, PREVENTION) YOUNG ADULT CANCER OUTREACH PROGRAM

Anthony Audino, Stacy Whiteside, Nicholas Yeager. Nationwide Children's Hospital, Columbus, Ohio, United States of America

**Background:** Nearly 70,000 Adolescent and Young Adult patients (AYAs) between the ages of 15 and 39 are diagnosed with cancer each year. While the incidence of AYA cancer has steadily increased, the overall survival rates have not improved to the degree seen in other age groups. One possible explanation is delayed diagnosis due to unrecognized risk factors and symptoms of malignancy by AYAs. In addition, providers may not consider cancer in this age group, and symptoms may be attributed to fatigue, stress or other common causes.

**Objectives:** To educate AYAs and physicians regarding common AYA cancers, so that we may diagnose and treat AYA patients earlier.

**Design/Method:** With the support from the Prevent Cancer Foundation, the “LEAP (Learning, Education, Awareness, and Prevention) Young Adult Cancer” outreach program was developed targeting physicians in training and healthy high schools students. A curriculum was developed regarding the most common AYA cancers with a focus on presenting signs and symptoms, as well as methods of prevention. Medical students and pediatric residents presented this information at local high schools. Pre and post-test were given to learners to assess the outcome of these sessions on their knowledge of AYA cancer.

**Results:** We presented our information to over 100 trainees who subsequently presented to over 1000 high school students in the Columbus Ohio area, 80% of which were from inner city schools. In the medical trainees, pre and post-testing demonstrated an increase in base AYA cancer knowledge of 75%, while high school students had an increase of 90%.

**Conclusion:** The community response to the “L.E.A.P” program was overwhelming. Many other schools have made contact with our community outreach coordinator to schedule training sessions in their schools. Several teachers have developed entire lesson plans on cancer and are using our presentations to supplement their material. The enthusiasm of the high schools students is echoed in the results of their post-tests. By empowering medical professionals with this knowledge early in their learning, we hope to impact the way they examine and educate patients in the future, allowing for improved prevention strategies and earlier detection of cancer in AYAs.
THE STATUS OF HEALTH-RELATED QUALITY OF LIFE AIMS IN COG STUDIES
Puja Gupta, Patricia Cullen, Christine Trask, Fiona Schulte, Rajaram Nagarajan, Lillian Sung, Donna Johnston. University of Arizona, Tucson, Arizona, United States

Background: As pediatric oncology survival has increased, more attention has been placed on maximizing health-related quality of life (HRQL) for both children expected to survive and also those who have a poor prognosis. The COG and the Division of Cancer Prevention have invested tremendous resources to conduct HRQL studies within COG and legacy groups. However, in spite of the vast resources placed in HRQL studies, little is known about the outcomes of these studies.

Objectives: In studies supported by COG or the legacy groups in which a HRQL instrument was utilized, we described the proportion of closed protocols that successfully accrued patients to the intended sample size or considered sufficient for analysis. Secondary objectives included the number of studies analyzed, led to a peer-reviewed publication, or were presented at a national or international conference.

Design/Method: We reviewed all closed COG and legacy studies and identified those that involved a HRQL validated instrument. Demographic information was obtained from the protocol and case report forms. We created a descriptive survey for the HRQL PI to complete. After completion, we evaluated the stated objectives.

Results: Demographic data was collected in 16 identified studies. Eight of the 16 studies closed in 2005 or earlier. HRQL aims were considered the primary aim in 7 (44%) studies and we identified the HRQL PI in the protocol in 10 (77%) studies. Fifteen of the 16 HRQL surveys were completed. Nine (60%) of studies were successful in accrual, whereas six (40%) failed accrual goals. Seven of 16 (46%) studies completed analysis, 9 (56%) studies have presented their work and 6 (40%) studies have published. Of the nine studies that accrued successfully, only 6 (67%) have completed analysis and published their findings. Only 40% of studies have data available within COG.

Conclusion: The survey describes 40% failure of HRQL studies to accrue sufficient sample sizes in cooperative group studies. 54% of studies have not been analyzed despite 50% of studies closing in 2005 or earlier. 60% of studies have not been published. This qualitative data suggests an inadequate consideration of HRQL at design and implementation stages.
ASSESSMENT OF MUSCULOSKELETAL FUNCTION AND MOOD IN HAEMOPHILIA A ADOLESCENTS: A CROSS-SECTIONAL STUDY

Nelly Raafat, Tamer Hassan, Mohamed Badr, Sherif Badawy. Zagazig University, Zagazig, Egypt

Background: Hemophilia A is characterized by the occurrence of frequent spontaneous intra-articular and intramuscular bleeding. If inadequately treated, it results in progressive damage to joints and muscles leading to crippling deformities and musculoskeletal dysfunction. These complications result in lifelong chronic pain and disability that may greatly affect the patients' mood.

Objectives: We aimed to evaluate the musculoskeletal function in our hemophilia A patients and its correlation to depressed mood in these patients and determine the impact of degree of factor VIII deficiency, different replacement therapy regimens and frequency of hemarthrosis, on both musculoskeletal function and mood.

Design/Method: A cross-sectional study was carried out on 50 adolescent haemophilia A patients. Musculoskeletal function was assessed using Functional Independence Score for Hemophilia (FISH) and mood status was assessed using Beck Depression Inventory-Short Form (BDI-SF).

Results: The mean FISH score was 23.32 ± 4.69 (range 13-28) and the tasks that obtained lower scores were step climbing, squatting and walking. Of our 50 patients included, 16(32%) were not depressed, 18(36%) were with mild depression, 11(22%) were with moderate depression and 5(10%) were with severe depression. There was a highly significant negative correlation between mean FISH score and mean BDI-SF score (P < 0.001).

Conclusion: The better the replacement therapy regimen, the better the musculoskeletal function that could be obtained in haemophilia A patients and the better the mood.
DAILY BATHING WITH CHLORHEXIDINE AND ITS EFFECTS ON NOSOCOMIAL INFECTION RATES IN PEDIATRIC ONCOLOGY PATIENTS
Chittalsinh Raulji, Kristin Clay, Cruz Velasco-Gonzalez, Lolie Yu. LSUHSC/ Children's Hospital of New Orleans, New Orleans, Louisiana, United States of America

**Background:** Oncology patients are extremely prone to infections. The main contributing factors are immunosuppression and presence of invasive catheters. Most catheter associated blood stream infections (BSIs) result from contamination of the catheter by bacteria residing on patients’ skin. Chlorhexidine gluconate is a topical antiseptic which has been shown to reduce the rates of BSI when used for daily cleaning for patients in ICU.

**Objectives:** To compare the rates of nosocomial infections in pediatric oncology patients before and after the implementation of daily Chlorhexidine bathing.

**Design/Method:** This retrospective study examined all pediatric oncology inpatient admissions over a 14-month span from December 2008 – January 2010 at Children’s hospital in New Orleans. Patients admitted before implementation of Chlorhexidine bath served as control group and were compared to the study group which received daily Chlorhexidine bathing. Patients were divided into age groups 0-4, 4-7, 7-12 and 12-21 years. Infections were recorded based on presence of fever more than 24 hours after admission and/or presence of positive cultures obtained from bodily fluids. Incidence density (ID): The rate of infections (number of occurrences/100 days). Hospital-acquired infections (HAI): Presence of positive cultures and fever, or just cultures alone. Nosocomial fever of unknown origin (nFUO): Presence of fever with no culture confirmation.

**Results:** We had 330 patient admissions with 190 in the control group and 140 in the study group. The rate of infection in the study group was found to be lower than that of control group in all age groups except the 0-4 years. Especially, 12-21 years old had a statistically significant decrease in infection rate (p = 0.0343). The ID of nFUO and HAIs was 1.19 and 1.42 in the control group and 0.86 and 0.73 in the study group, respectively (p = 0.49, 0.15), indicating a decreased rate of infection. For neutropenic patients (ANC<500) Chlorhexidine bathing reduced the ID of infections, most notably in 12-21 years of age, [8.86 in control group compared to 0 in study group (p = 0.039)].

**Conclusion:** Chlorhexidine bathing was successful in reducing the incidence density of infection amongst pediatric oncology patients, especially those older than 12 years of age.
PATIENT SATISFACTION WITH HURRICANE PLAN GIVEN TO HEMATOLOGY-ONCOLOGY PATIENTS AT CHILDREN’S HOSPITAL IN NEW ORLEANS

Chittalsinh Raulji, Maria Velez, Renee Gardner. LSUHSC/ Children's Hospital of New Orleans, New Orleans, Louisiana, United States of America

**Background:** Because of increased frequency and intensity of hurricanes in the New Orleans region, many patients following at Hematology-Oncology clinic at Children’s Hospital (CHNOLA) are relocated temporarily during these periods. Each year at beginning of Hurricane season patients are given a hurricane plan in form of a questionnaire, which asks them about pertinent patient identification data; their evacuation plan in case of a hurricane; if there is a hospital nearby; if they know which pharmacy they will be using. They are asked to have an updated copy of roadmap with them. This information is then scanned to a flash drive along with their roadmap for treatment and is available to the staff in case of evacuation. The families are given information about where the clinic will be held in case of evacuation.

**Objectives:** Our goal was to assess the barriers to providing healthcare to Hematology-Oncology patients by evaluating the effectiveness of hurricane plan given to the families.

**Design/Method:** We distributed a survey to patient’s families at time of clinic visits. The patient or the family representatives were asked to participate in the study. We excluded patients who started following up with us after the hurricane season ended. The questionnaire included questions about diagnosis, previous evacuations, evacuation plan, factors that figured in their decision to evacuate, and if they had treatment plan and medicine available to them, etc.

**Results:** Majority of patients (73%) evacuated during previous hurricane seasons and most (77%) had a plan for where they were going to evacuate. The most important factor influencing that decision was availability of a children’s hospital nearby. Although a majority (71%) had medicines with them to last for 2 weeks, a significant number (43%) did not have treatment plans available with them and many (28%) did not have emergency contact information for staff as well. Most patients (78%) found information given to them helpful.

**Conclusion:** Most of our patients found the hurricane action plan implemented at CHNOLA helpful. We suggest implementation of similar plans to other departments as well. We are in process of comparing our present data to data available before implementation of the action plan.
IFOSFAMIDE-INDUCED ENCEPHALOPATHY IN CHILDREN AND YOUNG ADULTS: THE MD ANDERSON CANCER CENTER EXPERIENCE

Daniela Egas Bejar, John Slopis, Maria Ceja, Fernando Corrales-Medina, Cynthia Herzog, Najat Daw.
The University of Texas MD Anderson Cancer Center, Houton, Texas, United States of America

Background: Ifosfamide-induced encephalopathy (IIE) occurs in 5-30% of patients after intravenous administration. Limited information exists on IIE clinical manifestations and treatment.

Objectives: To describe the clinical manifestations, treatment, and outcome of children and young adults treated at our institution who experienced IIE.

Design/Method: We reviewed the clinical records of cancer patients aged ≤ 30 years who experienced IIE and received methylene blue (MB) from June 2002 to May 2012.

Results: A total of 24 patients, median age 17.6 years (range, 4 to 30 years), were identified. Fifty four percent were male and 71% had bone or soft tissue sarcoma. Ifosfamide was given either alone or in combination with other agents (dose range, 1.5–3.3 g/m2/day). Thirteen patients (54%) developed IIE with bolus infusion (over 1-3 hours) and 11 (46%) with continuous infusion (over 24 hours). IIE occurred after a median cumulative dose of 18 g/m2. Two patients had prior history of IIE and 3 had prior brain irradiation. Neurological symptoms occurred within few hours and up to 5 days after starting the infusion and resolved within a few hours and up to 5 days after onset of symptoms. All patients but one had mental status changes; 8 (33%) patients had drowsiness and 6 (25%) had confusion. Twelve patients had grade 3 IIE (severe somnolence, agitation, confusion), 5 grade 4 (coma, seizures), 4 grade 1 (mild somnolence, agitation), 2 grade 2 IIE (moderate somnolence, agitation) and 1 grade 0 (hemiparesis without mental status changes). Twenty patients received MB; 19 (95%) had IIE resolution. CT or MRI brain obtained in 8 (33%) and 5 (21%) patients, respectively, and the scans showed no findings attributable to IIE. Ten patients were rechallenged with subsequent ifosfamide doses and 5 received prophylactic MB; 5 had IIE recurrence (3 in the MB group and 2 in the group without MB).

Conclusion: IIE can occur with bolus or continuous ifosfamide infusion. It manifests as altered mental status, seizures, and rarely hemiparesis. Symptoms are transient but can last up to 5 days. IIE resolved in most patients treated with MB, but MB did not prevent IIE recurrence in all patients.
METADHERIN, A LAMININ RECEPTOR, IS ESSENTIAL FOR METASTASIS AND IS ASSOCIATED WITH POOR SURVIVAL IN OSTEOSARCOMA
Limin Zhu, Pingyu Zhang, Yanwen Yang, Wei-Lien Wang, Dafydd Thomas, Dennis Hughes. UT MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Understanding metastasis is vital to improving osteosarcoma survival. Metadherin (MTDH) is essential in tumorigenesis and metastasis in many cancer types. The role of MTDH in osteosarcoma has not been reported, and there is controversy about the orientation and subcellular localization of the molecule, leading to differing models for how MTDH affects metastasis.

Objectives: To assess the role of MTDH in osteosarcoma metastasis and elucidated the mechanisms underlying its metastasis-promoting activity.

Design/Method: To evaluate MTDH expression in patient-derived materials, tissue microarrays (TMAs) containing primary and metastatic archival tumors were examined by immunohistochemistry for MTDH. A cDNA array expression database made from pretreatment diagnostic biopsies of high-grade osteosarcoma patients was used to assess the correlation between MTDH expression and patient outcome. Western blot, qPCR, and flow cytometry measured MTDH expression in a panel of osteosarcoma cell lines. MTDH-specific shRNA reduced endogenous MTDH expression, and anti-MTDH antibodies blocked cell surface MTDH in functional assays, including transwell migration and matrigel invasion assays. The relationship between MTDH expression and pulmonary metastasis was studied in an orthotopic xenograft mouse model. To investigate the role of MTDH in cell-extracellular matrix (ECM) interaction and to identify the extracellular binding partner for cell surface MTDH, a series of adhesion assays were performed, followed by bidirectional co-immunoprecipitation.

Results: MTDH is up-regulated in osteosarcoma cell lines and archival tumors compared with normal human osteoblasts. MTDH is upregulated in metastatic lesions compared to primary tumors and is correlated with shorter survival in osteosarcoma patients. MTDH knockdown and blockade of cell surface MTDH reduced migration and invasion in osteosarcoma cells. MTDH shRNA delayed primary tumor growth and prevented pulmonary metastasis. Flow cytometry defined MTDH as a type II transmembrane protein. Adhesion assays using specific shRNA and scrambled control osteosarcoma cells showed that MTDH mediates binding to matrigel proteins, specifically laminin, a basement membrane protein. Bidirectional co-immunoprecipitation proved the interaction of MTDH and laminin.

Conclusion: MTDH mediates its effect on metastasis by facilitating binding to laminin when endothelial linings are disrupted, exposing basement membrane, which completely alters the paradigm for how this molecule is thought to function. Therapies directed at disrupting the MTDH-Laminin interaction may have therapeutic benefit.
STEMNESS IS AN INDUCIBLE PHENOTYPE IN OSTEOSARCOMA
Rocio Rivera-Valentin, Yingqi Hua, Yi Zhang, Tiffany Lynch, Nupur Lala, Yanwen Yang, Dennis Hughes. The Children's Cancer Hospital at MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Osteosarcoma death arises from metastasis, spurring interest in defining the biology of metastatic potential. In tumors or cultured cells, not all cells can form new tumors in xenograft systems; cells capable of generating new tumors are termed tumor initiating cells (TICs), similar to “cancer stem cells” in other malignancies. Several markers have been proposed to identify TICs, including Stro1, ALDH, Hoechst “side population”, and expression of EMT-associated genes such as OCT4 and Nanog. We showed that Her-4 expression is required for neuroblastoma metastasis, and is abundant in osteosarcoma.

Objectives: To evaluate the role of Her-4, Stro1 and other stemness markers in osteosarcoma cell survival, metastasis and “stemness”.

Design/Method: Stemness marker expression was measured by FACS, Immunohistochemistry (IHC), western blot and/or Q-PCR after manipulating culture conditions (normal, high-density or “Sarcospheres”), serum starvation, hypoxia or chemotherapy (methotrexate, cisplatin, doxorubicin and 4-OH-ifosfamide). Functional measures included proliferation, cell cycle, and apoptosis. The CCH-OS-O xenograft model assessed the impact of Her-4 knockdown or Stro1 expression on metastasis.

Results: Her-4, CD117 and Stro1 expression increased with sarcosphere culture in most lines, while Her-4 also increased with serum starvation. Hypoxia increased Her-4 cleavage to the 80KD intracellular fragment. Her-4 expression, assessed by IHC, is higher in metastatic lesions than primary tumors (p>0.01). Her-4 shRNA reduced proliferation, increased apoptosis and increased sensitivity to methotrexate (60% increase in apoptosis) but not to other chemotherapies. Sarcosphere culture increased Stro1 expression, but Stro1-negative cells, sorted by FACS, still formed sarcospheres. Expression of Oct4 and Nanog, present in all cells, did not vary with culture conditions. Intratibial injection of CCH-OS-O cells in NOD/SCID/IL2Rg-/- mice, allowing spontaneous pulmonary metastasis, assessed metastatic potential. Her-4 knockdown nearly eliminated metastasis, with re-expression of Her-4 found in the rare metastases of knockdown mice. Stro1 negative cells still formed primary and metastatic tumors, but fewer than Stro1 cells.

Conclusion: Proposed “stemness” markers do not identify a specific subpopulation of TICs in osteosarcoma, but are either uniformly expressed or are inducible in negative cells, depending upon culture conditions. Cells lacking expression of Stro1, a putative stemness marker, still form tumors. Her-4 expression was most closely associated with metastatic potential in vivo.
SUCCESSFUL TREATMENT OF SEVERE REFRACTORY HEMORRHAGIC CYSTITIS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH HYPERBARIC OXYGEN AND PALIFERMIN A RECOMBINANT HUMAN KERATINOCYTE GROWTH FACTOR

Rolla Abu-Arja, Smita Bhaskaran, Sanjay Ahuja, Linda Cabral, Kristen Nagle, Rachel Egler, Ghada Abusin. Rainbow Babies and Children's Hospital, Cleveland, Ohio, United States of America

Background: Hemorrhagic cystitis (HC) is a major cause of morbidity after hematopoietic stem cell transplantation (HSCT). Despite the use of multiple preventive strategies, severe hemorrhagic cystitis has a transplant related mortality of 70%. Conventional therapies have been successfully used to treat mild to moderate cases whereas severe HC treatment is much more challenging.

Objectives: We report a successful treatment of a pediatric patient with severe refractory HC using a combination of KGF and hyperbaric oxygen therapy (HOT).

Design/Method: A twelve-year old female with relapsed AML underwent a matched unrelated bone marrow donor transplant. Post transplant complications included sinusoidal obstruction syndrome and anuric acute kidney injury requiring prolonged renal replacement therapy. On day 22 post transplant she developed grade IV hemorrhagic cystitis that failed conventional therapies including continuous bladder irrigation, intra-vesicular and intra-venous Cidofovir, prostaglandins, amphotericin washes, fulguration and major transfusion support. HOT was started as a last measure 147 days post transplant, along with KGF.

Results: HOT was given 5 days a week for 8 weeks with KGF 3 days a week for 4 weeks. She tolerated this therapy well and achieved complete remission 4 weeks in to her therapy.

Conclusion: This is the first report of combined use of KGF and HOT to treat refractory HC in a pediatric patient post allo-HSCT. The use of KGF and HOT was well tolerated in our patient and provides a safe alternative for patients with refractory HC. If administered early in the disease course, KGF may be successful in diminishing the number of HOT sessions.
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN A PATIENT WITH EMANUEL SYNDROME (SUPERNUMERARY DERIVATIVE CHROMOSOME 22) - CASE REPORT
Ghada Abusin, Oleg Shchelochkov, Natalie Kameros, Rolla Abu-Arja, Shawki Qasim. University of Iowa Carver College of Medicine, Iowa City, Iowa, United States of America

Background: Supernumerary Derivative Chromosome 22 or Emanuel syndrome (ES) (47,XY+22,der(22)t(11;22)(q23;q11.23)) is characterized by microcephaly, failure to thrive, ear anomalies, cleft or high-arched palate, micrognathia, kidney abnormalities, congenital heart defects and genital abnormalities. Our review of medical literature does not suggest a known link between Emanuel syndrome and ALL. However such association cannot be rejected altogether. No hematological and/or oncological manifestations specifically for ES have been reported in the observable medical literature to date.

Objectives: We describe a patient with ES and ALL and delineate the clinical course in this patient

Design/Method: Case report

Results: A three-year-old Caucasian male with previously known diagnosis of ES presented with fevers, fatigue and generalized pain. On initial evaluation, the patient had mild cervical lymphadenopathy but no hepatosplenomegaly. Initial CBC was significant for WBC 4,800/mm³, hemoglobin 6.1 g/dL and platelets 59,000/mm³, bone marrow evaluation demonstrated precursor-B ALL, cytogenetics showed (47,XY t(8;14)(q24;q11.2), add19p13.3 & derivative(22)t(11;22)(q23;q11.23)). CNS was negative. He was stratified as standard risk and treated according to COG-AALL0932. Morphologic and molecular remissions were achieved by day 29 of Induction. We hypothesize that the abnormal copy number variants encompassing dosage-sensitive genes on chromosome 22 and 11 confers increased risk of tumorigenesis. We are not aware of studies that demonstrate the need to modify current treatment protocols for patients with Emanuel syndrome. Our patient tolerated his chemotherapy without increased toxicity or signs of relapse

Conclusion: To date, no associations between Emanuel Syndrome and ALL have been reported, thus raising awareness of the possible non-random association between this genetic syndrome and observed hematological phenotype.
MALIGNANT HYPERCALCEMIA IN A CHILD WITH METASTATIC EWING SARCOMA
Hawazen Alsaedi. Medical University of South Carolina, Charleston, South Carolina, United States of America

**Background:** Malignant hypercalcemia is a complication rarely seen in children. It is estimated to occur in approximately 0.4 to 0.7% of the pediatric oncology cases and is often associated with terminal malignancy. Symptoms of hypercalcemia include vomiting, constipation, polyuria, polydipsia, restlessness, seizure, arrhythmias, and coma. Treatment is based upon the degree of hypercalcemia, acuity of its development, presence of absence of symptoms, and renal function. Among pediatric patients, malignant hypercalcemia has been described in a variety of solid tumors, but is usually more commonly seen in hematological malignancies.

**Objectives:** To discuss a unique case of primarily metastatic Ewing sarcoma in a young child who presented with malignant hypercalcemia

**Design/Method:** Case report and Literature review

**Results:** 2-year-old female presented with intermittent abdominal pain and severe constipation. Physical examination revealed presence of palpable abdominal mass and severe abdominal distention. Image studies revealed extensive abdominal and pelvic mass, bilateral hydronephrosis, ascites, extensive adenopathy involving mediastinum, left neck and left supraclavicular areas as well as along the anterior chest wall, and multiple pleural-based lesions circumferentially surrounding both lungs. Laboratory work is significant for hyperuricemia, and hypercalcemia (serum Ca level is 17 mg/dl). Tumor biopsy was consistent with Ewing sarcoma. There was no bone marrow involvement or metastatic bone disease. She received alternating cycles of chemotherapy that included vincristine, ifosfamide, etoposide, doxorubicin, and cyclophosphamide. Hypercalcemia was treated by pamidronate. Her clinical condition improved, with improvement of hypercalcemia and overall status. However, after 5 cycles of chemotherapy, she developed constipation and hypercalcemia with serum calcium level between 14-16 mg/dl, and abdominal distention. Image studies confirmed progression of disease. Hypercalcemia was associated with the production of parathyroid hormone-related peptide (PTHrP) (8 pmol/L, normal range < 2 pmol/L). She was started on intravenous fluids, pamidronate, calcitonin, and furosemide with suboptimal control of hypercalcemia. Salvage chemotherapy with irinotecan and temozolamide was initiated, along with emergent radiation therapy. Despite all efforts, clinical condition of patient showed little improvement and she died of disease progression.

**Conclusion:** Malignant hypercalcemia is a very rare complication in pediatric age group; however it correlates with disease progression.
BREAKTHROUGH PULMONARY MUCORMYCOSIS IN A TEENAGER WITH LEUKEMIA SUCCESSFULLY TREATED WITH AMPHOTERICIN B AND POSACONAZOLE WITHOUT SURGERY

Harbir Arora, Basim Asmar, Mara Rubenstein, Ravindranath Yaddanapudi, Nahed Abdel-Haq.
Children's Hospital of Michigan, Detroit, Michigan, United States of America

Background: Pulmonary mucormycosis is a challenging infection affecting patients with leukemia especially those receiving voriconazole prophylaxis. Mortality of mucormycosis is reported to be ≥ 40%. Timely diagnosis is often difficult due to poor yield of respiratory cultures. Combination of surgical and medical management is recommended but guidelines for surgical intervention are lacking. Polynenes are the cornerstone of medical therapy. Due to rarity of the condition, randomized controlled trials to investigate alternative antifungals are lacking.

Objectives: We report a 13 year old male with AML who developed pulmonary mucormycosis while receiving voriconazole prophylaxis. He was successfully treated with IV Amphotericin B and oral posaconazole without surgical intervention.

Design/Method: 13 year old male with AML diagnosed 3 months earlier was seen for fever for 1 week. He had been neutropenic for the last 3 months and had been receiving oral voriconazole for prophylaxis. Examination revealed no apparent focus of infection. Treatment with IV amphotericin B, vancomycin, meropenem and oral voriconazole were started. CT scan of the thorax showed a cavitary lesion in the left lung apex measuring 5.2 x 6.5 x 4.7cm. Bacterial, fungal and mycobacterial cultures from blood and BAL sample were negative. BAL galactomannan, pan bacterial and fungal PCR tests were negative. Due to persistent fever, CT guided needle biopsy of the lung lesion was obtained. Tissue cultures for bacteria, mycobacteria and fungi were negative. Tissue pan fungal PCR was positive for Rhizopus microsporus/azygosporus. Patient's neutropenia resolved with GCSF treatment. Patient defervesced after 3 weeks and was discharged on IV amphotericin B.

Results: Follow up CT scan 3 months later showed improvement in cavitary size to 2.7 X 1.7 X 2cm. Therapy was changed to oral posaconazole (400 mg BID) 2 months later with serum levels maintained ≈1 µg/ml. Patient remained asymptomatic and repeat chest CT showed residual scar after 5 months of posaconazole therapy.

Conclusion: Breakthrough pulmonary mucormycosis should be strongly suspected in febrile leukemia patients with neutropenia receiving voriconazole prophylaxis. Obtaining lung tissue for molecular testing (PCR) is vital in its diagnosis. Oral posaconazole appears to be a good alternative to IV amphotericin B once neutropenia resolves and pulmonary lesion is non progressive.
USE OF RAPAMYCIN IN COMPLICATED VASCULAR TUMORS
Akua Asante, Reuben Antony, Beth Speckhart, Eric Bugaieski, Kenneth Frasier, Alessandro de Alracon, Karen Fernandez. UICOMP Children’s Hospital of Illinois, Peoria, Illinois, United States of America

**Background:** The treatment of complicated vascular tumors is not standardized. Treatment approaches include various pharmacological agents and sometimes surgery. The successful use of Rapamycin, has been reported in some individual cases of vascular tumors.

**Objectives:** To describe two patients with aggressive vascular tumors who had a remarkable response to Rapamycin.

**Design/Method:** Case series

**Results:** Patient 1: A 3-Kg term female neonate had been found to have an abdominal mass on a prenatal ultrasound. Post-natal MRI revealed a complex heterogeneous lobulated mass measuring 7cm x 4cm x 5cm (volume 140 cm³), extending from the liver to the right pelvis. Patient also had disseminated intravascular coagulation (DIC). At 6 days-of-life a biopsy confirmed Kaposiform Hemangioendothelioma (KHE). Treatment with Dexamethasone, Vincristine and Propranolol was started without benefit. At 7 weeks-of life Rapamycin was started (0.8 mg/m²/dose) with resolution of DIC within one week of treatment. At 15 weeks-of-life an ultrasound demonstrated a dramatic reduction of the tumor mass to 2.3cm x 1.6cm x 1.5cm (volume 5.52 cm³). No surgical resection was needed. Patient remains asymptomatic at 2.5 years. Residual lesion is no longer visible. Patient 2: A 15-year-old male with an 8 month history of recurrent sinusitis was found by MRI to have a mass in the right maxillary-sinus extending to the sphenoid-sinus, infiltrating the clivus and encroaching upon the right orbital apex. Endoscopic biopsy confirmed juvenile nasopharyngeal angiofibroma (JNPA). Surgical resection was deemed extremely risky. Patient underwent embolization of the right distal internal maxillary artery. Four weeks after embolization Rapamycin (6 mg daily) was started. MRI at 6 and 12 weeks post Rapamycin showed a significant reduction in tumor size. Rapamycin was discontinued when the patient began to have drainage of foul smelling yellowish material from the right nostril and recurrent epistaxis. Ultimately patient underwent extensive surgical resections without major bleeding complications. He is currently alive but experiencing residual pain.

**Conclusion:** The use of Rapamycin is safe and can significantly reduce the size of complex vascular tumors, preventing surgical intervention or allowing for a less morbid surgical procedure. To our knowledge we present the youngest patient with KHE and the first patient with JNPA treated with Rapamycin.
HEMOGLOBIN CINCINNATI: A NOVEL BETA GLOBIN GENE MUTATION CAUSING DOMINANT BETA THALASSEMIA
Nihal Bakeer, Hong-Yuan Luo, Michael Grimley, Mary Risinger, Panayotis Manganaris, Amber Hogart Begtrup, David Chui, Theodosia Kalfa. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

Background: Dominantly inherited beta-thalassemias are a rare group of disorders due to monoallelic beta-globin gene mutations leading to synthesis of highly unstable beta-chains, which readily precipitate and result in hemolysis and ineffective erythropoiesis.

Objectives: To describe a new variant, beta-globin Cincinnati, arising from a de novo frameshift mutation in codons 115/116 (–C), GCCCAT>GCC–AT.

Design/Method: Case report and gene sequencing after family’s informed consent.

Results: a 15-month-old Caucasian female was referred to our clinic for evaluation of a transfusion-dependent, non-immune hemolytic anemia since the age of 8 months. Blood smear revealed transfused red blood cells (RBC) along with her own poikilocytic cells, nucleated RBC, and impressive basophilic stippling. Hemoglobin electrophoresis indicated elevated fetal hemoglobin (up to 19%) despite her transfusions. Globin gene sequencing showed normal alpha genes and heterozygosity for a novel codons 115/116 deletion (–C) in the beta gene, shifting the reading frame and resulting in an elongated beta-chain with 156 amino acids. A similar elongated beta chain has been reported before as beta globin Geneva with codons 114/115 deletion and missense mutation CTGGCC> -GGGCC, leading also to frameshift and an elongated beta chain, differing from beta-Cincinnati only in the amino-acids 114 and 115 (Gly-Pro instead of Leu-Ala). Beta-globin Geneva was the mutation found in the first family described with dominantly-inherited beta thalassemia, named also inclusion-body beta-thalassemia trait (Stamatoyannopoulos et al, NEJM 1974). In order to evaluate if there was an additional RBC cytoskeleton or enzyme disorder, DNA was isolated from peripheral blood, enriched and subjected to a comprehensive Next-Generation sequencing assay for 27 hemolytic anemia-related genes. Only a novel PIEZO1 mutation (c.6905G>A, p.R2302H) was identified, considered as possibly damaging by Polyphen-2 (score of 0.809), which might have been associated with xerocytic RBC changes aggravating the patient’s phenotype. Matched sibling bone marrow transplant provided a successful therapy for this patient’s transfusion-dependent anemia.

Conclusion: Beta-thalassemia including the rare dominant forms should be considered in the differential diagnosis of non-immune hemolytic anemia, even in patients with negative family history, especially when the disease presents in the second half of infancy.
AUTOIMMUNE FEATURES IN A CHILD WITH SETTLE AND A NOVEL GENETIC MUTATION
Diana Bradford, Patroula Smpokou, Christopher Rossi, Joseph Van der Walde, Marianna Horn. Children's National Medical Center, Washington, District of Columbia, United States of America

Background: Spindle epithelial tumor with thymus-like differentiation (SETTLE) is an extremely rare tumor of the thyroid gland thought to originate from branchial pouch or thymic remnants. First defined in 1991, there have been less than thirty-five cases reported, with a mean age of 17.9 years. There is a slight male predominance, with reported male: female ratios ranging from 1.1-1.8. Treatment is usually limited to partial or complete thyroidectomy; in few cases, up-front addition of chemotherapy and/or radiation has been reported. Although considered to have low malignant potential, long-term surveillance is required in these patients given the risk of late metastasis. The tissue of origin of SETTLE has not been established definitively. The only genetic alteration found to date in a case of SETTLE is mutation of the Ki-ras oncogene.

Objectives: To report a patient with SETTLE tumor with autoimmune history and novel genetic mutation.

Design/Method: Case Report

Results: We report on a 10 year old male with a history of alopecia totalis and a pituitary cyst who presented with a left-sided thyroid mass. He underwent fine needle aspiration of the mass which demonstrated a cytologically bland spindle cell proliferation; subsequently left hemithyroidectomy demonstrated a biphasic spindle and glandular neoplasm consistent with SETTLE. Chest CT at diagnosis and six weeks post-operatively revealed a ground glass opacity of the left lower lobe; wedge resection revealed no evidence of metastatic disease. Given the patient’s diagnosis and history of alopecia and pituitary cyst, he was referred to genetics. A microarray revealed deletion of a portion of 4q24 involving the CISD2 gene. Missense mutations of CISD2 have been implicated in Wolfram syndrome; though our patient does not display features of this syndrome, the syndrome does carry autoimmune features (juvenile insulin dependent diabetes mellitus). Heterozygous 4q24 microdeletions have been reported in hematologic malignancies, but not in SETTLE.

Conclusion: SETTLE tumor is a rare tumor of unclear histogenesis. We report the case of a 10 year old male with autoimmune history and genetic mutation not previously associated with SETTLE to assist further characterization of this rare malignancy. Further genetic testing of the tumor tissue may provide further insight and is underway.
EARLY THERAPY-RELATED MYELOID SCARCOMA AND DELETION OF CYTOGENETIC INTERVAL 9q22.32 TO 9q31.1: A CASE REPORT
Molly Brickler, Donald Basal, Gabriela Gheorghe, David Margolis, Michael Kelly, Matthew Ehrhardt. 
Medical College of Wisconsin, Milwaukee, Wisconsin, United States of America

Background: Advances in childhood neuroblastoma therapy have improved survival and decreased therapy-related toxicities. Therapy-related acute myeloid leukemia (t-AML) is a rare complication occurring in fewer than 2% of children treated for neuroblastoma. Myeloid sarcoma represents an extramedullary collection of leukemic myeloblasts that precedes overt bone marrow involvement in 2-4% of childhood acute myeloid leukemia (AML). Therapy-related myeloid sarcoma (t-MS) has not been reported in children and the treatment is therefore undefined. We describe the first reported case of t-MS in a child treated for neuroblastoma.

Objectives: A 13 month old male with developmental delays and intermediate risk neuroblastoma developed a scalp nodule 5 months into therapy. Biopsy revealed a dense lymphoid infiltrate composed of large atypical cells with fine chromatin, variably prominent nucleoli, and relatively large amounts of cytoplasm occupying the dermis and subcutaneous tissue. Immunohistochemical staining of the atypical cells revealed diffuse positivity for CD45, CD68, CD43, CD33, and lysozyme with focal myeloperoxidase positivity. The atypical cells were negative for CD34 and CD117. Cytogenetic and fluorescent in situ hybridization evaluations of cultured tumor cells identified a t(8;16). Bone marrow biopsy and positron emission tomography were normal. These findings were consistent with an isolated t-MS. The presence of developmental delays and the occurrence of two distinct malignancies prompted genetic evaluation. A chromosomal microarray identified a 7.3 mb deletion within cytogenetic interval 9q22.32 to 9q31.1. The patient underwent a myeloablative 5/6 umbilical cord transplant. Conditioning included busulfan, fludarabine, thiotepa, and anti-thymocyte globulin. Graft versus host disease prophylaxis included cyclosporine and mycophenolate mofetil. The child remains in remission from both malignancies approximately 8 months posttransplant.

Design/Method: n/a

Results: n/a

Conclusion: Unusual presentations of rare diseases necessitate a multidisciplinary approach and adaptation of standardized protocols to accommodate increased risks imposed by genetic variants. Although early initiation of AML therapy is associated with improved survival for patients with de novo MS, cure for t-AML requires hematopoietic stem cell transplantation. Therapy for t-MS has not been described and our approach was therefore extrapolated from that of de novo MS and t-AML. We believe that this child remains at increased risk for subsequent cancers and therefore requires vigilant surveillance.
CONGENITAL PERIBRONCHIAL MYOFIBROBLASTIC TUMOR: CASE REPORT OF AN ASYMPTOMATIC INFANT WITH A RAPIDLY ENLARGING PULMONARY MASS
Katharine Brock, Florette Kim Gray Hazard, Beverly Newman, Neyssa Marina. Stanford University, Palo Alto, California, United States of America

**Background:** Congenital peribronchial myofibroblastic tumor (CPMT) is a rare, benign lung tumor of infants with only 15 reported cases worldwide. It is often diagnosed by prenatal imaging or in the immediate postnatal period due to co-morbidities such as polyhydramnios, fetal hydrops, respiratory distress, and heart failure.

**Objectives:** We report the oldest known infant diagnosed with CPMT at 8 weeks of age, and present his clinical course including relevant imaging (X-ray, CT, and MRI), histopathologic findings (morphology, immunohistochemistry, and FISH), surgical management, and over 13 months of follow-up.

**Design/Method:** We review and contrast other developmental, benign, and malignant pulmonary lesions such as sequestration, pleuropulmonary blastoma (PPB), and fetal lung interstitial tumor (FLIT), that can present in the neonatal period.

**Results:** This case was unusual in its rarity, lack of prenatal imaging findings, the asymptomatic nature of the child, and the difficulty in pathology diagnosis.

**Conclusion:** Pediatric oncology providers should be aware of congenital peribronchial myofibroblastic tumor and include it in the differential of infants with lung masses. While these masses can be difficult to distinguish, these differences are clinically relevant. Treatment for CPMT is complete surgical resection; local recurrences and metastases following complete excision have not been described. In comparison to pleuropulmonary blastoma, chemotherapy and/or radiotherapy are not indicated for CPMT.
AUTOSOMAL RECESSIVE HEREDITARY SPHEROCYTOSIS IN PATIENTS WITH THE c.4339-99C>T αLEPRA MUTATION IN THE SPTA1 GENE

JESSICA CONNOR, Neha Dagaonkar, Satheesh Chonat, Mehdi Keddache, Kejian Zhang, Amber Begtrup, Theodosia Kalfa, Phillip Dexheimer. Cincinnati Children's Hospital, Cincinnati, Ohio, United States of America

Background: Hereditary spherocytosis (HS) due to biallelic mutations in α-spectrin (SPTA1) present as severe hemolytic anemia requiring frequent blood transfusions.

Objectives: To describe five cases of autosomal recessive HS.

Design/Method: Case Series. Next-Generation sequencing was performed on DNA isolated from peripheral blood for 27 hemolytic anemia-related genes, after informed consent within an IRB-approved research study. All mutations were confirmed by Sanger sequencing of the exon or intron involved in the patients’ as well as parental samples.

Results: Two of the patients presented with severe hemolytic anemia in early infancy, requiring transfusions every 4-5 weeks. Patient 1 had the novel nonsense mutation p.L1432* in trans to αLEPRA (Low Expression Prague): c.4339-99C>T at position -99 of intron 30, leading to activation of an acceptor splice site at position -70 of intron 30, causing frameshift and premature termination (Wichterle et al, JCI, 1996). Patient 2 had αLEPRA in the compound heterozygous state with the nonsense mutation p.L1701*. Both of these patients had partial splenectomy with fair response; the first one being two years now after the procedure has again occasional transfusion requirement and may require total splenectomy. After splenectomy, ektacytometry performed in non-transfused sample from both patients showed typical HS curve. Patient 3 had αLEPRA in trans with the nonsense mutation p.Y1089*. He presented with transfusion-dependent hemolytic anemia requiring monthly transfusions since a year of age, a fairly late presentation for severe HS. He was also found to have α-globin gene triplication which would cause a thalassemia trait phenotype; concurrence of thalassemia and HS have occasionally be described to present with a milder that anticipated phenotype for either disease. Patients 4 and 5 are siblings with moderate to moderately severe HS, requiring only occasional transfusions. The older sibling had partial splenectomy 2 years ago, maintaining hemoglobin>10g/dL since then. Both siblings have αLEPRA in trans with the 6531-12C>T αLELY (Low Expression Lyon) mutation, securing some expression of viable α-spectrin chains.

Conclusion: Next generation sequencing is an effective diagnostic tool HS, especially useful when frequent transfusion requirement does not allow reliable red blood cell testing and may provide insights for phenotype-genotype correlation.
ATYPICAL HEMOLYTIC UREMIC SYNDROME IN THE SETTING OF PEDIATRIC PRE B ALL
Abigail Cruz, Phillip Neff, Daniel Ranch, Holly Kubaney, Chatchawin Assanasen. University of Texas Health Science Center of San Antonio, San Antonio, Texas, United States

**Background:** Atypical hemolytic uremic syndrome (aHUS) is a hematologic disease caused by complement over-activation often resulting in renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. Germline mutations have been associated with disease risk. However, triggers for its clinical presentation have not been well documented.

**Objectives:** We describe a case of atypical HUS in a child in maintenance therapy for precursor B ALL.

**Design/Method:** The case involves a 23 month old male with standard risk Pre-B ALL. Overall, he tolerated therapy without any significant adverse events or delays in therapy. He continued on standard maintenance therapy noting only that oral therapy was escalated to 125% due to elevated ANC per protocol. Shortly after a standard maintenance cycle of steroids and Vincristine, he presented with fever, jaundice, and pancytopenia (ANC 296, HGB 3.7, PLT 14,000, Tbili 4.6, BUN 14, and creatinine 0.4). Urinalysis was positive for large blood and protein. He was admitted for broad-spectrum antibiotics and hematologic support. Chemotherapy was withheld. His clinical condition rapidly declined with persistent non-immune hemolytic anemia, thrombocytopenia, and elevations in BUN and creatinine 57 and 1.7, respectively. Schistocytes were identified and pediatric nephrology confirmed the diagnosis of atypical hemolytic uremic syndrome recommending acute plasmapheresis therapy. ADAMTS 13 was noted to be 54% with undetectable haptoglobin, negative cultures, and LDH 1660.

**Results:** Five cycles of plasmapheresis were provided with minimal improvement. Following hematology’s recommendations, meningococcal vaccine and cefdinir were provided prior to initiating therapy with the C5 inhibitor Eculizumab. Response was noted within 48 hours and 4 days after his second dose of eculizumab his ANC and platelet count had fully recovered and renal function normalized. Oral chemotherapy was gradually restarted and escalated to 100% with no further relapse of his aHUS or other complication. The patient continues to receive eculizumab every 2 weeks without any adverse reactions. Genetic testing for known aHUS mutations was ordered but remain unavailable.

**Conclusion:** aHUS is no longer solely a renal disease. Pediatric hematologists face new challenges in the diagnosis and appropriate management of aHUS. Triggers of disease presentation and future risk of recurrence affect management options warranting further study.
HYPERSENSITIVITY TO PARENTERAL VITAMINS IN A PATIENT WITH STAGE 4, HIGH-RISK NEOBlastoma LEADING TO NUTRITIONAL DEFICIENCY RESULTING IN WERNICKE ENCEPHALOPATHY

Wendy Darlington, Navin Pinto, Hillary Hecktman, John Cunningham, Susan Cohn, James LaBelle
University of Chicago, Chicago, Illinois, United States of America

Background: Children undergoing prolonged hospitalization for cancer therapy frequently require caloric supplementation with total parenteral nutrition (TPN). Occasionally, parenteral vitamins are removed from TPN due to hypersensitivity reactions to a carrier protein in the formulation. These children are at risk of developing vitamin deficiency syndromes when chemotherapy treatment is intensive enough to curtail adequate oral intake.

Objectives: To describe a case of thiamine deficiency resulting in Wernicke encephalopathy in a TPN dependent oncology patient.

Design/Method: We present the case of a 5 year old patient who developed unusual neurologic symptoms while undergoing consolidation therapy with carboplatin, etoposide and melphalan followed by autologous stem cell transplant for stage 4, high-risk neuroblastoma.

Results: The patient first initiated TPN due to poor oral intake while receiving her third cycle of induction chemotherapy per COG protocol ANBL0532 with cisplatin and etoposide. Upon discharge from the hospital, the patient was maintained on TPN for her nutritional needs. Two days after initiation of TPN at home, the patient developed a hypersensitivity reaction including symptoms of generalized erythema, puritic urticaria, nausea and vomiting. Multivitamins were removed from her TPN formulation as the most likely cause of her hypersensitivity reaction. The following twenty-one weeks that included consolidation chemotherapy and stem cell transplant, the patient had limited, but measurable oral intake per parental report and was maintained on TPN. Twenty-six days after stem cell infusion, the patient developed rapid onset altered mental status, ataxia, and tachycardia. An MRI of the patient’s brain demonstrated bilateral enhancement of the medial thalami, hippocampi and mamillary bodies, which was consistent with Wernicke encephalopathy. Her serum thiamine level was 26 nmol/L (normal range 70-180 nmol/L). The patient received 100 mg thiamine intramuscularly for 7 days for repletion. Full resolution of her neurologic symptoms was observed within 24 hours of completion of the 7 day thiamine course.

Conclusion: Wernicke encephalopathy is an acute neurologic condition caused by thiamine deficiency infrequently seen in pediatrics. Children undergoing cancer therapy who require prolonged nutritional support are at risk of nutritional deficiencies, particularly those who do not tolerate parenteral vitamins. Close monitoring of micronutrients is important in patient’s receiving prolonged courses of TPN.
MLL rearrangement in a pediatric patient with cutaneous B-lymphoblastic lymphoma
Nicole Drezner, Dragos Luca, Gary Rogers, Leigh Marcus, Children's National Medical Center, Washington, District of Columbia, United States of America

**Background:** Non-Hodgkin lymphomas represent 4-6% of pediatric malignancies and are divided into B and T-cell subgroups with less than 20% of B-cell origin. B lymphoblastic lymphoma (B-LBL) involves extranodal organs at presentation including the skin, with approximately 50 cases of pediatric patients with cutaneous B-LBL described in the literature. Although the lymphoblasts in B precursor leukemia and B-LBL are identical and express an immature B-cell phenotype, a well-described minority of B precursor leukemia cases involve a translocation of the mixed lineage leukemia (MLL) gene on chromosome 11q23, historically associated with a poor prognosis. This represents an understudied subtype of B-LBL.

**Objectives:** We describe the only case of a pediatric patient with cutaneous B-LBL demonstrating a rearrangement of the MLL region. A 19-month-old female presented with a 5-6 week history of an enlarging mass on her forehead and underwent excision of the mass. FISH studies detected a rearrangement of the MLL region in 90% of the interphase cells. A positron emission tomography-CT scan demonstrated the primary lesion within the soft tissues of the right nasofrontal region that did not display significant FDG avidity, with maximum SUV of 1.5. Bilateral bone marrow biopsies and aspirates as well as cerebrospinal fluid were negative for abnormal cells. She was diagnosed with stage I B-LBL.

**Design/Method:** The patient started treatment per the Children’s Cancer Group protocol CCG-1991 for standard risk acute lymphoblastic leukemia beginning with a 28-day induction. She experienced poor wound healing after port placement during this time, and veno-occlusive disease in delayed intensification. She is currently in the maintenance phase of therapy.

**Results:** The patient achieved remission with a negative positron emission tomography-CT after induction.

**Conclusion:** The presence of the MLL rearrangement in B-LBL is unique and has been described in two cases of B-LBL, both of which were adults. There is a case report of pediatric MLL-duplicated gastrointestinal B-LBL. The presence of the MLL rearrangement was instrumental in confirming our diagnosis. Localized lymphoblastic lymphoma has an excellent prognosis. Our patient may represent a subtype of cutaneous B-LBL with MLL rearrangement that harbors a worse prognosis or increased risk of relapse despite the favorable staging and historical outcomes.
A COINCIDENCE OF RENAL CELL CARCINOMA AND HODGKIN'S LYMPHOMA: A CASE REPORT

Mohamed Elsaid, University of Wisconsin, Madison, Wisconsin, United States of America

**Background:** Coexistence of renal cell carcinoma (RCC) with hematologic malignancies does occur in adult population; however, such an association has not been reported in pediatrics. Furthermore, genetic predisposition for these concurrent malignancies has not been established despite its high degree of association in adults.

**Objectives:** To increase the awareness of simultaneous existence of Hodgkin’s lymphoma (HL) and RCC in adolescent population.

**Design/Method:** We report an unusual case of a 16 year old female who presented with a lump in the right clavicular region. CT scan of the chest revealed a conglomeration of enlarged lymph nodes in the right superior and anterior mediastinum. CT-guided biopsy of the mediastinal mass determined the diagnosis of Classical HL, nodular sclerosing variant. Incidentally, the staging CT scan demonstrated a mass in the inferior pole of the right kidney. A laparoscopic partial nephrectomy and regional lymphadenectomy was performed and the mass was found to be a RCC, localized to the kidney.

**Results:** The HL was treated with four cycles of multi-agent chemotherapy consisting of doxorubicin, bleomycin, vincristine, cyclophosphamide, etoposide and prednisone and 58% tumor reduction was achieved. Patient’s presentation with two simultaneous malignancies raised concerns of her predisposition to developing cancers. Radiotherapy was therefore, not given. Furthermore, HL is a highly salvageable cancer, even if primary therapy fails. Following complete excision of the renal mass, no further treatment was indicated for RCC. Patient underwent genetic evaluations for known genes that predispose to RCC. No mutations or genetic variations were found in the 18 genes analyzed: EPCAM, FH, FLCN, MET, MITF, MLH1, MSH2, MSH6, PMS2, PTEN, SDHA, SDHB, SDHC, SDHD, TP53, TSC1, TSC2, and VHL. Patient is now three months from completion of treatment and is doing well.

**Conclusion:** This is the first case described in the medical pediatrics literature where HL and RCC coexists.
AUTOIMMUNE HEMOLYTIC ANEMIA FOLLOWING HAEMOPHILUS INFLUENZA TYPE B VACCINATION
Elizabeth Finch, Kelly Lastrapes, Pauline Balkaransingh, Marieka Helou. Children's Hospital of Richmond at VCU, Richmond, Virginia, United States of America

**Background:** Autoimmune hemolytic anemia (AIHA) associated with immunization administration has been reported in the literature with Diphtheria tetanus and acellular pertussis (DTAP) or measles, mumps and rubella (MMR) vaccines being implicated as the cause most often. However, there are no cases of AIHA associated with the Haemophilus Influenza Type B (Hib) vaccine reported in the literature.

**Objectives:** We present a case of a four month old male who developed hemolytic anemia shortly after receiving his four month immunizations including DTAP, Hib, rotavirus, pneumococcal conjugate, and poliovirus vaccine inactivated (IPOL). We also describe the method for isolating the causative vaccine, Hib, during his 6 month immunizations.

**Design/Method:** Case Report

**Results:** Following two days of irritability, vomiting, and dark stools, a four month old male was found to have an initial hemoglobin of 2.7 g/dL at a community hospital. He was transferred to our academic center where he had a weakly positive direct antiglobulin test with negative complement component 3 and immunoglobulin G. Further testing revealed immunoglobulin A mediated autoantibodies. Significant improvement in his hemoglobin was observed after oral corticosteroid administration. A staggered approach was utilized for administering his 6 month immunizations which included serial complete blood counts following each individual vaccine to monitor for evidence of hemolysis. IPOL and DTAP vaccines were given without incident. However after administration of the Hib vaccine, his hemoglobin dropped to 7.0 g/dL, with hemolysis, suggesting that this vaccine was responsible for the initial episode. We plan to give him further Hib vaccine doses with steroid pretreatment.

**Conclusion:** We believe this case illustrates a novel method for not only confirming immunization associated AIHA but also isolating the causative vaccination.
DIVERSE PRESENTATIONS OF SEVERE COMBINED IMMUNODEFICIENCY
Jessica Garcia, Penelope Sandiford, Reuben Antony, Karen Fernández. University of Illinois College of Medicine, Peoria, Illinois, United States of America

Background: Severe combined immunodeficiency (SCID) occurs in 1 per 75,000 births. Most patients present before 3 months of age and die of infection within 6 to 12 months of age if not treated.

Objectives: To describe diverse presentations of 3 children with SCID.

Design/Method: Case series

Results: Case 1: A 7-week-old male presented with fever, diarrhea, severe eczematous rash and respiratory distress developed disseminated CMV, poly-microbial sepsis and multi-organ failure. Ommen syndrome was suspected: T+(low) B- NK+, absent CD45RA and increased CD45RO cells with activated T cells expressing HLA-DR and high IgE. RAG mutation analysis not done. Case 2: A 5-month-old male with a polyclonal B cell lymphocytic infiltrate of the left hip developed PCP-pneumonia. He was identified with T-B+ NK- phenotype. SCID was confirmed with genetic testing finding a frameshift mutation at position 327 of chromosome X. Patient received gene therapy. Case 3: A 2-year-old male presented with rash after MMR and varicella immunization. He then had recurrent URI, RSV pneumonia, chronic diarrhea, rash and FTT. He had hypogammaglobulinemia and received IVIG and Pentamidine. T+(low) B+ NK+, reduced CD45RA and absent HLA-DR cells (hypomorphic SCID) and was finally diagnosed with MCH-II deficiency. He underwent allogeneic BMT. Table 1 shows details of each case.

Conclusion: Diagnosis of SCID is difficult due to diverse presentations. Most common presentations are viral or fungal infections. However, others may present with lymphoproliferative masses that mimic lymphomas and others with rashes that mimic eczema or allergies. An early diagnosis is important for the outcome of these patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Age/Sex</th>
<th>Symptoms</th>
<th>CBC</th>
<th>Immunoglobulins</th>
<th>T &amp; B Cell enumeration</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ommen Syndrome</td>
<td>7 yr/M</td>
<td>Rash, Diarrhea, Fever, Respiratory Distress, Multiorgan Failure</td>
<td>WBC: 5.4 x10^9/μl, ANC: 2,860, ALC: 1,300, Plt: 10.7 x10^9/μl,</td>
<td>A mg/dl: &lt;5, G mg/dl: 618, M mg/dl: 17, E IU/mL: 89,225, T: Low 608, B: Low 174, NK: Low 143</td>
<td>Antibiotics, Mechanical Ventilation</td>
<td>Deceased</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>X-Linked SCID</td>
<td>5 mo/M</td>
<td>Lymphoproliferative mass, PCP Pneumonia</td>
<td>WBC: 8.4 x10^9/μl, ANC: 1,180, ALC: 4540, Plt: 9.7 x10^9/μl,</td>
<td>A mg/dl: 19, G mg/dl: 916, M mg/dl: 131, E IU/mL: 2</td>
<td>Low 8, High 1956, Low 21</td>
<td>Gene Therapy</td>
<td>Alive doing well 18 mo after transplant</td>
</tr>
<tr>
<td>3</td>
<td>MHC II Deficiency</td>
<td>2 yr/M</td>
<td>Rash s/p MMR/Var, Diarrhea, Recurrent URI, RSV Pneumonia, Failure to Thrive</td>
<td>WBC: 5.5 x10^9/μl, ANC: 3,900, ALC: 715, Plt: 11.2 x10^9/μl,</td>
<td>A mg/dl: &lt;7, G mg/dl: &lt;60, M mg/dl: 321, E IU/mL: 0.2</td>
<td>Low 180, NML: 492, NML: 417</td>
<td>Allogeneic BMT</td>
<td>Alive doing well 26 mo after transplant</td>
</tr>
</tbody>
</table>
HEPATOSPLENIC GAMMA-DELTA T-CELL LYMPHOMA IN A CHILD WITH SICKLE CELL DISEASE

Jenna Gedminas, Yanxia Li, Ammar Hayani. Advocate Children's Hospital and Christ Hospital, Oak Lawn, Illinois, United States of America

**Background:** Hepatosplenic T-cell lymphoma is a very rare and aggressive malignancy. It is most commonly seen in young adult males and typically presents with thrombocytopenia and splenomegaly. There is currently no standard of care for treatment and prognosis is poor. There have been a number of case reports in patients with Crohn’s disease on immunosuppressive therapy, but to our knowledge, this is the first reported case in a patient with sickle cell disease.

**Objectives:** We present a case of an 11-year old male with sickle cell disease (Hg SC) who is not on immunosuppressive therapy, diagnosed with hepatosplenic gamma-delta T-cell lymphoma after presenting with persistent anemia and hepatosplenomegaly.

**Design/Method:** Case Report

**Results:** An 11 year old male with hemoglobin SC disease initially presented with massive splenomegaly, severe anemia (Hg 2.7 g/dL), and thrombocytopenia (plts 84k). He was diagnosed with splenic sequestration crisis and splenectomy was performed. Pathology report at that time described red pulp congestion and white pulp depletion. Following splenectomy, hemoglobin and platelet levels normalized for the next 3 months, during which time the patient was started on hydroxyurea. One month after initiation of hydroxyurea, the patient developed massive hepatomegaly with severe anemia and thrombocytopenia, which persisted despite multiple transfusions and red cell exchange pheresis. Blasts appeared in the peripheral blood and bone marrow aspiration was performed. The bone marrow showed 30% lymphoblasts expressing CD3, CD7, CD56, gamma and delta, but negative for CD5, CD4, and CD8. Cytogenetic analysis of the bone marrow aspirate showed isochromosome 7(q10) which confirmed the diagnosis of hepatosplenic gamma-delta T-cell lymphoma. Retrospective examination of the splenic tissue revealed evidence of lymphoma. The patient has received his first cycle of ICE (ifosfamide, carboplatin, etoposide) to which he has responded well.

**Conclusion:** This is the first report of hepatosplenic T-cell lymphoma in a patient with sickle cell disease. The case illustrates a diagnostic challenge in sickle patients as the initial presentation mimics splenic sequestration, particularly given the transient improvement following splenectomy. It additionally demonstrates the importance of maintaining a suspicion for other pathological processes in the setting of persistent and evolving symptoms despite aggressive therapy in this patient population.
A UNIQUE CASE OF SCURVY MASQUERADING AS A TREATMENT RELATED SECONDARY MALIGNANCY
Michael Gleason, Jeffrey Lebensburger, Thomas Howard. Children's of Alabama, Birmingham, Alabama, United States of America

Background: 13q deletion syndrome is associated with retinoblastoma, dysmorphic facial features, psychomotor retardation, hypo- or epispiadas, congenital heart disease and various other features. Patients with this syndrome who develop retinoblastoma have an increased risk of developing treatment related secondary malignancies including MDS and AML. We report a unique case of a patient with 13q deletion syndrome treated for bilateral retinoblastoma who presented 6 years later with symptoms concerning for treatment related secondary malignancy but ultimately diagnosed with vitamin C deficiency and scurvy.

Objectives: To describe the case of a 7-year-old girl with 13q deletion syndrome, with history of bilateral retinoblastoma who presented with scurvy masquerading as a treatment related secondary malignancy.

Design/Method: Single Case Report

Results: A 7-year-old girl with 13q deletion syndrome and psychomotor retardation, treated for bilateral retinoblastoma with carboplatin, etoposide, vincristine and cryotherapy, developed bilateral leg pain and refusal to walk. She saw an orthopedic surgeon and was casted for 6 weeks due to a bilateral leg MRI showing edema of the bones. Development of gingival hypertrophy, bleeding gums, a petechial rash and significant weight loss resulted in referral to Pediatric Oncology. Concern for treatment related MDS or AML prompted further evaluation. Complete history revealed severe dietary limitations (pudding and canned spaghetti). Blood work showed anemia (10.3 G/dL), ESR and LDH elevation, uric acid 5.5 mg/dL and normal coags. Bilateral tibia/fibula x-rays were concerning for leukemic infiltration and verified on MRI. Bone marrow biopsy demonstrated hematopoietic marrow with rare atypical clusters of histiocytic-like cells. Bone biopsy of distal femur and tibia showed non-specific intertrabecular fibrosis. Due to her poor diet, bleeding gums without thrombocytopenia and unwillingness to walk, a vitamin C level was checked (undetectable) and supplementation started. Within one week she was walking and showed improvement in her gingival hypertrophy.

Conclusion: The diagnosis of scurvy is rare in America. Patients with scurvy present with anemia, bone pain, bruising, weight loss, gum disease and poor wound healing. Based on the history of 13q deletion and retinoblastoma, treatment related secondary malignancy was high on the differential. This case underscores the importance of a complete medical history, especially diet history, in children with developmental delay.
HORMONAL SUPPRESSION EXPERIENCE FOR OVARIAN PRESERVATION DURING CHEMOTHERAPY
Allison Grimes, Randal Robinson, Chatchawin Assanasen, Jennifer Knudtson. UT Health Science Center San Antonio, San Antonio, Texas, United States of America

**Background:** With more adolescent females surviving childhood cancer, chemotherapy-induced ovarian decline remains a significant problem. No standard of care for fertility preservation in this population exists. Controversy has surrounded the use of gonadotropin-releasing hormone agonists (GnRHa), though a recent meta-analysis among young adult women suggests temporary ovarian suppression with GnRHa’s significantly reduces the risk of chemotherapy-induced premature ovarian failure (POF). This counters the ASCO guidelines published several months earlier based on limited data for efficacy. Although the systematic review included few adolescent patients, the meta-analysis suggests a role for this pharmacologic approach in a population to which oocyte cryopreservation is often not feasible. Further evaluation will follow in a new COG trial.

**Objectives:** In 2013, several adolescents at our institution unable to pursue cryopreservation were initiated on GnRHa therapy. This report describes our local experience using hormonal suppression for ovarian preservation.

**Design/Method:** In 3 adolescent females undergoing chemotherapy at our institution, a GnRHa, Leuprolide, was provided as an intramuscular depo injection 11.25mg q3mo, and continued until chemotherapy completion. To minimize vasomotor symptoms associated with estrogen suppression, oral Norethindrone 5mg was given once daily during Lupron therapy. Baseline labs obtained included luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), and anti-mullerian hormone (AMH). FSH, LH, and E2 are standard evaluations for assessing ovarian reserve. Ovarian function is best assessed with AMH since it does not vary throughout the menstrual cycle, is detectable in both pre-pubertal and pubertal children, and decreases during chemotherapy in female patients of all ages. A detailed menstrual history was recorded at baseline and at follow-up visits throughout treatment.

**Results:** In both patients with available baseline labs, the AMH, LH, FSH, and E2 were within reference range for age. Both patients completed therapy and laboratory evaluation is ongoing. Menses has resumed in Patient 2. Patient 3 remains on therapy. No patients exhibited symptoms of estrogen depletion including hot flashes or headaches during treatment.

**Conclusion:** Although adult studies suggest that GnRHa’s reduce chemotherapy-induced POF, larger studies in adolescents are needed to determine whether the same effect can be achieved in this population. Pre-treatment serum hormone levels are critical to assess ovarian function after chemotherapy.
OCCURRENCE, EVALUATION AND OUTCOMES OF INCIDENTALLY OBSERVED NEUTROPENIA IN A PEDIATRIC OUTPATIENT POPULATION

Neel Bhatt, Sherif Badawy, Edwin Forman. Elmhurst Hospital Center/Icahn School of Medicine, Elmhurst, New York, United States of America

**Background:** Incidental neutropenia, defined as Absolute Neutrophil Count (ANC) <1500/mm3, discovered by a complete blood count (CBC) during routine child visits is often a cause of anxiety among general pediatric practitioners. Due to a lack of standard workup guideline, it is a common cause of referral to a hematologist.

**Objectives:** To address the necessity of standard workup guidelines for pediatric patients with incidental neutropenia.

**Design/Method:** This was a retrospective chart review of pediatric patients referred by general pediatric practitioners to a single hematologist, working at 2 urban hospitals from 2009-13. Charts were abstracted for demographics, White blood cells (WBC)/ANC levels, family history of neutropenia, history of major infections/hospitalizations, lab workup, and final diagnosis.

**Results:** 46 consecutive patients with persistent neutropenia, who were referred for hematologic evaluation, represented the study population. Their average age was 9.6±5.5 years and 65% were male. Their average initial WBC and ANC level were 4.09±2.67 x 10^3/µL and 770 ± 410 /mm3, respectively. 8 had low platelets (mean platelet: 146±46 x 10^3/µL), and 4 had low hemoglobin, (mean hemoglobin: 10.5±1.4 gm/dl), but none had all 3 cell lines abnormal. 4 had previous hospital admissions. Only 1 of them was due to persistently low ANC with fever and recurrent mouth sores, and was managed by Neupogen with an excellent response within 24 hours. None of the other 3 patients with hospitalizations were neutropenic at admission. No patients developed serious bacterial/fungal infections. 18 were evaluated by additional tests such as Immunoglobulin levels, Antinuclear Antibody, Serum Uric Acid, Lactate Dehydrogenase, and Antinuclear Cytoplasmic Antibody, but none of those tests were abnormal. 39 were diagnosed with presumptive Benign/ Ethnic/ Familial neutropenia based on a benign personal history regarding infections and a positive history of benign neutropenia or racial/ethnic background (African American, Middle Eastern, Asian, Hispanic), 3 with autoimmune neutropenia and 1 newborn with neutropenia secondary to maternal anti-psychotics use.

**Conclusion:** Benign/ Ethnic/ Familial neutropenia should be considered high in the differential diagnosis list when evaluating an asymptomatic incidental neutropenia patient without major infections/hospitalizations. A standardized approach is necessary with judicial use of diagnostic tests to evaluate such patients.
FUNCTIONAL ASSESSMENT OF PAIN IN PATIENTS WITH SICKLE CELL DISEASE
Prasad Bodas, Sarah Friebert, Ann Stratton, Lisa Sidebotham. Akron Children's Hospital, Akron, Ohio, United States of America

Background: Sickle cell disease is characterized by recurrent episodes of severe pain. Pain crises occur at various frequencies; some patients experience daily or more frequent episodes. A subset of patients exhibits a chronic pain phenotype. Assessment and treatment methods targeted at acute crisis detection and management are insufficient, and may have limited functional relevance for such patients. The role of multi-disciplinary care, including pediatric palliative care in this population is underexplored.

Objectives: This case series describes a novel functional pain assessment and management protocol for patients with sickle cell disease with recurrent vaso-occlusive crises.

Design/Method: Five patients (age, 12-19y) with recurrent and chronic pain were identified during routine care at the Pediatric Sickle Cell Disease Program at Akron Children’s Hospital. Assessment included determination of acute pain frequency and description of intensity via standard instruments (1-10 scale, FACES) and determination via narrative interviewing of effects of pain on daily life in three domains: i) family interpersonal dynamics; ii) extracurricular and social activities; and iii)school and/or employment. Personalized intervention plans were generated for each patient and implemented in an interdisciplinary pain clinic with expertise from both hematology and palliative care. Pharmacologic and non-pharmacologic interventions were utilized with each patient.

Results: In 5 patients, deficits in all domains were identified. Targeted interventions resulted in qualitative improvements in family dynamics and participation in social activities. Measurable improvement in grade attainment and/or achievement and maintenance of employment were demonstrated in all patients, as were decreases in emergency department, clinic, and hospital utilization for pain-related complaints. Hospital days per year decreased in all patients in the year after intervention relative to the year prior, with an overall decrease ranging from 14-76%. All patients showed improvement in school/employment, as indicated by enrollment in school, academic achievement, and grade attainment, and through maintenance of steady employment.

Conclusion: A model interdisciplinary pain intervention strategy for sickle cell related acute and chronic pain – combining traditional pain assessment/management strategies, qualitative and narrative assessments, and life domain-based interventions – yields improved pain-related outcomes and should be explored longitudinally in a larger group.
STUDY OF CD4+ CD25+ T-REGULATORY CELLS IN CHILDHOOD ACUTE IMMUNE THROMBOCYTOPENIC PURPURA

Mervat Hesham, Nahla Elattar, Ebtesam Ahmed, Laila Sherif, Mona Salah. Zagazig University, Zagazig, Sharkia, Egypt

Background: Although the breakdown of self-tolerance is a hallmark of ITP, its etiology and pathogenesis are not fully understood. Accumulating evidence support that T-regulatory cells play an essential role in controlling and preventing autoimmunity. Changes in the number of T-regulatory cells or its activity can be considered possible causes for the observed disturbances of immune regulation in patients with active Immune Thrombocytopenic Purpura (ITP).

Objectives: We aimed to study the expression and number of T regulatory (T-regs) as CD4+CD25high T cells in patients with acute ITP, and to analyse their relationship with the clinical features and treatment of acute ITP in children.

Design/Method: A prospective case control study was conducted on thirty children with acute ITP (15 males and 15 females) aged 2-15 years and fifteen age and sex matched healthy children as a control group at Pediatric and Clinical Pathology departments of Zagazig University Hospitals- Sharkia, Egypt in the period from July 2011 to August 2012. All patients and controls were subjected to full history, thorough clinical examination and laboratory investigations which included: Complete blood picture, Coomb’s test, Bone marrow aspiration (for patients only) and specific investigation for counting of the T regulatory cells CD4+CD25high cells by Flow cytometry (FAC Scan, Becton Dickinson and CELLQuest TM Software).

Results: There was a highly significant decrease in the percentage expression of CD4+CD25high T cells (T-regs) in children with acute ITP compared with controls. Our results showed no relation between CD4+CD25high count and the clinical data of the patients. A significant positive correlation was found between CD4+CD25high percentage and platelet count while CD3+/CD4+ showed no correlation. There was a significant reduction in CD4+CD25high percentage in patients received (steroid and IV immune globulin) treatment than patients who did not receive treatment or received steroid alone. While, CD3+/CD4+ showed no differences in patients with different lines of treatment.

Conclusion: A significant decrease in the percentage expression of CD4+CD25+ T cells (T-regs) in children with acute ITP suggesting specific role of these cells in the pathogenesis of childhood acute ITP.
THE UTILITY OF THE DDAVP CHALLENGE TEST IN PATIENTS WITH LOW VON WILLEBRAND FACTOR LEVELS AND VON WILLEBRAND DISEASE (VWD)
Natasha Archer, Mihail Samnaliev, Rachael Grace, Carlo Brugnara. Boston Children's Hospital, Boston, Massachusetts, United States of America

Background: VWD, the most common inherited bleeding disorder, is characterized by quantitative or qualitative defects of von Willebrand factor (VWF). Desmopressin (DDAVP), a synthetic derivative of vasopressin, promotes the release of VWF multimers resulting in a concomitant rise in factor VIII (FVIII) levels. The DDAVP challenge test is used to identify those patients in whom DDAVP can be used to treat and prevent bleeding episodes.

Objectives: To determine the utility of the DDAVP challenge test in patients with low VWF levels and VWD.

Design/Method: The hospital records for 251 pediatric patients who underwent DDAVP challenge testing from January 1, 2005 to December 31, 2013 at the Boston Children’s Hospital were retrospectively reviewed. Demographic and clinical data were collected. Patients with a ristocetin cofactor activity (VWF:RCo) level of 30-50% were diagnosed with low VWF levels and those with VWF:RCo level < 30% were diagnosed as VWD. Criteria for a DDAVP challenge complete response included a two-fold increase in BOTH post-VWF:RCo and FVIII procoagulant activity (FVIII:C) OR post-response levels >100%.

Results: Of the 251 patients, 40% were male with a median age of 9 years (range 1-23). 73% had blood type O. 170 (68%) had low VWF levels, 42 (17%) had type 1 VWD, 5 (2%) had type 2 VWD, and 34 (14%) had normal VWF levels. A complete response to DDAVP challenge was found in 161 (95%) with low VWF levels vs. 36 (86%) with type 1 VWD. 8 out of 9 (89%) patients with low VWF levels that did not have a response based on our criteria, had post-challenge levels within the normal range (VWF:RCo and FVIII:C levels > 50%). 4 (80%) with type 2 VWD responded to DDAVP. There were no statistically significant differences in race, blood type, pre-challenge labs, and desmopressin route in the DDAVP responders vs. non-responders with type 1 VWD.

Conclusion: Our data suggests that almost all patients with low VWF levels will have a complete response to DDAVP. Limiting the DDAVP challenge test to patients with type 1 and 2 VWD would result in a significant reduction in resource utilization and cost without a predicted increase in bleeding episodes.
A MULTICENTER STUDY OF INFERIOR VENA CAVA FILTERS IN THE PEDIATRIC POPULATION

Erin Blevins, Karen Glanz, Yuan-Shung Huang, Leslie Raffini, Russel Shinohara, Char Witmer. The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States of America

Background: Inferior Vena Cava (IVC) filter use in adults has increased dramatically over the past three decades with concerns regarding the indication for placement, timely retrieval, and long-term complications. Contrary to current recommendations, IVC filters are frequently used for primary prophylaxis in adults without DVT. It is unknown if these changes in IVC filter use are similar in the pediatric population due to sparse data that consists of only single center case reports or case series.

Objectives: To describe IVC filter use in pediatric patients admitted to U.S. children’s hospitals.

Design/Method: This retrospective multicenter cohort study utilized data from the Pediatric Health Information Systems (PHIS) administrative database, with 44 participating children’s hospitals. Subjects were included for analysis if they were less than 21 years of age, admitted to a PHIS hospital between 1-1-2004 to 12-31-2012 and had a procedure code for IVC filter placement. ICD-9-CM discharge codes were used to determine if a deep venous thrombotic (DVT) event occurred during the admission.

Results: During the 9 year study period 276 subjects met the inclusion criteria. The median age of subjects was 15 years. 54.7% (151) were male. 74.3% (205) had an ICD-9 code for DVT. 4% (11) had both a PE and DVT. 2.2% (6) had an isolated PE. The mean number of IVC filters placed per year was 6 per 100,000 admissions (min 4.9- max 7.1), which was constant throughout the study period (p-value- 0.17). The median number of filters placed by center was 4.5 (min 0-max 32). 27.3% (12) hospitals did not place filters during the study period. 37.3% (103) of subjects had an admission diagnosis of DVT and 2.2% (6) died during their admission.

Conclusion: IVC filter placement in pediatric patients remains a rare event and is most common in adolescents. Unlike in adults, the placement of an IVC filter in pediatric patients does not appear to be increasing over time, although there was a wide variation in IVC filter use by hospital. There appear to be fewer filters placed for primary prophylaxis because the majority of patients had a concurrent diagnosis of DVT during their admission.
CORRELATION BETWEEN MUSCULOSKELETAL FUNCTION AND RADIOLOGICAL JOINT SCORES IN HEMOPHILIA A ADOLESCENTS
Khaled Elgerby, Tamer Hassan, Mohamed Badr. Zagazig University, Zagazig, Egypt

Background: Hemophilic arthropathy is a very common complication of severe hemophilia, being provoked by recurrent articular bleedings. Since early 1980s, the severity of hemophilic symptomatic arthropathy has been assessed with conventional radiography according to the Pettersson score. Later on, MRI allowed a precise noninvasive assessment of all the articular and periarticular structures, which is the main limitation of conventional radiography. The functional independence score in hemophilia (FISH) is a performance-based instrument used to assess musculoskeletal function in patients with hemophilia.

Objectives: We aimed to evaluate the functional independence of hemophilia A adolescents and its correlation to radiological joint scores.

Design/Method: A cross-sectional study was carried out on 50 adolescent hemophilia A patients. Musculoskeletal function was assessed using the FISH and individual joints were assessed radiologically using the Pettersson score and MRI scale.

Results: The mean age of our patients was 16 ± 1.1 with a mean FISH of 23.32 ± 4.69 (range 13–28) and a mean Pettersson score of 2.32 ± 3.09 (range 0–13) for the knees, 1.86 ± 2.67 (range 0–11) for ankles and 1.42 ± 2.17 (range 0–10) for elbows. The mean MRI score for the knees was 3.92 ± 2.74 (range 0–10) while that for ankles was 3.16 ± 2.64 (range 0–10) and for elbows was 2.34 ± 2.63 (range 0–10). There was highly significant correlation between both radiological joint scores and FISH and between degree of factor VIII deficiency and each of FISH, Pettersson score and MRI score. MRI was superior to conventional radiography in detection of subchondral cyst formation and erosions at joint margins.

Conclusion: Given the highly significant correlation with both radiological joint scores, FISH appears to be a reliable tool for assessment of functional independence in adolescents with hemophilia A. MRI is more sensitive than conventional radiography in detection of early joint abnormalities.
OPTIMAL MANAGEMENT OF A RARE COAGULATION DISORDER: FACTOR V DEFICIENCY

Mohamed Elshinawy, Abdlhakimrawas, Yasser Wali. Sultan Qaboos University Hospital, Muscat, Oman

**Background:** Congenital factor V deficiency is a very rare coagulation disorder, with a prevalence of 1/1,000,000. In literature, Most of the reported cases are characterized by a mild to moderate bleeding phenotype.

**Objectives:** To review the initial presentations, clinical course and management of congenital factor V deficiency cases in Oman.

**Design/Method:** Case series.

**Results:** Two infants presented with intracranial hemorrhage at the ages of 4 weeks and 10 days respectively. The first baby was found to have markedly prolonged PT and aPTT, correctable with mixing study. Factor assay revealed severe congenital factor V deficiency. Fresh frozen plasma (FFP) was given repeatedly and he underwent neurosurgical evacuation of his parieto-temporal hematoma. Unfortunately, the second baby was misdiagnosed as late hemorrhagic disease of newborn in a peripheral hospital. She sustained a recurrent intracranial bleed which negatively impacted her neurodevelopment. The sibling of the 1st baby was delivered by an elective cesarean section in our center, screened at day 3 of life and diagnosed with severe factor V deficiency. Despite the lack of international guidelines, the three babies were started on regular prophylaxis with FFP twice weekly; through a port-a-cath. Our fourth patient has moderate factor V deficiency, manifested by joint bleeds, requiring on-demand FFP. All Data are displayed in Table I.

**Conclusion:** Early recognition and optimal management of rare coagulation disorders are major determinants of prognosis. Compared to on-demand therapy, life-long prophylaxis in severe coagulation disorders is the standard of care. However, many difficulties exist including lack of commercially available purified products, viral transmission and venous access.

**Table I: Clinical Characteristics and Management of Factor V Deficiency Cases**

<table>
<thead>
<tr>
<th>Case</th>
<th>1*</th>
<th>2</th>
<th>3*</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age</td>
<td>4 years</td>
<td>4 years</td>
<td>9 months</td>
<td>10 years</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age of presentation</td>
<td>4 months</td>
<td>10 days</td>
<td>3 days</td>
<td>5 years</td>
</tr>
<tr>
<td>Bleeding phenotype</td>
<td>Spontaneous intracranial</td>
<td>Spontaneous intracranial</td>
<td>Asymptomatic</td>
<td>Post-traumatic musculoskeletal</td>
</tr>
<tr>
<td>Neurodevelopmental outcome</td>
<td>Normal</td>
<td>Delayed</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Factor V level</td>
<td>0.03 %</td>
<td>0.04 %</td>
<td>0.02 %</td>
<td>4.5 %</td>
</tr>
<tr>
<td>FFP Therapy</td>
<td>Prophylaxis</td>
<td>Prophylaxis</td>
<td>Prophylaxis</td>
<td>On-demand</td>
</tr>
</tbody>
</table>

* Cases (1) and (3) are siblings
AUTO IMMUNE CYTOPENIAS IN PEDIATRIC HODGKIN LYMPHOMA PATIENTS
Syed Nasir Abbas Bukhari, Mehboob Ahmed, Shazia Riaz. Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Punjab, Pakistan

Background: Autoimmune cytopenias such as auto immune hemolytic anemia (AIHA) and autoimmune thrombocytopenia (AITP) are known phenomenon seen with malignant lymphomas. They are more frequently seen in non Hodgkin lymphomas, similar complication are rarely reported in Hodgkin lymphoma (HL). The association between auto immune cytopenias and HL has been reported in adult patients’ population. Such complications are less frequently reported in pediatric HL patients

Objectives: To report a case series of pediatric HL patients with immune cytopenias with regard to clinical and laboratory features and treatment outcome

Design/Method: We identified 5 pediatric patients of Hodgkin lymphoma who had auto immune cytopenias at time of diagnosis. The male to female ratio was 4:1. Four male suffered with autoimmune hemolytic anemia and only female with autoimmune thrombocytopenia. Stage of HL ranged from I to IV. Direct Coombs test was positive in all AIHA patients and AITP was confirmed by bone marrow biopsy. Patients were treated with alternating cycles of ABVD(Adriamycin, Bleomycin, Vincristine, decarbazine) /COPDac(cyclophosphamide, vincristine, decarbazine, prednisolone,) depending upon the stage of Hodgkin disease and no specific treatment was given for immune cytopenias

Results: Autoimmune cytopenias resolved including normalization of laboratory investigation by treating lymphoma only. Patients are on regular follow-up without any complication

Conclusion: Our case series shows that HL of any stage may occur with Autoimmune Cytopenias and chemotherapy according to HL stage results in resolution of immune cytopenias.
URINARY BIOMARKERS ARE ASSOCIATED WITH TOXICITY AND DRUG EXPOSURE IN PEDIATRIC ONCOLOGY PATIENTS TREATED WITH HIGH DOSE METHOTREXATE  
Andrew Bukowinski, Tomoyuki Mizuno, Tsuyoshi Fukuda, Alexander Vinks, Adam Lane, Stuart Goldstein, Maureen O'Brien. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

**Background:** High-dose methotrexate (HD-MTX) with leucovorin rescue is a critical component of therapy for pediatric malignancies. Because MTX can precipitate in renal tubules safe administration requires hyperhydration and alkalinization. The ability to identify patients at risk for acute kidney injury (AKI) with delayed MTX clearance and subsequent systemic toxicities is limited. Specific urinary biomarkers can predict development of AKI and severity in the settings of sepsis, aminoglycoside therapy, and cardiopulmonary bypass.

**Objectives:** To evaluate associations between urinary biomarkers [Neutrophil gelatinase associated lipocalin (NGAL), Kidney injury molecule-1 (KIM-1) and Interleukin-18 (IL-18)], kidney function, methotrexate associated toxicities and drug exposure in patients receiving HD-MTX.

**Design/Method:** 18 patients received 1-12g/m2 HD-MTX over 4-24 hours. Serum creatinine and MTX were measured per the oncology treatment protocol. Urine samples were obtained prior to the infusion of HD-MTX at scheduled intervals during the infusion, at 24 hours, and daily thereafter. Urinary NGAL, KIM-1, and IL-18 were measured by enzyme linked immunosorbent assay and normalized to urine creatinine. Clinical toxicities (delayed MTX clearance, mucositis, and myelosuppression resulting in chemotherapy delay) were collected by chart review and correlated to biomarker levels using the Wilcoxon Rank sum test. MTX area under the curve (AUC) was calculated with MWPharm software using Bayesian estimation. Linear regression was performed using log of urinary biomarker levels and log of AUC to evaluate for correlations.

**Results:** Patients with toxicity demonstrated significantly higher AUC levels (p<0.05). Elevated NGAL levels at 24 and 36-48 hours are associated with toxicity and MTX AUC (p<0.02, p<0.01 respectively). KIM-1 levels at 12-16 and 36-48 hours are correlated with MTX AUC (p<0.01, p<0.03 respectively). KIM-1 levels at 36-48 hours are not associated with clinical toxicity (p<0.09) but is limited by cohort size. IL-18 levels were not associated with any measured parameters.

**Conclusion:** Urinary NGAL levels are associated with both MTX exposure (AUC) and clinical toxicity. KIM-1 levels are associated with MTX exposure. Further evaluation of urinary NGAL and KIM-1 levels and their predictive value for toxicities in an expanded patient cohort is ongoing with the goal of integration of these biomarkers to adjust supportive care for patients receiving HD-MTX.
DEVELOPMENT AND IMPLEMENTATION OF NOVEL ELECTRONIC TOOLS FOR OBESITY PREVENTION IN PEDIATRIC LEUKEMIA PATIENTS AND SURVIVORS
Rhea Li, Alicia Beltran, Margaret Raber, Thomas Baranowski, Joya Chandra. Children's Cancer Hospital at MD Anderson, Houston, Texas, United States of America

Background: Approximately 80% of children diagnosed with cancer survive their disease, but are frequently burdened with health problems later in life, including obesity and obesity-related health issues such as cardiac dysfunction, risk of second cancers and endocrinopathies. Being overweight or obese affects quality of life among survivors of childhood tumors because of its relationship with other chronic diseases. Our recent cross-sectional survey with 170 pediatric cancer survivors at the Children’s Cancer Hospital (CCH) at MD Anderson (MDACC) revealed that the majority of survivors failed to meet national guidelines for dietary intake and physical activity (PA). Strongest interest in diet or PA interventions was expressed for computer-based programs.

Objectives: To address the need for energy balance interventions in pediatric oncology, we have designed a multidisciplinary program called, ON (Optimizing Nutrition) to Life. Components of the program include development of an electronic cookbook being used in personalized energy balance counseling, and use of innovative video games to promote healthy behaviors. Biomarkers such as oxidative stress are being assessed in concert with these interventions.

Design/Method: We have designed and launched an electronic cookbook with calorie and micronutrient content, and search engines customized for symptoms experienced by cancer patients. Personalized counseling using the cookbook in a randomized trial is ongoing, and measurement of oxidative stress as a biomarker for diet and exercise change is being conducted. To test the receptivity of pediatric oncology patients and survivors to serious video games that aim to improve energy balance behaviors, we completed qualitative research on two video games, originally designed for healthy children.

Results: Improved health behaviors were reported by users of the eCookbook enrolled in the personalized counseling intervention. Video games were found to be well received by the majority of subjects, with few changes suggested.

Conclusion: These pilot studies demonstrate the potential positive impact of a web-based cookbook and video games on health behaviors in pediatric cancer patients and survivors. Future studies will test the efficacy of combining these modalities into a game that directs players to the eCookbook.
AZACITIDINE IS WELL TOLERATED IN A PEDIATRIC PATIENT WITH FANCONI ANEMIA (FA) AND ACUTE MYELOGENOUS LEUKEMIA (AML) - A CASE REPORT
Hilda Ding, Ghada Abusin, Rachel Egler, Sanjay Ahuja, Yousif Matloub, Rolla Abu-Arja. Case Western Reserve University, Cleveland, Ohio, United States of America

Background: AML in FA patients is associated with extremely poor prognosis. This is mainly due to chemosensitivity that makes treatment challenging. Currently, the only definitive treatment for these patients is stem cell transplantation (SCT). The role of pretransplant chemotherapy is unknown. However, bulky leukemia may reduce the success of SCT. We present a patient with AML secondary to FA in whom we treated with azacitidine prior to SCT and again prior to donor lymphocyte infusion (DLI) after relapse.

Objectives: To report a case of a patient with Fanconi Anemia and AML treated with azacitidine.

Design/Method: Case report.

Results: Thirteen year-old male with FA presented with leukocytosis, anemia, thrombocytopenia and splenomegaly. Bone marrow (BM) evaluation revealed 78% blasts with 7q deletion and 1q duplication in all cells. Induction included reduced dose cytarabine (1 gm/m2/dose every 12 hours on days 1, 2, 8 & 9). Following the third dose, he developed respiratory failure and catecholamine resistant shock secondary to rapid tumor lysis. Given rising WBC count, remaining cytarabine doses were given with gradual increase in dosing and premedication with dexamethasone. End of induction BM showed hypocellularity with 10% blasts and unchanged cytogenetics. At 5 weeks post induction, blasts reappeared without signs of BM recovery. He was then started on azacitidine (50 mg/m2/day for 7 days every 21 days) for two cycles while awaiting SCT. He suffered bilateral lower extremity pain as a side effect, which was controlled with oxycontin. Repeat BM evaluation thereafter revealed hypocellular bone marrow with <10% blasts. Cytogenetics revealed 41.6% of cells with 7q deletion and normal signal pattern in remaining cells. Patient underwent allogeneic reduced intensity SCT and achieved complete remission on day 30. On day 94, he relapsed with 40% blasts in the BM. He again received one cycle of azacitidine followed by low dose cytarabine prior to DLI. He achieved complete remission with 98% donor chimerism 30 days post-DLI.

Conclusion: Azacitidine is well tolerated in patients with FA. Although the effect may not be sustainable, it could be an option to bridge FA patients to HSCT and/or DLI. Further studies are needed.
IMPROVED OUTCOME OF PHILADELPHIA POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA WITH AGGRESSIVE CHEMOTHERAPY WITH IMATINIB IN CHILDREN: A RETROSPECTIVE ANALYSIS FROM TATA MEMORIAL HOSPITAL MUMBAI
Pankaj Dwivedi, Avinash Pandey, Sumit Gujral, Arora Brijesh, Banavali Shripad. Tata Memorial Hospital, Mumbai, Maharashtra, India

Background: Philadelphia positive acute lymphoblastic leukemia (Ph +ve ALL) is a very high risk subset of childhood ALL with historically poor outcomes without stem cell transplantation before the advent and use of Imatinib Mesylate. There is paucity of data on outcome of Ph+ve ALL from India where stem cell transplantation is not affordable for most patients.

Objectives: outcome of Philadelphia positive Acute lymphoblastic leukemia with aggressive chemotherapy with Imatinib in children: A retrospective analysis

Design/Method: We audited records of 54 pediatric patients diagnosed between January 2004-December 2010 with Ph +ve ALL treated with institutional ALL protocol (MCP-841) with or without Imatinib. No patient underwent stem cell transplantation. PFS and OS were calculated from date of diagnosis to date of relapse/progression and date of last follow up respectively.

Results: Median age of presentation was 11.3 years (3-17.7 years). The presenting WBC counts ranged from 870 to 6,42,000 cells/mm3 (Median 1,18,000 cells/mm3). Thirty one had CNS I status, four were CNS II and nine had CNS III status. Of 54 patients, thirty five patients received Imatinib during their treatment; 12/35 received Imatinib during induction and 23/35 received Imatinib post induction. 14 didn’t receive Imatinib any time during treatment. For whole group median overall survival (OS) was 18.33 (13.4-23.12) months. OS for patients who received Imatinib was superior, Median OS was 35.2 (13-57.38) months as compared to patients who didn’t receive Imatinib the Median OS was 6.9 months (0-18 months). Patients who initiated Imatinib during induction did poorly Median OS 10.9 (8-13.85) months due to increased toxic deaths compared to the patients who started it after induction in which median is not reached (one year OS 73.4% and two year OS 66%). In multivariate analysis Imatinib received and timing of Imatinib were found to be statistically significant factors that had impact on overall survival compared to the patients who started it after induction in which median is not reached (one year OS 73.4% and two year OS).

Conclusion: Outcome of Ph+ALL without Imatinib and stem cell transplantation is dismal. However, combined therapy including aggressive chemotherapy and Imatinib improves outcome especially in patients without hyperleukocytosis. Imatinib should preferably be initiated after induction therapy to minimize treatment related toxicity and death.
HODGKIN LYMPHOMA IN CHILDHOOD: CLINICOPATHOLOGICAL FEATURES AND THERAPY OUTCOME AT TWO EGYPTIAN CENTERS

Laila Ebraheim, Usama Elsafy, Elhamy Abdelkhalek, Seham Azab, Tamer Hassan, Mohamed, Beshir.
Zagazig University Pediatric Oncology Unit, Zagazig, Sharkia, Egypt

Background: Hodgkin lymphoma account for 5-6% of all childhood cancer. It displays characteristics epidemiological, clinical and pathological features according to various geographic areas.

Objectives: to assess the epidemiological aspects, clinicopathological features and treatment outcome of pediatric Hodgkin lymphoma (HL) treated at two Egyptian centers: Zagazig University pediatric oncology Unit as well as Benha Special Hospital Pediatric Oncology Unite over 8 years.

Design/Method: This was a cross-sectional study. Data were collected by a retrospective review of 59 medical record of children with HL admitted to the 2 oncology unites during the period of January 2004 to January 2012.

Results: The age at presentation ranged from 3-14 years with mean of 39.8±24.months. Male: female ratio was 1.7:1. Lymphadenopathy was the most common presentation 96.6%. Mixed cellularity subtype was dominant 50.8% of cases, followed by nodular sclerosis 28.9%, lymphocyte predominant 18.6% and the least common subtype was lymphocyte depletion 1.7% of cases respectively. More than half of patients had advanced disease (Ann Arbor stage III / IV disease) 55.9%. The duration of follow up ranged from 5-87 months (mean 39.7624±23 months), the 5 years OS and EFS for all patients was 96.6% and 84.7% respectively. None of the clinical, epidemiological or pathological characteristics had a significant association with the probability of survival.

Conclusion: HL occurs in younger age, with a higher incidence of mixed cellularity subtype and advanced disease. The outcome of HL in our two centers were satisfactory approaches the international percentage.
THE NATURAL HISTORY OF SKIN-LIMITED LANGERHANS CELL HISTIOCYTOSIS: A SINGLE INSTITUTION EXPERIENCE
Matthew Ehrhardt, Stephen Humphrey, Michael Kelly, Yvonne Chiu, Sheila Galbraith. Medical College of Wisconsin, Milwaukee, Wisconsin, United States of America

Background: Prior reports of Langerhans cell histiocytosis (LCH) suggest that isolated skin involvement is rare and that many children presenting with isolated skin manifestations rapidly develop multisystem disease. These reports reflect an era in which decreased disease awareness and availability of dermatology specialists may have led to referral bias and missed diagnoses of skin-limited LCH.

Objectives: The objective of this study was to estimate the incidence of progression from skin-limited to multisystem LCH in a cohort spanning an era of increased provider awareness and access to pediatric dermatology care.

Design/Method: A retrospective chart review was performed on all patients newly diagnosed with LCH between 2001 and 2012 at the Children’s Hospital of Wisconsin. Data was collected for patients with biopsy-proven skin LCH. Skin-limited disease was confirmed through extensive review of laboratory, physical examination, and imaging reports. Descriptive statistics were generated.

Results: Sixteen individuals with skin-limited LCH were identified. The median age at onset of skin eruption was birth (range: birth to 9 months), while the median time from onset to diagnosis was 18 days (range: 1 day to 12 months). The median duration of follow-up was 19.5 months (range: 2 weeks to 10 years) from the time of diagnosis. Only 1 patient (6%) progressed to multisystem LCH. One additional patient (6%) experienced refractory skin-limited disease. All others experienced complete resolution. For patients without progressive or refractory disease, resolution of skin findings occurred within 7 months from onset compared to 17 months for the patient with progressive disease.

Conclusion: Progression of skin-limited to multisystem LCH likely occurs less frequently than previously described. Patients with protracted skin-involvement may be at higher risk for progression to multisystem disease.
EVALUATION OF BONE MINERAL DENSITY IN CHILDREN WITH ACUTE LYMPHOBlastic LEUKEMIA (ALL) AND NON – HODGKIN S LYMPHOMA (NHL)
Saghi Elmi, Reza Erfani Sayyar, Sam Elmi Dr.Sheikh Children Hospital, Mashhad, Khorasan-E-razavi, Iran

Background: Acute lymphoblastic leukemia (ALL) and Non-Hodgkin's Lymphoma (NHL) are the most common childhood and adolescence malignancy respectively. Therapies such as corticosteroids, cytotoxic and radiotherapy effect on bone density and put the child at risk of osteoporosis and pathological fractures.

Objectives: Evaluation of Bone mineral density and bone biomarkers in children with Acute lymphoblastic leukemia (ALL) and Non-Hodgkin's Lymphoma (NHL) referred to Dr Sheikh hospital.

Design/Method: This 3-year cross sectional study was performed in Dr. Sheikh Children's Hospital in Mashhad on 50 children with ALL (n = 25) and NHL (n = 25). Half of them were received (n = 25) chemotherapy alone and half of them chemotherapy plus radiotherapy (n = 25). All children were in the remission phase. We assessed them by DEXA bone mineral densitometery (BMD) on the lumbar spine and femoral neck (hip). We also measured some bone biomarkers include calcium (ca), phosphorus (p), parathoromone (PTH), alkaline phosphatase (ALP) in plasma. Results by age, height, sex and Body Mass Index (BMI) were adjusted with special software.

Results: Mean age was 8.28 ± 3.93 years. There was no significant difference on bone biomarkers (Ca, P, ALP, PTH) between ALL, NHL and also between the two treatment groups. Children with ALL had lower density at the hip and lumbar spine (respectively p value < 0.001 and p value = 0.018). A total of 50 patients, the hip BMD showed normal results in 3 patients (6%), in 14 patients (28%) osteopenia were seen and 33 patients (66%) had osteoporosis. In whom received radiotherapy plus chemotherapy, one patient had normal BMD and 24 patients (48% of total patients) at the hip and 22 patients (44%) at lumbar spine had decreased BMD. In contrast, in whom had only chemotherapy, 24 patients (48%) had osteoporosis at hip and 23 (46%) at the lumbar spine. There was no significant difference in BMD between the sexes.

Conclusion: Given that 94% of children had abnormal bone density, seem to pay more attention to the metabolic status and BMD in children with cancer can develop appropriate strategies to improve health and quality of life.
HIGH LEVELS OF FLT3 LIGAND (FL) REVERSE ETOPOSIDE RESISTANCE IN FLT3-MUTANT ACUTE LEUKEMIA VIA SUBSTRATE INHIBITION: IMPLICATIONS FOR TREATMENT

Yarden Fraiman, Colleen Annesley, Daniel Magoon, Di Sun, Patrick Brown. Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America

Background: FLT3 is a tyrosine kinase receptor expressed on hematopoietic progenitors. Normally activated by FLT3 ligand (FL), FLT3 is essential in the development and proliferation of hematopoietic progenitors. Pediatric leukemias often express high levels of FLT3. 20-25% of AML and 5% of ALL harbor FLT3-activating mutations which are poor prognosticators. Earlier experiments have shown that though constitutively activated, FL can further activate FLT3 mutated leukemia cells. No studies have examined FL levels in pediatric patients. The effect of FL on chemotherapeutic efficacy has never been examined.

Objectives: 1) Determine FL levels of pediatric patients during myelosuppressive chemotherapy 2) Examine the functional effect of FL on both WT and activated FLT3 leukemias.

Design/Method: 1) Characterizing the FL trend- Plasma from 4 multi-center clinical trials of AML and ALL pediatric patients analyzed by FL ELISA in duplicate. 2) Functional effect of FL- Cells were plated for 72hr at etoposide IC50 with increasing concentrations of recombinant human FL. Cell cycle was analyzed by propidium iodide staining and apoptosis was determined by annexin V and 7-amino-actinomycin (7-AAD) binding. 3) Mechanism of FL effect- Cells were incubated for 72hr in serum-free conditions with either 4,000pg/mL, 62.5pg/mL or no FL. Following incubation, total and phosphorylated FLT3 levels were assessed by Western blot following FL stimulation.

Results: 1) Pediatric patients undergoing chemotherapy experience rise in FL with mean peak at day 14 (p<0.0001) following initiation of therapy 2) FLT3-activated cell lines demonstrate resistance to etoposide killing and induced cell cycle arrest at low concentrations of FL with sensitivity returning at high concentrations in a dose-dependent manner. 3) Cells incubated in 4,000pg/mL FL had diminished baseline pFLT3 relative to tFLT3.

Conclusion: Pediatric patients undergoing myelosuppressive chemotherapy experience characteristic rise in FL with peak 14 days after treatment initiation. In vitro results demonstrate that prolonged exposure to low levels of FL induces resistance to etoposide while high levels of FL ensure sensitivity to etoposide in FLT3 via a mechanism of substrate inhibition. These results suggest the potential of utilizing the chemotherapy-induced FL peak at day 14 as an optimal time to initiate etoposide to ensure further killing of FLT3-activated cells that have escaped chemotherapy.
POTENTIAL DRUG-DRUG INTERACTIONS AMONG HOSPITALIZED CHILDREN WITH CANCER


**Background:** Polypharmacy in hospitalized pediatric cancer patients is substantial. Oncology patients are at risk for potential drug-drug interactions (PDDI), which can lead to adverse events, increased toxicity, compromised symptom management, and potentially altered cure rates.

**Objectives:** To elucidate the prevalence, and potential severity, of potential drug-drug interactions (PDDI) in hospitalized children with cancer.

**Design/Method:** Retrospective cohort study of 39,612 hospitalized pediatric patients with an ICD-9 diagnosis of malignancy from the Pediatric Health Information System database (44 hospitals, 2011). Clinically relevant drug exposures were analyzed daily for each patient, and using the Micromedex Index (Truven Health Analytics Inc., Ann Arbor, MI), we determined the frequency and severity of PDDI (contraindicated, major, moderate, minor) during each hospitalization.

**Results:** Patients in this cohort were exposed to 1227 distinct medications, of which 456 were involved in PDDI. Morphine (6.2%) and ondansetron (5.4%) were the most common drugs involved in PDDI with other medications, while anti-infectives (18.0%) followed by opioids (17.8%) were the most common therapeutic classes involved in PDDI. The proportion of hospitalizations containing at least one major PDDI was 59.7%, moderate PDDI 47.4%, and contraindicated PDDI 9.9%. Patients <1 year of age had the greatest proportion of contraindicated PDDI, whereas major and moderate PDDI were most prevalent in patients aged 15-20 years. The prevalence of any PDDI by tumor class was similar: 71.6% (leukemia/lymphoma), 71.2% (solid), 72.4% (CNS) and 77.5% (multiple/secondary tumors). With increasing length of stay, the proportion of hospitalizations having any PDDI increased linearly: 61.5% (1 day admission), 63.3% (2-3 days), 72.4% (4-7 days), 88.3% (8-14 days), 94.2% (15-30 days) and 98.4% (>30 days). Accordingly, the median number of PDDI increased with longer hospital stays: 1 (1 day hospitalizations), 1 (2-3 days), 2 (4-7 days), 5 (8-14 days), 8 (15-30 days) and 23 (>30 days).

**Conclusion:** Potential drug interactions in hospitalized pediatric cancer patients are highly prevalent and associated with moderate or major potential harm. Elucidating the patient and disease characteristics associated with PDDI, and the subsequent patient safety outcomes, is the focus of our ongoing work.
TARGETING CALM-AF10 LEUKEMIA CELLS WITH NUCLEAR EXPORT INHIBITORS
Stephanie Fritch Lilla, Amanda Conway, Catherine Lavau, Daniel Wechsler. Duke University, Durham, North Carolina, United States of America

**Background:** The t(10;11) chromosomal translocation gives rise to the CALM-AF10 fusion protein and has been identified in pediatric and adult patients with T-cell ALL and AML. We have shown that CALM contains a nuclear export signal (NES) that plays a critical role in CALM-AF10 dependent transformation. Nuclear Export Inhibitors (NEIs) are compounds that bind to the nuclear transport receptor CRM1 and block its ability to interact with NES-containing proteins.

**Objectives:** We hypothesize that blocking the interaction of CALM-AF10 with CRM1 using NEIs will interfere with its oncogenic properties, thereby inhibiting leukemia cell proliferation. The mechanism by which NEIs decrease CALM-AF10 leukemia cell proliferation was evaluated by assessing apoptosis, cell differentiation and colony formation.

**Design/Method:** We derived CALM-AF10 leukemia cell lines by retroviral transduction of murine hematopoietic precursors with CALM-AF10. Rates of cell proliferation in vitro were assessed using flow cytometry following exposure to two different NEIs: leptomycin B [LMB] and KPT-KPT330 (Karyopharm Therapeutics, Inc.). Normal murine bone marrow was also treated with NEIs. Apoptosis was evaluated by measuring annexin V binding. Mac-1 and GR-1 staining were performed to assess cell differentiation. The frequency of colony formation was assessed in NEI-treated and -untreated cells.

**Results:** CALM-AF10 cell lines demonstrated decreased cell viability in the presence of NEIs. The IC50 for LMB was 0.1 nM - 0.15 nM. The IC50 of KPT-330 was 150 nM – 250 nM. Normal bone marrow cells tolerated doses up to 500 nM of KPT330 with only 20% decrease in cell viability. We found increased apoptosis (2-10 fold) in LMB- or KPT-treated cells compared with untreated cells. Cell differentiation and colony formation were not significantly affected by NEI treatment.

**Conclusion:** We have shown that both NEIs limit the proliferation of CALM-AF10 leukemia cells in vitro, while largely sparing normal hematopoietic precursors. Apoptosis appears to contribute to the cytotoxicity of NEIs. We are currently evaluating the response of CALM-AF10 leukemia cells to additional Karyopharm NEIs, in hope of identifying an agent that is more specific for the CALM NES:CRM1 interaction. Treatment with NEIs represents a potential novel adjunctive therapeutic approach in patients with CALM-AF10 mediated malignancies.
ALLOPURINOL USE DURING MAINTENANCE THERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA AVOIDS MERCAPTOPURINE RELATED HEPATOTOXICITY
Nicole Giamanco, Laura Foster, Dina Parekh, Anne Warwick, Kenneth Lieuw. Walter Reed National Military Medical Center, Bethesda, Maryland, United States of America

**Background:** 6-Mercaptopurine (6-MP) is an integral part of treatment for acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma. 6-MP is metabolized into the pharmacologically active metabolite, 6-thioguanine nucleotide (6-TGN) which is primarily responsible for the myelosuppresive effects of 6-MP as well as 6-methylated metabolite (6-MMPN) which is associated with hepatotoxicity. Other enzymes such as xanthine oxidase metabolize 6-MP into thiouric acid resulting in variable levels of 6-TGN. Although guidance for dose reduction in TPMT deficient patients exists, current protocol guidance for wild type TPMT patients with excessive 6-MMPN and hepatotoxicity is to hold 6-MP until transaminitis has improved. While simple adjustments in 6-MP dosing will result in adequate 6-TGN levels with acceptable 6-MMPN levels in most patients, some patients preferentially shunt 6-MP into 6-MMPN. It was recently recognized that combination therapy with allopurinol and 6-MP alters the metabolism of 6-MP towards increasing 6-TGN levels and decreasing 6-MMPN levels through an unexpected indirect mechanism.

**Objectives:** We discuss a six year old male with lymphoblastic lymphoma with wild type TPMT levels who developed recurrent grade four hepatotoxicity from daily 6-MP during standard maintenance therapy per AALL0932 protocol. Analysis of thiopurine metabolites showed he had elevated 6-MMPN causing severe transaminitis. We thus successfully utilized combination therapy with allopurinol with reduced 6-MP dosing to shunt 6-MP metabolism away from 6-MMPN towards 6-TGN. His 6-TGN levels have remained significantly above levels shown to be correlated with improved outcomes and he has tolerated this combination therapy for over one year with adequate 6-TGN levels and normal transaminase levels.

**Design/Method:** n/a

**Results:** n/a

**Conclusion:** There have been several studies which have correlated 6-TGN levels to event free survival in ALL patients, and it is now accepted that there is prognostic importance to delivering maximum tolerated doses of 6-MP. We report the successful combination therapy with allopurinol and 6-MP to avoid hepatotoxicity resulting in adequate 6-TGN levels in a patient on an ALL protocol. We suggest that combination therapy with allopurinol and 6-MP can be safely delivered in an ALL protocol and can provide potential benefits to other patients whose pharmacogenetic profile shunts 6-MP metabolism towards lower 6-TGN levels and high 6-MMPN levels.
REGULATION OF CELL CYCLE PROGRESSION BY CASEIN KINASE II (CKII) VIA IKAROS AND ROLE OF CKII INHIBITORS IN LEUKEMIA
Chandrika Gowda, Chunhua Song, Xiaokang Pan, Mansi Sachdev, Kimberly Payne, Sinisa Dovat.
Penn State University Medical Center, Hershey, Pennsylvania, United States of America

Background: Casein Kinase II (CK2) is an oncogenic kinase that is overexpressed in leukemia. The molecular mechanism by which CK2 exerts its oncogenic function is largely unknown. We have previously demonstrated that CK2 directly phosphorylates the Ikaros tumor suppressor in vivo at multiple, evolutionarily conserved amino acids. CK2-mediated phosphorylation of Ikaros results in reduced DNA binding affinity, loss of pericentromeric localization and impaired Ikaros transcriptional repression.

Objectives: To test the effects of specific CK2 inhibitors on Ikaros function as a transcriptional regulator of genes that promote cell cycle progression. We hypothesize that the pro-oncogenic activity of CK2 in leukemia involves functional inactivation of Ikaros, and that CK2 inhibition will result in restoration of the tumor suppressor function of Ikaros and have an anti-leukemia effect.

Design/Method: 1) quantitative Chromatin Immunoprecipitation (qChIP), 2) Luciferase reporter assay 3) Retroviral transduction 4) Cytotoxicity assay 5) Leukemia Xenograft mouse model

Results: qChIP showed that Ikaros binds to the promoters of two genes that are essential for mitosis, CDC25A, ANAPC1 and ANAPC7, in leukemia cell lines and in primary leukemia cells. Increased expression of Ikaros via retroviral transduction was associated with increased binding of Ikaros to the promoters of CDC25A, ANAPC1 and ANAPC7 and their transcriptional repression. Luciferase reporter assay confirmed that Ikaros can directly repress transcription of both ANAPC1 and ANAPC7. These data suggest that Ikaros negatively regulates cell cycle progression during mitosis and that Ikaros function as a repressor of CDC25A, ANAPC1 and ANAPC7 is impaired in leukemia. To evaluate ability of CK2 inhibition to restore Ikaros repressor activity in leukemia, we treated pre-B acute lymphoblastic leukemia (B-ALL) cell line, Nalm6 with a specific CK2 inhibitor. We also treated murine xenograft model of B-ALL with specific CK2 inhibitor. Treatment resulted in increased Ikaros binding to promoters of CDC25A, ANAPC1 and ANAPC7, along with transcriptional repression of both genes. This was associated with prolonged survival of B-ALL xenograft mice that were treated with CK2 inhibitor.

Conclusion: These data suggest that CK2 inhibitors can regulate cell cycle progression in leukemia cells by restoring the transcriptional repressor function of Ikaros. Our results demonstrate efficacy of CK2 inhibitors as a novel treatment for leukemia.
SARCOIDOSIS-LYMPHOMA SYNDROME IN A PEDIATRIC PATIENT
Nathan Hall, Children's Mercy Hospital, Kansas City, Missouri, United States of America

**Background:** Sarcoidosis-lymphoma syndrome (SLS) is uncommon, but a well documented association in middle aged individuals whom initially present with sarcoidosis and develop lymphoma within years. Worldwide, sarcoidosis is most often diagnosed in the third and fourth decades of life, and rarely presents in pediatric patients. In 1986, H. Brickner postulated the coexistence of sarcoidosis and malignancy as lymphoma was noted to be 5.5 times more common in middle aged patients. Sarcoidosis-lymphoma syndrome includes the following features: (1) the onset of sarcoidosis precedes lymphoma by at least 1-2 years; (2) the median age is greater than 40 years old; the associated lymphoma is most frequently Hodgkin disease (Cohen and Kurzrock, 2007). SLS additionally poses a diagnostic dilemma as FDG-PET is a well known diagnostic tool in the diagnosis of Hodgkin lymphoma, but is becoming widely used as well in the diagnosis of sarcoidosis.

**Objectives:** The objective of this case study is to inform the medical community of a rare association of an adult disease process in a pediatric patient and the importance of histopathology when repeat PET scans are positive in conjunction with the diagnosis of sarcoidosis.

**Design/Method:** Case report

**Results:** A 12 year old male who was diagnosed at the age of 4 with sarcoidosis, who 8 years later developed Hodgkin lymphoma. The earliest published cases of SLS was noted by Brickner et al in 1989 where a 16 year old was found to have the association.

**Conclusion:** This is the youngest case of SLS known in the literature to date whom without tissue biopsy may have been misdiagnosed with recurrence of sarcoidosis. Reference:Cohen, PR, Kurzrock, R, Clinics in Dermatology, 2007.
PROTON THERAPY FOR TREATMENT OF THE MEDIASTINUM IN PEDIATRIC PATIENTS WITH HODGKIN LYMPHOMA


**Background:** Mediastinal radiation therapy is an integral component of multi-modality treatment for many children with Hodgkin Lymphoma (HL). Proton therapy may allow improved normal tissue sparing, which is particularly important for this population, for whom prognosis is excellent and survivorship is expected to be of long length.

**Objectives:** To investigate tolerability, outcomes, and toxicities associated with proton therapy for treatment of the mediastinum.

**Design/Method:** 19 consecutive HL patients at The Children’s Hospital of Philadelphia received mediastinal double scattered proton therapy. Most (12) were girls; median age was 17 years (range 6 – 20) and 3 patients were receiving re-irradiation for relapsed disease. Depending on clinical factors, either a single anterior or posterior proton field was used, with matching to photon fields when necessary. All radiation planning utilized 4D CT planning and Eclipse treatment planning software, and doses are reported in radiobiologic equivalent-weighted absorbed dose (cGy-RBE).

**Results:** During treatment planning, an anterior proton beam was selected for 13 patients and a posterior for 6; fields were matched to photon fields for treatment of the neck/axilla for 14 patients, with a single matchline change technique. Prescription dose was 2100 – 3900 cGy(RBE) (average 2415), and dose to 50% of the heart ranged from 0.15 – 1212 cGy(RBE) (average 311). Posterior proton beams resulted in near zero breast dose. Radiation was very well tolerated, with only grade 1 toxicity encountered (8 dermatitis, 11 esophagitis, 1 xerostomia, 6 fatigue). With median 18 months follow-up (range 1-30), 17 patients are alive without evidence of disease, 1 patient is alive after relapse, and 1 patient is dead of disease. No patient has developed significant late cardiac or other radiation-related late toxicity.

**Conclusion:** Double scattered proton therapy for HL is very well tolerated, even in the setting of re-irradiation to the mediastinum. Relapse-free survival appears similar to photon series, and cardiac and breast sparing are significantly improved; when possible, a single posterior proton beam allows essential elimination of breast radiation. This is expected to translate to improved overall health status for survivors.
THERAPEUTIC TARGETING OF THE CYCLIN D3:CDK4/6 COMPLEX IN COMBINATION WITH CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
Nicholas Vitanza, Elizabeth Raetz, Julia Meyer, William Carroll, Iannis Aifantis. New York University (NYU) Langone Cancer Institute, New York City, New York, United States of America

**Background:** Breakthroughs in the treatment of childhood ALL have led to overall survival rates of 90%, but high risk subsets remain, making it essential to characterize the molecular pathways of disease initiation and maintenance. Cell cycle dysregulation is a hallmark of ALL and PD-0332991 is a specific CDK4/6 inhibitor that blocks the cyclin D3:CDK4/6 complex. Recent studies have suggested that the molecular targeting of the interaction of D-type cyclins with cell cycle dependent kinases (CDK4/6) using small molecule inhibitors could efficiently suppress human ALL growth and disease progression in vivo.

**Objectives:** To determine the effects of CDK4/6 pharmacologic inhibition in combination with chemotherapy on the proliferation and survival of leukemic cell lines.

**Design/Method:** B (Reh, UOCL1) and T cell (CUTL1, Jurkat) leukemic cell lines were each treated with 1 µM PD-0332991 and varying concentration of prednisolone, doxorubicin, and etoposide in three sequences: (a) chemotherapy for 24 hours followed by PD-0332991 for 48 hours, (b) PD-0332991 and chemotherapy simultaneously for 24 hours, and (c) PD-0332991 for 48 hours followed by chemotherapy for 24 hours. Cell cycle changes were determined by proliferation assay with bromodeoxyuridine (BrdU). Cells were labeled with propidium iodide and anti-BrdU antibody, then evaluated by fluorescence-activated cell sorting (FACS) using a FACScan flow cytometer (BD Scientific). Apoptosis was evaluated by FACS using anti-7AAD and anti-Annexin V-PE.

**Results:** Treatment with PD-0332991 induced G1 phase cell cycle arrest with the percentage of cells in S phase decreased by more than 80% in all cell lines. The effect of PD-0332991 with chemotherapy was sequence dependent. Pretreatment with PD-0332991 followed by chemotherapy resulted in the most significant increases in apoptosis in all cell lines (e.g. apoptosis increased 5-40x at the lowest effective prednisolone doses, p=0.02-0.0005). When PD-0332991 and chemotherapy were given simultaneously, no increase in apoptosis occurred.

**Conclusion:** PD-0332991 dramatically blocks cell cycle progression and significantly potentiates apoptosis when given before chemotherapy in B and T-lineage leukemic cell lines. PD-0332991 pretreatment prior to chemotherapy is an attractive combination to further explore in childhood ALL.
Chemotherapy Errors in the Era of Electronic Medical Records: Can They Be Prevented?
Erin Barr, Kyle Mays, Julie Kasap, Mohamad Al-Rahawan. University of Illinois College of Medicine at Peoria, Peoria, Illinois, United States of America

**Background:** The number of hospitals converting to electronic medical records (EMR) and the number of physicians engaging in direct EMR physician ordering is increasing. Attention to the number and nature of ordering errors is essential. Very few studies have evaluated chemotherapy ordering errors within pediatric oncology after the advent of EMR.

**Objectives:** To determine the impact of upfront pharmacy involvement on the accuracy and safety of EMR physician chemotherapy ordering at our inpatient pediatric oncology center.

**Design/Method:** Interim analysis of a prospective study. All scheduled pediatric inpatient chemotherapy orders were included. The study compared the number and nature of chemotherapy order entry errors before and after the intervention.

**Results:** Interim analysis included 25 prospective patients with 155 order entries and 32 historic patients with 367 entries. Patients aged 1-23 years of age. Among historic entries 24.8% (91/367) had one or more error, whereas 17.4% (27/155) of the prospective entries had at least one error. Chi-square analysis approached significance at p=0.066. There was a significant decrease in the number of ‘route of administration errors’ after the intervention (p < 0.05). No single chemotherapy drug seemed to have a higher rate of error; however, Hodgkin’s Lymphoma and solid tumors seemed to be associated with a higher rate of error. The higher prevalence of errors in this group on the inpatient unit may be biased since they account for most of the inpatient chemotherapy orders.

**Conclusion:** Interim analysis shows that our pharmaceutical intervention seems to have decreased the EMR chemotherapy order entry errors but did not reach significance. Our sample was small but follow up data collection and analysis are underway at our institution. Pharmacy intervention may help prevent EMR chemotherapy ordering errors and improve patient safety.
WHO AM I? IMPROVING QUALITY OF DATA COLLECTION FOR RACE/ETHNICITY AND LANGUAGE

Paula Aristizabal, Foyinsola Ani, Erica Del Muro, Teresa Cassidy, William Roberts, Erin Stucky Fisher. University of California San Diego/Rady Children's Hospital, San Diego, California, United States of America

Background: Reliable racial/ethnic reporting is critical, as initiatives to address healthcare disparities remain priorities on the national agenda. Hispanic children have been cited as having a higher incidence of leukemia/lymphoma but poorer survival rates. Accurate attribution of disease incidence and outcome to specific populations is central to ensuring appropriate family communication, resource distribution and research funding. Analysis of 2000-2010 local Hematology/Oncology data found a 13.02% discrepancy rate for race/ethnicity accuracy and 21% self-reported rate. While there is consensus regarding the importance of self-reporting of race/ethnicity, we identified both significant lack of self-report race/ethnicity and varied forms used to collect patient demographics at our site. Research has shown that most observers including administrative staff will accurately identify individuals as white or black, but Hispanic and multiracial individuals are often misidentified.

Objectives: Global Aim: Improve resource allocation and patient-provider engagement through correct race/ethnicity/language attribution. SMART Aim: Within 6 months, a uniform and accurate system for data collection on race/ethnicity/language will be implemented for the hematology/oncology population at our hospital with a reduction of missing/discrepant data to <2% and increase in self-report rate by 50%.

Design/Method: Plan-Do-Study-Act method was used. P: Key stakeholders used Fishbone analysis and flow charting, identifying process barriers and possible interventions. A new form (English/Spanish) was created to obtain self-reported race/ethnicity/language information. A decision map to aid parents in question answering and information sheet were created. Staff were trained to assist parents and document in Electronic Medical Record (EMR). D: Tools/processes piloted during a 6-week period. S: Pre/Post self-report and accuracy rates were compared. A: Results were presented to Hospital Quality Council; next PDSA cycle: Embed tools in EMR; pilot second population.

Results: Seven different forms were replaced by 1 new form. Study period N=196 patients: 1.2% discrepancy rate (↓of 90%; Chi-square 19.073, p<0.001); 97% Self-reported rate (↑of 76%; Chi-square 191.318, p <0.001).

Conclusion: Identifying barriers, reducing variability with a single data collection tool, and adjunct tools improve race/ethnicity/language accuracy. Next cycles will embed tools and EMR hard stops and diffuse change throughout the entire hospital. Collecting accurate information on patients' race/ethnicity/language should be an universal practice, enabling to understand and address disparities in childhood cancer.
SIGNIFICANT INCONSISTENCY AMONG PEDIATRIC ONCOLOGISTS IN THE USE OF THE NEUTROPENIC DIET

Lauren Braun, Heidi Chen, Haydar Frangoul. Vanderbilt University Medical Center, Nashville, Tennessee, United States of America

**Background:** The role of the diet in the development of infections in oncology and stem cell transplant (SCT) patients is controversial. There is no data on the use of the neutropenic diet among pediatric oncologists.

**Objectives:** We sought to determine the practice across pediatric cancer centers with implementation of the neutropenic diet and to determine factors influencing current practices in an effort to standardize the care of pediatric oncology and transplant patients.

**Design/Method:** A self-administered electronic survey was sent to 1,639 pediatric oncologists at 198 institutions who are members of Children's Oncology Group. A pediatric dietitian and pediatric oncologists developed, pretested, and modified the survey for item clarification.

**Results:** Five hundred fifty seven physicians responded representing 174 (87%) of the 198 member institutions. More than half of respondents (57%) report implementing the neutropenic diet at their facility. Factors significantly influencing the use of the neutropenic diet include less years of practice (p=0.006), female gender (0.022), larger centers with 150 or more new diagnoses per year (p<0.001), academic centers (p=0.001) and centers that perform allogeneic SCT (p<0.001). Among physicians who implemented a neutropenic diet, absolute neutrophil count was the trigger for initiating the diet in oncology patients (72%) while admission and start of preparative regimen was used for SCT patients (84%). The majority of respondents (82%) stop the neutropenic diet when oncology patients are no longer neutropenic while the practice varied significantly in the SCT patients. There were also significant variations among practitioners on the type of food allowed when using a neutropenic diet. Based on Fleiss Kappa (FK) of <0.6 indicating inconsistent response, providers at the same institution were not consistent in implementation of the diet (FK=0.347), patient populations placed on the neutropenic diet including oncology patients (FK=0.465), SCT patients when neutropenic (FK=0.247) and SCT patients regardless of neutropenia (FK=0.352), parameters for initiation of the diet for oncology patients (FK=0.188) and SCT patients (FK=-0.028), discontinuation of the diet for oncology patients (FK=0.386) and SCT patients (FK=0.114) and specific food restrictions.

**Conclusion:** The implementation of the neutropenic diet by pediatric oncologists is quite variable even among those at the same institution.
IDENTIFYING BARRIERS TO TIMELY CARE FOR FEBRILE CHILDREN WITH SICKLE CELL DISEASE AND IMPLEMENTING AN EDUCATIONAL INTERVENTION TARGETING FAMILIES WITH LIMITED ENGLISH LITERACY

Kelly Faulk, Christopher McKinney, Lisa Rose, Sean Rose, Anne Gillespie, Rebecca Coughlin, Joanne Hilden, Rachelle Nuss, Amy Brown. Children's Hospital Colorado, Aurora, Colorado, United States of America

Background: National quality standards of care for sickle cell disease patients include the recommendation that antibiotics be administered to febrile patients within 60 minutes of triage; however, some patients may have prolonged fever at home before receiving medical attention, limiting the efficacy of in-hospital process improvements.

Objectives: We sought to identify socioeconomic, educational, and cultural barriers to care and to test the feasibility of an educational intervention for families with limited English literacy.

Design/Method: As part of an ongoing quality improvement effort, we retrospectively reviewed visits for fever and sickle cell disease to determine the duration of fever at home and explore potential correlations with known barriers to healthcare. We then developed a survey to assess parents’ knowledge of fever management, which was administered prior to the educational materials.

Results: There were 41 total visits (9 clinic, 32 Emergency Department [ED]) between January to June 2013, reflecting 31 individual patients. All patients seen in the clinic called prior to arrival; however, only 13 of the 32 ED visits (40.6%) were preceded by a phone call. The baseline median duration of fever at home was 6 hours; the range was 30 minutes to 72 hours. Most patients were African-American (31/41, 75.6%), spoke English as a primary language (35/41, 85.4%), had Medicaid (28/41, 68.3%) and had access to their own transportation (30/35, 85.7%). Between October and December 2013, 20 families received the pre-survey and educational intervention. Only one parent was unable to identify temperatures indicating a fever; all identified appropriate reasons to check for a fever. 75% (15/20) correctly reported that they would call their doctor for a fever; however, 25% (5/20) reported that they would give medicine but not call a provider, and another 35% (7/20) reported that they would give medicine prior to speaking with a provider.

Conclusion: Institutional process improvement must account for social factors and structural inequality outside the institution. We documented a clear delay in accessing care and important gaps in parental knowledge. This preliminary quality improvement project provides the foundation for further study of the relationships between socioeconomic factors, parental knowledge, and access to care, and the efficacy of targeted educational interventions.
EFFICACY OF THE INFLUENZA VACCINE IN PEDIATRIC PATIENTS WITH MALIGNANCIES: A PROSPECTIVE ANALYSIS OF IMMUNE RESPONSE AND CLINICAL OUTCOMES

Daniel Choi, David Walterhouse. Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, United States of America

Background: Previous studies assessing the immune response to influenza vaccine in pediatric cancer patients have produced mixed results. Some studies suggest that the absolute lymphocyte count (ALC) at vaccination influences development of a protective immune response. Few studies have directly examined development of influenza infection following vaccination in children receiving chemotherapy.

Objectives: Our objectives were to (1) prospectively determine the proportion of patients with immunogenic responses following administration of the influenza vaccine in children receiving chemotherapy and (2) assess whether a protective immunogenic response correlated with a decreased rate of clinical influenza infection or influenza-like illness (ILI).

Design/Method: We conducted a prospective cohort study over two influenza seasons (2012-2014) in order to assess seasonal variation in influenza infection.

Results: Here we report results for influenza season one (2012-13), during which 112 patients were enrolled. Median ALC at vaccination was 776 cells/mm³ (65-4,603 cells/mm³). Sixty-eight percent (65/112) were lymphopenic (ALC<1000 cells/mm³) at vaccination. Twenty-three patients had complete serologic data for influenza season one, and 74% (17/23) had a sero-response to the vaccine.

Median ALC at vaccination was not different among sero-responders versus non-responders (836 cells/mm³ vs. 572 cells/mm³, p<0.286). Twenty-nine percent (32/112) reported symptoms consistent with ILI. Median ALC at vaccination in patients with ILI was 646 cells/mm³ (190-4,603 cells/mm³) versus 836 cells/mm³ (65-3,958 cells/mm³) in ILI-negative patients (p<0.385). Twenty-one patients had confirmed influenza positive infection. The median ALC at vaccination for influenza positive patients was 530 cells/mm³ (190-4,603 cells/mm³). There was no statistically significant difference in median ALC between influenza positive and negative patients who received the vaccine (p=0.08).

Clinical complications included (1) inpatient hospitalization for influenza symptoms in 29% (6/21), concurrent bacteremia in 20% (4/21), and delayed chemotherapy in 100% (21/21).

Conclusion: Influenza infection remains a significant source of morbidity in children undergoing chemotherapy. Lymphopenia at the time of vaccination did not affect immunogenic response. Correlations between immune response and clinical symptoms could not be assessed during influenza season one due to limited complete serologic data. An additional sixty-seven patients (145 total) have been enrolled in influenza season two, and complete serologic data has been obtained on a majority of patients.
VITAMIN D DEFICIENCY IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOMA
Melissa Claar, Alexis Maciej, Joseph Neglia, Christopher Moertel. University of Minnesota Amplatz Children's Hospital, Minneapolis, Minnesota, United States of America

**Background:** Vitamin D is vital to maintaining calcium homeostasis and bone mineralization. Evidence also suggests potential extraskeletal effects promoting muscular, immune and cardiovascular health. Pediatric oncology patients with acute lymphoblastic leukemia or lymphoma (ALL-L) are at particular risk for vitamin D deficiency. Chronic glucocorticosteriods given as part of their chemotherapeutic regimen cause increased catabolism of vitamin D and inhibition of intestinal vitamin D-dependent calcium absorption.

**Objectives:** Determine the prevalence of vitamin D deficiency in pediatric ALL-L patients. Develop standard practice guidelines for vitamin D screening and management to improve vitamin D status in pediatric ALL-L patients. Evaluate the impact of implementation on the frequency of vitamin D screening in this population.

**Design/Method:** An initial assessment revealed very limited vitamin D screening. Assessments often occurred following the diagnosis of complications such as avascular necrosis (AVN) or osteopenic fracture. After reviewing the literature and current recommendations, we formulated standard practice guidelines which included prospective screening to identify patients with vitamin D deficiency or insufficiency, supplementation guidelines, follow-up recommendations and an educational intervention for patients and families regarding vitamin D. An algorithm was constructed as a guide for all pediatric oncology patients in our practice.

**Results:** 43 patients were screened over the course of one year. Twelve pediatric ALL-L patients (28%) were vitamin D sufficient, 11 (25%) were insufficient (25(OH)D < 30 ug/L) and 20 (47%) were deficient (25(OH)D < 20). With typical supplementation, 92% of adherent patients (71% total) achieved sufficiency within 8-12 weeks. In contrast, the year prior to implementation, only 5 patients were screened for vitamin D deficiency, all were either post-BMT or diagnosed with AVN.

**Conclusion:** Pediatric ALL-L patients are at increased risk of adverse bone, muscle, nerve and immune effects; all of which can be exacerbated by vitamin D deficiency. The guidelines were effective in improving the vitamin D status of our patients. Supplementation was well tolerated and sufficiency was achieved in most patients.
INCIDENCE OF DELIRIUM IN CHILDREN WITH CANCER

**Background:** Delirium is a disturbance of consciousness that consists of fluctuating mental status, inattention, and the inability to receive, process, or store information. There are limited data on delirium in children. Previous studies have focused on the pediatric intensive care setting. These studies, which included some children with cancer as well as a wide variety of other diagnoses, have found a rate as high as 16.9%. Adult inpatient oncology data has shown a rate of 18%. No previous studies have examined the rate of delirium in the general pediatric oncology setting. Delirium has been associated with higher hospital costs, longer hospital stays, and increased morbidity and mortality.

**Objectives:** To determine the incidence of delirium in children with cancer in an inpatient setting.

**Design/Method:** Retrospective chart review.

**Results:** We identified 72 patients during July 2011-June 2012, with 293 hospitalizations. Inclusion criteria included all pediatric patients with an oncologic diagnosis admitted to the inpatient oncology unit. Exclusion criteria included age less than 1 year or greater than 21 years. Diagnostic criteria were used as defined by the Diagnostic and Statistical Manual of Mental Health Disorders, 4th edition, Text Revision. Delirium was diagnosed if there was documentation that the patient met all diagnostic criteria. The incidence of delirium was 9.7% (7 patients). Three patients had delirium secondary to medication effects (ifosfamide, methotrexate, and dexamethasone-induced). Four patients had delirium secondary to their medical condition (hypocalcemia, renal failure, 2 patients with multi-organ failure).

**Conclusion:** Delirium occurs in nearly one out of ten children with cancer in an inpatient setting; the condition may be under-diagnosed and unrecognized. Our data suggest the need for further research and education on delirium in this patient population, as effective prevention and treatment of delirium may reduce patient morbidity and hospital costs.
COMPARISON OF A ROTARY POWERED BONE MARROW ASPIRATION AND BIOPSY DEVICE TO THE TRADITIONAL MANUAL DEVICE IN CHILDREN

Maria Falcon-Cantrill, Paul Thomas, Victor Saldivar, Chatchawin Assanasen. Children's Hospital of San Antonio, San Antonio, Texas, United States of America

Background: In 2007, an FDA-cleared battery powered bone marrow aspiration and biopsy system (OnControlTM by Vidacare) was developed. Multiple studies have evaluated the use of the powered device in adults and found decreased procedure time, decreased pain, and improved core biopsy specimens.

Objectives: Compare the rotary powered bone marrow aspiration and biopsy device to manual devices in children.

Design/Method: A randomized controlled trial was developed to enroll a total of 44 patients between 2 and 18 years old requiring a bone marrow evaluation for either hematologic or oncologic diagnoses. Patients were assigned to have a single procedure carried out using the powered device or the traditional manual device. Data was also collected in patients needing bilateral marrow evaluations for direct comparison between the two devices. The time to obtain the aspirate and biopsy were recorded, as was the pain score post-procedure. A blinded pathologist recorded the length, width, and overall quality of the specimen. The operator performing the procedure also completed a survey to evaluate the safety and their satisfaction with the device.

Results: The quality of specimens obtained using the manual device was superior to the powered device in children. The powered device produced larger volume samples. The biopsy time was comparable but tended to be shorter using the powered device. Aspiration and biopsy times were more clinically significant when compared directly in patients receiving bilateral procedures. These times improved as expected with continued experience with the powered device. No significant complications were observed using either device though operators commented that the powered device was useful when performing procedures on older patients and those with blast-packed marrows.

Conclusion: In children, the powered rotary marrow device may provide benefit over manual methods as reported in previous adult studies. In this study, we found that the OnControlTM biopsies were obtained safely, in less time, and of good quality compared to those obtained using traditional manual devices. Operators performing procedures noted increased satisfaction with the powered rotary device in both clinical use and ease in training future providers.

Supported by a grant from Vidacare Corporation.
Background: The timely management of febrile neutropenia (FN) in children receiving chemotherapy is used as a quality of care (QOC) in pediatric oncology practices within the US. The recommended time-to-antibiotic administration (TTA) for oncology patients with FN is less than 60 minutes. A retrospective review (July 2012 to February 2013) at the Children’s Hospital of Illinois of FN admissions revealed an average TAA of 105 minutes and < 60 minutes in only 30% (Total N = 37).

Objectives: To improve the TTA in the pediatric oncology unit of the Children’s Hospital of Illinois.

Design/Method: A Quality Improvement (QI) project was implemented in August of 2013. The process involved: 1) Unit Charge-nurse took verbal orders from the attending physician and entered orders in the EMR upon patient arrival (a preference list for FN orders was created), 2) Charge nurse alerted pharmacy, 3) Pharmacy sent antibiotic as soon as possible. 4) Bedside-nurse promptly administered antibiotic to patient, 5) On-call resident evaluated patient within 30 minutes. Additional orders were placed after discussion with the attending physician.

Results: A total of 38 patients with FN were admitted over 5 months. TTA improved to an average of 28.5 minutes (range 9 – 56 minutes). One patient had a TTA greater than 60 minutes due to central access problems (excluded). In 76% (28/37) of FN admits TTA was < 35 minutes. The average time for the unit charge-nurse to enter orders was 6 minutes (range 1 to 17 minutes). The average time from order entry to antibiotic delivery from pharmacy was 20 minutes (range 5 to 47 minutes). The average time from antibiotic arrival to antibiotic administration was 5 minutes (range 1 to 19 minutes).

Conclusion: The introduction of this QI project was effective in achieving a TTA of less than 60 minutes in 100% and to reduce the time to less than 35 minutes in 76% of FN admissions. The team effort involving nurses, pharmacists, residents and attending physicians was key and the active involvement of the nursing staff in the ordering process was essential in achieving this goal.
IMPROVING TIME TO ANTIBIOTICS FOR PEDIATRIC ONCOLOGY PATIENTS WITH FEBRILE NEUTROPENIA BY APPLYING LEAN PROCESS IMPROVEMENT METHODOLOGY

IWK Health Centre, Halifax, Nova Scotia, Canada

**Background:** Prompt broad-spectrum antibiotics are the standard of care for febrile neutropenia (FN). A retrospective study (FN study) conducted by the Atlantic Provinces Pediatric Hematology and Oncology Network (APPHON) identified that the 60 minutes standard for time to administration of antibiotics (TTA) from presentation was not always being met in the emergency department (ED) or outpatient oncology clinic. Median TTA were 99 minutes (Interquartile range [IQR] 72-132) and 60 minutes (IQR 45-110), respectively.

**Objectives:** To analyze the process for FN patients presenting to the ED and clinic using Lean methodology.

**Design/Method:** Lean methodology identifies “process wastes” and defines value and non-value added steps based on 5 phases: Define, Measure, Analyze, Improve, and Control. The current FN process was mapped with stakeholders (physicians, nurses, lab personnel, ward clerks, pharmacists), led by a Lean methods expert, to create a current state value stream maps (VSM). VSM are a visual representation of the steps required in the process. The FN APPHON study was utilized to understand the processing time of each step. Through analysis of the current state VSM, stakeholders categorized the “process wastes” and identified root causes of these wastes.

**Results:** Types of wastes identified were waiting, over processing, defect, and skills. Table 1 summarizes areas for improvement and suggested changes.

**Conclusion:** Lean methodology successfully identified root causes and improvement solutions to facilitate rapid administration of antibiotics to FN patients. Implementation of a future state VSM will be analyzed through Plan-Do-Check-Act cycles to confirm the TTA goal of 60 minutes is achieved.

<table>
<thead>
<tr>
<th>Type of waste</th>
<th>Area for improvement</th>
<th>Changes to be implemented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waiting</td>
<td>Patients waiting for registration</td>
<td>ED clerk to register patient in patient’s room using work station on wheels</td>
</tr>
<tr>
<td></td>
<td>Waiting for lab technician to collect blood work</td>
<td>Clinic clerk to preregister patient and direct patients to bypass registration line</td>
</tr>
<tr>
<td></td>
<td>Waiting for topical anesthetic prior to portacath access</td>
<td>Access portacath and collect required blood samples by nurse</td>
</tr>
<tr>
<td></td>
<td>Apply topical anesthetic at home</td>
<td>Nurse to access port regardless of topical anesthetic application</td>
</tr>
<tr>
<td></td>
<td>Nurses waiting for antibiotic orders</td>
<td>Physician to start antibiotics orders prior to absolute neutrophil count (ANC) report</td>
</tr>
<tr>
<td></td>
<td>Waiting for ANC report</td>
<td>Ward clerk to label ANC blood work “stat”</td>
</tr>
<tr>
<td>Over Processing</td>
<td>Excess time explaining to families the ED FN process</td>
<td>Nurse to administer antibiotics at 45 minutes after arrival even if ANC results still pending</td>
</tr>
<tr>
<td></td>
<td>Different physicians using different management processes</td>
<td>Include ED information and tour in initial family education</td>
</tr>
<tr>
<td></td>
<td>Implement a consistent FN process for ED and Clinic</td>
<td>Adapt FN family information card to include specific instructions (ex: topical anesthetic, bypass triage line)</td>
</tr>
<tr>
<td>Defect</td>
<td>Missing information on the FN family information card</td>
<td>Develop patient-specific FN information on electronic medical record</td>
</tr>
<tr>
<td></td>
<td>Patients forget FN family information card</td>
<td></td>
</tr>
<tr>
<td>Skills</td>
<td>Using 2 nurses to access portacath in ED</td>
<td>Access portacath using 1 nurse technique (as used by clinic nurses)</td>
</tr>
</tbody>
</table>
ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH SICKLE CELL DISEASE
Melissa Acquazzino, Matthew Myrvik, John Scott. Medical College of Wisconsin, Milwaukee, Wisconsin, United States of America

Background: Neurocognitive deficits, including difficulties with attention and executive function, as well as poor school performance, are well described in children and adolescents with sickle cell disease (SCD). Given such deficits, individuals with SCD appear at particular risk for attention deficit/hyperactivity disorder (ADHD), a neurobiological disorder characterized by persistent, pervasive, impairing and developmentally excessive levels of hyperactivity, impulsivity and inattention. Currently, there is a paucity of data examining ADHD within SCD beyond the known neurocognitive deficits. As such, additional research is needed to learn more about ADHD in children and adolescents with SCD.

Objectives: To determine the prevalence and characterize the type of ADHD and corresponding treatment in a cohort of children and adolescents with SCD referred for neuropsychological testing.

Design/Method: A retrospective chart review was conducted of children with SCD ages 4-18 years who were referred for complete neuropsychological evaluation due to academic or behavioral concerns. 96 patients with SCD (66 HgbSS, 19 HgbSC, 9 HgbSβ+, 1 Hgb G-Philadelphia, and 1 HgbSβ0) met inclusion criteria. A diagnosis of ADHD was determined using diagnostic criteria from the Diagnostic Statistical Manual -Fourth Edition -Text Revised (DSM-IV-TR). Patients with a known history of stroke, silent stroke or other neurologic disorder were excluded.

Results: 23 patients (24%) met the diagnostic criteria for ADHD (16 HgbSS, 6 HgbSC and 1 HgbSβ+). Of the patients diagnosed with ADHD, 52% were male and 48% were female. In terms of ADHD subtypes, 13 patients (56.5%) were diagnosed with ADHD primarily inattentive type, 7 (30.5%) with ADHD combined type and 3 (13%) with ADHD primarily hyperactive-impulsive type. Only 8.7% of patients diagnosed with ADHD were found to be taking medication for ADHD.

Conclusion: We found a high rate of ADHD (24%) in patients with SCD referred for neuropsychological evaluation. The most common subtype of ADHD was inattentive type. Despite the high risk for academic underachievement, patients with SCD and ADHD were rarely found to be taking medication for ADHD.
HEPATOBILOGRY IMAGING IN SICKLE CELL ANEMIA
Claire Anderson, Vanessa Cumming, Anjeza Chukus, Gaurav Saigal, Ofelia Alvarez. University of Miami/Jackson Memorial Hospital, Miami, Florida, United States of America

**Background:** The acute abdomen is a frequent presentation with an extensive differential diagnosis, further complicated in patients with sickle cell disease (SCD). The hepatobiliary system is commonly affected in SCD. The well vascularized liver is susceptible to injury from the cumulative effects of tissue hypoxia, venous stasis and ischemia related to sickling within liver sinusoids. Chronic hemolysis causes hyperbilirubinemia and predisposes to cholelithiasis, with its attendant risks of biliary colic, cholecystitis and pancreatitis. Furthermore, transfusion-related iron overload exacerbates hepatic injury. Radiological studies prove imperative for the management of hepatobiliary complications in SCD.

**Objectives:** To determine the prevalence of abnormal hepatobiliary imaging in children and young adults with SCD.

**Design/Method:** Retrospective 10 year database review of images taken in children and young adults with SCD. Patients with concomitant liver disease (primary sclerosing cholangitis, autoimmune hepatitis, hepatitis B and biliary atresia) were excluded (n=6, 2.4%).

**Results:** Two hundred and forty-three patients’ images were reviewed. Mean subject age was 16.3 ± 5.6 years (range 2-25.1 years). A total of 656 scans were performed: 77.7% (510) abdominal US, 13.7% (90) CT scans, 5.9% (39) MRI, 2.1% (14) nuclear medicine imaging and 0.5% (3) ERCP/intraoperative cholangiograms. The most frequent indications for radiological studies were pain/acute abdomen, assessment of organomegaly, and abnormal LFTs. 69% (167) patients had abnormal imaging (Fig. 1). 10% (24) of patients had undergone cholecystectomy.

**Conclusion:** We found a prevalence of abnormal hepatobiliary imaging in patients with SCD of approximately 70%. Physicians should be cognizant of the hepatobiliary manifestations of SCD.

![Findings on hepatobiliary imaging](n=167)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>122</td>
</tr>
<tr>
<td>Gallstones</td>
<td>68</td>
</tr>
<tr>
<td>Sludge</td>
<td>19</td>
</tr>
<tr>
<td>Biliary tract dilation</td>
<td>26</td>
</tr>
<tr>
<td>Other</td>
<td>51</td>
</tr>
</tbody>
</table>

Other category includes: cholecystectomy (24); parenchymal changes (16); iron overload (4); acute cholecystitis (1); gallbladder polyp (2); CBD abnormality (2); gallbladder thickening (1); and unavailable (1)
ALLOIMMUNIZATION IN PEDIATRIC PATIENTS RECEIVING TRANSFUSION
Jessica Barry, Priscilla Figueroa, Suneeti Sapatnekar, Stefanie Thomas. Cleveland Clinic Foundation, Cleveland, Ohio, United States of America

Background: Pediatric patients with sickle cell anemia and other hemoglobinopathies are at high risk for the development of red cell antibodies, but little data are available on the risk for other pediatric patients. The lack of data is a handicap in anticipating the likelihood of alloimmunization and accurately assessing the risks of Red Blood Cell (RBC) transfusion.

Objectives: The purpose of our study is to determine the prevalence of alloimmunization against clinically significant red cell antigens among pediatric patients. The study was prompted by the lack of data on alloimmunization when attempting to develop a pre-transfusion testing protocol for pediatric patients expected to require urgent transfusion.

Design/Method: A 15-year retrospective analysis was performed of all transfusions in pediatric patients (up to 18 years old) at our hospital between Oct 1998 and Feb 2013. The analysis included the number of transfusions (with full units or aliquots) for each patient, patient age at first transfusion, prevalence of clinically significant red cell antibodies, and the patient’s underlying disease condition.

Results: Data were reviewed for 28,406 allogeneic RBC or Whole Blood transfusion episodes for 5,048 patients. Clinically significant alloantibodies were noted in 98 patients (1.93% of transfused patients), associated with a total of 867 transfusions. The average number of transfusions in these patients was 8.8 (median: 3.5, range 1-99). The average age at transfusion for all alloimmunized patients was 9.8 years (median 11 years). The major clinical conditions associated with the alloimmunization were: congenital heart disease (28%), sickle cell anemia (16%), neurological disease (13%), gastrointestinal disease (10%), solid organ transplantation (8%), and bleeding disorder (7%). When the patients with sickle cell anemia were excluded from analysis, the prevalence of alloimmunization declined to 1.42%.

Conclusion: The prevalence of clinically significant red cell alloimmunization among pediatric patients without hemoglobinopathy is lower than the rate of 2.9-4% observed in the general (adult) population (1,2). The mechanisms underlying the low risk of alloimmunization in this population is unclear but may reflect the relative immaturity of the pediatric immune system.

A NOVEL MODEL FOR CARE COORDINATION: THE LURIE SICKLE CELL NEWBORN COHORT PROJECT

Background: The Patient-Centered Medical Home (PCMH) has been proposed as a practice-based model of care delivery in complex conditions such as sickle cell disease (SCD); however, there are limited published data on implementation and outcomes. The Newborn Cohort Clinic (NCC) was established at Lurie Children’s Hospital (Chicago, IL) in May 2011 to optimize education, surveillance and care coordination for children with SCD from birth to age 3 years using core concepts of the PCMH and close collaboration with primary care providers (PCP). Core elements of the NCC included a personalized Parent Handbook, Care Plan and customized electronic medical record (EMR) templates for facilitating communication with the PCP.

Objectives: To evaluate implementation of the NCC care model, to assess early clinical outcomes of participants and measure parent satisfaction.

Design/Method: We evaluated 50 subjects from birth to age 3 years with SCD followed in the NCC. A customized survey tool was administered for feedback on the Handbook and to assess the following PCMH domains: comprehensive, coordination, family centered and culturally competent. Additional data on outcomes of the NCC were obtained from EMR review.

Results: The mean age for subjects at their first NCC visit was 2.9 months. Penicillin prophylaxis was initiated at a mean age of 2 months. Of patients > 24 months old, 14/20 (70%) received a Pneumovax and 12/20 (60%) had undergone a TCD. The proportion increased to 83% for both preventive measures by age 36 months. Ninety-eight percent had a documented PCP. There were 164 visits by 42 patients to the Emergency Department, of which 83% were for fever, pain or respiratory symptoms, and resulted in 109 hospitalizations. Nine (18%) were transfused, 2 chronically. Cross-sectional survey results (N=24) showed that 79% of parents were very satisfied with the NCC Handbook and 83% were very satisfied with care coordination provided by the NCC. Parents reported high satisfaction for both the SCD provider in the NCC and their child's PCP for all PCMH domains tested.

Conclusion: Early findings support successful use of NCC core elements that facilitate PCP communication and care coordination in young, vulnerable SCD patients, including routine preventive care with high parental satisfaction.
EXPERIENCE WITH SUBCUTANEOUS IMPLANTED CENTRAL ACCESS DEVICES IN CHILDREN AND YOUNG ADULTS WITH SICKLE CELL DISEASE UNDERGOING ERYTHROCYTAPHERESIS

Shelley Crary, Katherine Meche, Suzanne Saccente. University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States of America

Background: Chronic red cell transfusions are often used in patients with sickle cell disease (SCD) with severe or chronic complications such as stroke. A growing number of centers have advocated erythrocytapheresis as an alternative to simple transfusions to decrease iron overload. In many such children with SCD and poor venous access, central venous access devices (CVAD) have been utilized, but have been associated with various rates of complications, including premature removal, infection and thrombosis. At Arkansas Children's Hospital (ACH) we have an approximately 16 year experience with erythrocytapheresis in SCD. Over this period, most children have had an implantable single or double lumen CVAD from a single manufacturer (AngioDynamics). Our population is also unique in that the procedures for accessing the CVAD and for prevention of thrombosis and infections have remained relatively constant.

Objectives: To determine the rate of thrombotic and infectious complications of subcutaneous implanted CVAD in children and young adults with SCD undergoing erythrocytapheresis.

Design/Method: We performed a retrospective chart review on all patients with SCD actively being treated with erythrocytapheresis at ACH. Patients were initially identified in our local apheresis database. For each patient, we obtained demographic data, sickle cell genotype, date of CVAD placements and removals, indications for erythrocytapheresis, laboratory data including microbiology reports, and radiographic studies.

Results: Twenty-seven patients were identified. Median age at time of study was 15 years (range 6-35) and median age at time of first CVAD insertion was 7 years (range 2-20). A total of 54 catheters were placed in the 27 patients for a cumulative 102,068 catheter-days. Sixteen positive blood cultures were found for a presumed infection rate of 0.16 per 1000 catheter-days. Thrombosis (including fibrin sheath and catheter hub thrombosis) rate was 0.27 per 1000 catheter-days and the rate of catheter breakage or leakage was 0.13 per 1000 catheter-days.

Conclusion: Vascular access is one of the limiting factors for starting erythrocytapheresis in patients with SCD requiring a chronic transfusion program. We have a long-standing experience with implantable CVAD in this population with low complication rates suggesting this is a reasonable approach even in younger children.
BETA GLOBIN GENE MUTATIONS IN EGYPTIAN CHILDREN WITH β-THALASSEMA
Mohamed Elshanshory, Sheble Sheble, Youssef Al-Tonbary, Ahmed Mansour, Hoda Hassab, Mona Hamdy, Mohsen Elalfy, Layla Sherif, Adel Haggag, Ibrahim Badria, Amal Helmy, Enam Abd Al-Bar, Amany Aboelenin. Tanta University, Tanta, Gharbyea, Egypt

Background: The molecular defects resulting in a β-thalassemia phenotype, in the Egyptian population show a clear heterogenic mutations pattern. PCR based techniques, including direct DNA sequencing are effective on the molecular detection and characterization of these mutations.

Objectives: To evaluate the different β- globin gene mutations in one hundred Egyptian children with β- thalassemia.

Design/Method: This study included one hundred of β-thalassemic Egyptian children covering most of Egyptian Governorates. All patients were subjected to meticulous history taking, clinical examinations, complete blood count, reticulocytic count, and serum ferritin. Direct fluorescent DNA sequencing of the β-globin gene to detect the frequency of different mutations in those patients were done.

Results: The most common allele mutations among patients were IVS I-110(G>A) 48%, IVS I-6(T>C) 40%, IVS I-1(G>A) 19%, IVS I-5(G>C) 10%, IVS II-848 (C>A) 9%, IVS II-745(C> G) 8%, IVS II-1(G>A) 7%, codon"Cd"39(C>T) 4%, -87(C>G) 3%, and the rare allele mutations were: Cd37 (G>A), Cd8 (-AA), Cd29(-G), Cd5 (-CT), Cd6(-A), Cd8/9(+G), Cd 106/107(+G), Cd27(C>T), IVS II-16(G> C), Cd 28 (-C), Cap+1(A>C), -88(C>A), which represent 1%. There was a considerable variation in phenotypic severity among patients resulting from interaction of different β°and β+mutations, 79 (79%) cases were thalassemia major (TM) and 21(21%) were thalassemia intermedia (TI), without genotype phenotype association.

Conclusion: Direct DNA sequencing provides insights for the frequency of different mutations in β-thalassemic patients including rare and /or unknown ones.
PARVOVIRUS B19-MEDIATED APLASTIC CRISIS AND THE VIRUS-SPECIFIC IMMUNE RESPONSE IN CHILDREN WITH SICKLE CELL DISEASE
Jane Hankins, Rhiannon Penkert, Li Tang, Paul Thomas, Jason Rosch, Julia Hurwitz. St. Jude Children's Research Hospital, Memphis, Tennessee, United States of America

**Background:** Parvovirus B19 infection, which is typically subclinical in healthy individuals, can have catastrophic effects in individuals suffering from sickle cell disease (SCD). Infection from parvovirus B19 disrupts erythropoiesis, often resulting in aplastic crisis and other life-threatening complications in patients with SCD. Attempts to develop a safe and effective parvovirus B19 vaccine have yet to be successful and may be improved by a better understanding of natural immune responses to parvovirus B19 infections.

**Objectives:** To describe the frequency of parvovirus B19-specific antibody responses before or after an episode of aplastic crisis among children with SCD.

**Design/Method:** Retrospective analyses of records of children (ages 0 to 18) with history of a prior episode of aplastic crisis were conducted. Parvovirus-specific antibody results from a semi-quantitative commercially-available ELISA were examined as a function of time relative to the aplastic crisis episodes. IRB approval was granted for this retrospective analysis.

**Results:** From 2006 to 2013 there were 128 children with SCD who had an episode of aplastic crisis and had their parvovirus-specific antibody responses investigated. In this sample, (i) frequencies of seropositive immune responses in patients with SCD of various age groups were comparable to those of historical non-SCD controls (general population), with 67.8% and 88.7% IgG positive responses (index>0.5) among the 0 - 10 and 10 - 18 year old age groups, respectively, (ii) IgM parvovirus-specific responses were positive (index>0.5) in 84.4% at the time of the aplastic crisis diagnosis, (iii) IgG antibody responses were generally sustained for years after the aplastic crisis event, and (iv) no cases of recurrent aplastic crisis were observed in this sample.

**Conclusion:** Immune response to parvovirus B19 among children with SCD is rapid, sustained, and protective against a second episode of aplastic crisis. Ongoing studies that include further dissection of adaptive and innate immune responses toward parvovirus B19 infections in this patient population will help define correlates of protection against parvovirus disease.
IMMUNE DYSFUNCTION IN BETA THALASSEMIA MAJOR PATIENTS
Tamer Hassan, Hanan Amin, Asmaa Esh, Amira El Sadek. Zagazig University, Zagazig, Egypt

Background: The substantial improvement in survival rates and quality of life achieved in β-thalassemia major over the last several decades, owing to therapeutic advances and the close follow-up of patients in specialized centers, has redirected the attention of investigators to other collateral abnormalities that were previously neglected or overlooked. Abnormalities of the immune system represent one of the neglected areas in β-thalassemia major. There is inadequate and controversial evidence about immune system in patients with β-thalassemia major.

Objectives: We aimed to investigate different components of immunity in patients with β-thalassemia major and their relationship with epidemiological, transfusion and chelation characteristics of these patients.

Design/Method: This study included 40 patients (20 non-splenectomized and 20 splenectomized) with β-thalassemia major and 20 age and sex matched healthy children as controls. All epidemiological, transfusion and chelation data were collected. Serum levels of immunoglobulins, T-lymphocyte subsets, serum IL-6 level, phagocytic activity and oxidative burst of neutrophils were assessed in all groups.

Results: The mean age was 12.65± 2.7, 13.2± 2.46, and 12.2± 2.35 for non-splenectomized patients, splenectomized patients and controls respectively. Splenectomized patients had significantly higher levels of serum Ig A compared to non-splenectomized and controls. Patients especially splenectomized ones had significantly lower serum IL-6 levels and phagocytic activity compared to controls. Although patients had lower levels of oxidative burst activity compared to controls, only splenectomized ones showed statistical significant difference compared to controls. There was no significant difference between patients and controls as regards other immunoglobulin levels and CD4 / CD 8 ratio. Apart from higher levels of Ig A and Ig M in patients who received deferiprone, there was no significant relationship between types of chelation and any of immunological parameters.

Conclusion: Routine survey of different components of immune system seems to be needed in β-thalassemia major especially splenectomized patients and could be useful in better understanding of the higher rate of infections in these patients.
GLOMERULAR DYSFUNCTION IN EGYPTIAN BETA THALASSEMIA PATIENTS
Mona El Tagui, Rania Ismaiel, Ahmed Badr, Marwa Ragaaee, Doha Mokhtar, Mona Mohamed Hamdy Mahmoud. Children Hospital, Cairo University, Cairo, Egypt

Background: The kidney of β thalassemia patients has always been under evaluated. However, improved survival of these patients has attracted the attention to the development of latent renal complications.

Objectives: To study renal glomerular dysfunction among a group of Beta thalassemia patients with special attention to biochemical markers useful for early detection of such dysfunction and its correlation to different disease parameters.

Design/Method: Sixty beta thalassemia patients divided into group A; 43 thalassemia major (mean age= 10.98±4.52 years) & group B; 17 thalassemia intermedia (mean age= 12.24±4.12 years) together with 20 age and sex matched controls were included in this study. Both patients and control groups were subjected to clinical examination, serum ferritin, AST, ALT, conventional renal parameters in addition to albumin/ creatinine ratio (A/C), serum level of cystatin C and GFR (glomerular filtration rate).

Results: significant differences were observed between patients and control groups regarding serum ferritin, AST, ALT, BUN, Serum creatinine, cystatin C, GFR (P=0.01). Among the thalassemic patients, 13.3% (n=8) had GFR<89 ml/min/1.73m², 47% (n=28) had A/C >0.2mg/dl and 40% (n=24) had Cystatin C >1257 ng/ml while serum creatinine was within normal range. Enuresis was present in 6.9% (n=3) of group A and urinary frequency in 5.8% (n=1) of group B. Significantly higher A/C ratio was observed in group A versus group B (p=0.035) while other renal parameters showed non significant variability among the 2 groups. Elevated Cystatin C, A/C ratio and low GFR were evident among 41.9, 55.8 and 11.6% of group A versus 35.3, 17.6 and 17.6% of group B. Significant positive correlation was evident between A/C and serum ferritin level among cases (p=0.028) especially among those above 6 years of age (p=0.01). Cystatin C and GFR changes were not correlated with age of patients, duration of disease or type of chelation.

Conclusion: glomerular dysfunction in beta thalassemia is not a rare complication. Cystatin C is valuable for early prediction of renal glomerular impairment among thalassemia patients. Further studies including larger number of patients are needed to evaluate this issue.
STREPTOCOCCUS PNEUMONIAE INFECTION IN SICKLE CELL DISEASE PATIENTS
Pournima Navalkele, Eric McGrath, Paul Lephart, Bulent Ozgonenel. Children's Hospital of Michigan, Wayne State University, Detroit, Michigan, United States of America

Background: Patients with sickle cell disease (SCD) are at risk of fatal sepsis with encapsulated bacteria, such as Streptococcus pneumoniae, due to inherent auto-splenectomy. This risk is thwarted with oral penicillin prophylaxis until 5 years of age and with stringent vaccination against S. pneumoniae. With the introduction of heptavalent (PCV7) and 13-valent (PCV13) pneumococcal conjugate vaccines, incidence of invasive pneumococcal disease (IPD) has declined among children with SCD.

Objectives: To find the incidence of IPD in children with SCD followed at our institute over last 10 years and serotypes that have caused IPD.

Design/Method: Retrospective chart review was performed from January 1st, 2004 to December 31st, 2013. Electronic records were reviewed to identify IPD in patients aged 0-21 years. Clinical and laboratory data were collected on patients who had positive culture results for S. pneumoniae.

Results: Between 2004 and 2013, seven children with SCD (age range 2.25-9 years; 5 male and 2 female; 6 with homozygous hemoglobin S and 1 with hemoglobin S-O Arab) presented with IPD. All patients received PCV7 (after 2010, PCV13) and PPSV23 vaccines. 2 patients were still on penicillin prophylaxis, being less than 5 years of age. None had surgical splenectomy. 3 patients were tested for pneumococcal serotypes at Centers for Disease Control and Prevention, Atlanta, Georgia, all of which were non-vaccine serotypes (2 with 15C; 1 with 15A). All 3 serotypes were susceptible to penicillin. Most patients recovered from their illness except a 5 year old male who had fatal course.

Conclusion: This recent surge in IPD in SCD patients due to non-vaccine isolates is alarming. Prolongation of penicillin prophylaxis needs to be considered in patients with risk factors such as irregular follow-up or those with co-morbidities.
SIGNIFICANCE OF THE POSITIVE DIRECT ANTIBODY TEST IN NEONATAL ABO INCOMPATIBILITY

Geetika Kukreja, Latha Rao, Zohaib Ahmed, Bulent Ozgonenel. Children's Hospital of Michigan, Wayne State University, Detroit, Michigan, United States of America

Background: ABO hemolytic disease of the newborn occurs almost exclusively in infants of blood group A and B who are born to group O mothers. Although ABO incompatibility is common, its related hemolytic disease has been reported to be low. The clinical significance of a positive Direct Antibody Test (DAT) in the cord blood is controversial.

Objectives: to review the clinical spectrum of ABO incompatibility in newborns

Design/Method: We identified all ABO incompatible births from group O mothers from January 1, 2007 - December 31, 2008. We then reviewed the electronic medical records for demographic, laboratory values and clinical events (anemia, jaundice, hemolytic disease) only in babies born at 37 weeks or higher gestation.

Results: There were 10,973 live births during the study period and 1537 (14.0%) of these were ABO incompatible. ‘Black’ ethnicity was registered in 85.0% of these babies. DAT was positive in 17.6% of the cases: 14.8% weakly or 1+ positive, and 2.9% 2+ or 3+ positive. DAT was more commonly positive among BO-incompatible cases compared to AO-incompatible cases (21.5% versus 14.9%, p=0.001). Blacks had significantly more DAT positivity compared to non-blacks (18.8% vs 10.8%, p=0.003). Of the 348 term babies who had serum bilirubin investigation, severe hyperbilirubinemia (defined as total bilirubin >17 mg/dL, 95th percentile for term infants) was detected in 11.5% of babies. This was significantly associated with DAT positivity (17.0% in DAT-positive cases vs 8.9% in DAT-negative cases, p=0.028). 245 babies had complete hematologic data (i.e., hematocrit and reticulocyte counts). Hemolytic anemia (defined as hematocrit ≤ 45% and reticulocyte count ≥ 250,000/mm3 in the first week of life) was noted in 21.2% of these cases, and was significantly associated with DAT positivity (43.7% in DAT-positive cases vs 12.1% in DAT-negative cases, p<0.001), and with BO incompatibility (32.6% in BO vs 14.0% in AO, p=0.001).

Conclusion: Our study indicated that cord blood DAT was positive in 17.6% of ABO incompatible pregnancies. Both Black ethnicity and BO incompatibility were significantly associated with DAT positivity. DAT positivity also predicted significant hyperbilirubinemia and hemolytic disease in ABO incompatible babies.
Initial Experience with Ga-68 DOTATOC PET-CT in Children and Young Adults
Chenue Abongwa, Sue O'Dorisio, David Dick, Len Watkins, Thomas O'Dorisio, Gideon Zamba, Yusuf Menda. University of Iowa, Iowa City, Iowa, United States of America

**Background:** Somatostatin receptor imaging with Ga-68 DOTATOC PET-CT is a highly sensitive imaging tool for detection and staging of neuroendocrine tumors in adults. Somatostatin receptor expression has been also shown in several embryonal tumors in children, including neuroblastoma, medulloblastoma and Ewing’s sarcomas.

**Objectives:** To report the results of our initial experience with Ga-68 DOTATOC PET-CT in children and young adults with malignancies.

**Design/Method:** Ten children and young adults (age: 3-24 years) were imaged with Ga-68 DOTATOC PET-CT. Ga-68 DOTATOC was produced under a physician-sponsored investigational new drug (IND) approval using an automated 68Ge/68Ga generator coupled with a ModularLab PharmTracer fluid handling system (Eckert-Ziegler). PET-CT scans were obtained 60 min after the IV administration of 1.58 MBq/kg of Ga-68 DOTATOC (148 MBq in patients older than 18, maximum dose 111 MBq in children) combined with a low-dose non-contrast CT. Images were interpreted qualitatively with focal uptake above normal background considered positive for somatostatin receptor positive tumor.

**Results:** There were 6 females and 4 males with median age 11 years (range 3-24 years). There were 5 patients with small bowel carcinoids, 1 gastrinoma, 1 medulloblastoma, 1 cerebral neuroblastoma, 1 esthesioneuroblastoma and 1 atypical meningioma. Scans were performed for initial staging (7 patients) or restaging following treatment (3 patients). Patients had no adverse events from the administration of Ga-68 DOTATOC. Using histopathology, other imaging, clinical follow-up and tumor markers, there were 4 true positives, 3 true negatives, 1 false positive and 1 false negative. The last patient’s status is indeterminate pending results from surgery and histopathology. Ga-68 DOTATOC PET-CT identified metastatic disease not seen on high resolution, contrast enhanced CT that was later confirmed by MRI.

**Conclusion:** Initial studies demonstrate that Ga-68 DOTATOC PET-CT is a safe, sensitive, and accurate imaging technique in children and young adults with solid tumors, including brain tumors. If confirmed in a larger patient population, Ga-68 DOTATOC with its high accuracy, lower radiation dose and more patient friendly image scheduling with a single visit could replace In-111 Octreotide for somatostatin receptor imaging.
COMPARISON OF THYROID NODULE OCCURRENCE AND ULTRASOUND DETECTION IN CHILDHOOD CANCER SURVIVORS WITH AND WITHOUT THYROID RADIATION EXPOSURE
Caitlin Agrawal, Lory Guthrie, Mollie Strum, Laura Martin, Randal Olshefski, Sarah O'Brien.
Nationwide Children's Hospital, Columbus, Ohio, United States of America

Background: Children who receive radiotherapy of the head, neck or chest as treatment of primary malignancies are at increased risk for secondary cancers, including thyroid gland malignancy. Currently Children’s Oncology Group recommends yearly thyroid physical examination for the screening of secondary thyroid malignancy. Thyroid nodules can be difficult to palpate on physical exam.

Objectives: We hypothesized that with the current standards, there were a substantial number of missed thyroid nodules which could represent missed secondary thyroid malignancies. Thyroid ultrasound is non-invasive and can detect new or growing nodules not palpable on exam. The specific aims of our study were to 1) compare the ability of thyroid ultrasound to detect nodules versus the current standard, physical exam and 2) compare the incidence of thyroid nodules in thyroid radiation exposed patients versus cancer survivors without radiation exposure.

Design/Method: We performed a prospective study to determine the incidence of thyroid nodules in pediatric patients who have received head/neck/chest radiotherapy for various primary malignancies. We recruited 60 patients with thyroid radiation exposure and 60 patients with no thyroid radiation exposure from either our oncology or bone marrow transplant long-term survivorship clinics. Each patient had a blinded thyroid physical exam and a thyroid ultrasound performed.

Results: Thirty-three patients (27.5%) from the total study population had nodules >0.3 cm of which only two were palpated (6.1%). We found 22 radiated patients (36.7%) with nodules >0.3 cm versus 11 non-radiated patients (18.3%) (p = 0.02). Average time from radiation to nodule detection was 15.98 years. The majority of radiation-exposed patients with nodules (86.4%) had a radiation dose of ≤ 2600 cGY. Eleven patients were biopsied due a nodule that was either solid appearing, > 1 cm in size or had microcalcifications on ultrasound. One biopsy showed a secondary papillary thyroid carcinoma.

Conclusion: We were able to clearly show the superiority of thyroid ultrasound over physical exam as a surveillance test in this high risk population. The high incidence of nodules in non-radiated patients deserves further study to investigate any relationship with chemotherapy agents. Our study would support the incorporation of thyroid ultrasound into long-term survivorship follow up guidelines in radiation exposed patients.
MORAL DISTRESS IN PEDIATRIC HEMATOLOGY/ONCOLOGY PHYSICIANS
Dolly Aguilera, Robert Castellino, Sungjin Kim, William Woods, Karen Trotochaud. Emory University, Atlanta, Georgia, United States of America

Background: Moral distress is an emotional condition that occurs when a person is not able to carry the ethically appropriate action for a specific situation.

Objectives: To quantify moral distress in pediatric Hematology-Oncology physicians

Design/Method: Using SurveyMonkey.com, we surveyed practicing pediatric hematology/oncology attendings and fellows. We used the moral distress survey revised version. Respondents answered 21 questions, on a scale of 0 to 4, pertaining to the intensity and frequency of moral distress in their daily medical practice. Moral distress scores were calculated by multiplying intensity by frequency for each question and adding the scores from all questions for each respondent. Significance was determined with the general linear model, Wilcoxon rank-sum, Pearson’s correlation coefficient, or the Spearman correlation coefficient.

Results: Thirty-one of 50 eligible physicians answered most of the 21 questions. Maximum possible score is 336. The mean moral distress score was 50.2 (± SD, 23.6). Higher moral distress scores were associated with younger physician age (p = 0.033) and fewer years of clinical experience (p = 0.037). A multivariate analysis validated higher moral distress score in practitioners with less clinical experience. Physician age was negatively correlated with moral distress scores associated with questions pertaining to ordering of unnecessary tests, providers’ feelings of inadequacy in the treatment of complicated patients, and patient suffering due to lack of provider continuity. The questions with the highest total scores were: to watch patient suffer due to lack of provider continuity, decrease patient care quality due to poor team communication, and continue life support. The lowest scores for moral distress were: providing care that does not relieve a child’s suffering because of fear of increasing doses of pain medication and administration of sedatives to an unconscious child that could hasten the child’s death.

Conclusion: We demonstrate that increased experience with clinical management of pediatric hematology/oncology patients and older physician age are associated with lower levels of moral distress. Younger pediatric hematology/oncology attending physicians and fellow trainees experience higher levels of moral distress.
PREDICTORS OF PLEXIFORM NEUROFIBROMA (PN) GROWTH IN PATIENTS WITH NEUROFIBROMATOSIS 1 (NF1)
Srivandana Akshintala, Eva Dombi, Andrea Baldwin, Andy Gillespie, Wendy Goodspeed, Anne Goodwin, Patricia Whitcomb, Seth Steinberg, Brigitte Widemann. Pediatric Oncology Branch, National Cancer Institute, NIH, Bethesda, Maryland, United States of America

**Background:** PNs are complex benign nerve sheath tumors that can cause severe morbidity. There is a need for development of medical treatments for PNs, as surgical removal is not feasible in many cases. The natural history of PN growth is incompletely understood. A better understanding of PN growth rate patterns is essential for the design of meaningful clinical trials targeting PNs.

**Objectives:** Identify predictors of PN growth in NF1.

**Design/Method:** NF1 patients enrolled on a NCI natural history study with ≥ 1-year follow-up and ≥ 2 magnetic-resonance imaging (MRI) studies for PNs were included. PNs were classified according to location and MRI presentation (typical versus nodular). A semi-automated method of volumetric MRI analysis (MEDx v3.44) was used to measure PN volumes. PN growth rate (regression slope of percent change in PN volume plotted against time) was calculated for each patient (in percent change in volume per year).

**Results:** 38 patients (17 male) with 41 typical and 19 nodular PNs were evaluated. Median age at first MRI was 8.8 years (range 0.7 to 40.2), and the median follow-up was 3.3 years (range 1 to 12). The median growth rate for typical PNs was 12.8% per year (range -4.1 to 180.5) and for nodular lesions 18.3% per year (range -1.9 to 117.2). Table 1 describes baseline volumes and growth rate of typical PNs.

**Conclusion:** Large variability in PN growth rates was observed. Age, PN location, MRI presentation, and initial volume appear to influence PN growth kinetics. Multivariate analysis to identify independent predictors of PN growth is ongoing.

**Table 1: Median (range) of baseline volume and growth rate of typical PNs by patient’s age and tumor location**

<table>
<thead>
<tr>
<th>Total PNs N=41</th>
<th>Baseline volume (ml)</th>
<th>PN growth rate (% change per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>272.0 (3.7 to 6931.0)</td>
<td>12.8 (-4.1 to 180.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age range (number of patients)</th>
<th>Baseline volume (ml)</th>
<th>PN growth rate (% change per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 years (N=6)</td>
<td>43.6 (3.7 to 272.0)</td>
<td>106.1 (28.0 to 180.5)</td>
</tr>
<tr>
<td>6-10 years (N=18)</td>
<td>281.0 (27.1 to 1895.0)</td>
<td>12.9 (-1.8 to 60.1)</td>
</tr>
<tr>
<td>11-20 years (N=12)</td>
<td>378.0 (23.5 to 1840.0)</td>
<td>10.2 (2.7 to 46.7)</td>
</tr>
<tr>
<td>&gt;20 years (N=5)</td>
<td>3541.0 (9.8 to 6931.0)</td>
<td>0.6 (-4.1 to 28.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location (number of patients)</th>
<th>Baseline volume (ml)</th>
<th>PN growth rate (% change per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head (N=6)</td>
<td>190.0 (12.2 to 249.0)</td>
<td>3.7 (3.2 to 102.9)</td>
</tr>
<tr>
<td>Head/Neck (N=3)</td>
<td>289.0 (271.0 to 408.0)</td>
<td>14.0 (-1.8 to 14.2)</td>
</tr>
<tr>
<td>Neck/trunk (N=6)</td>
<td>526.0 (9.6 to 1895.0)</td>
<td>11.1 (3.3 to 26.0)</td>
</tr>
<tr>
<td>Trunk (N=13)</td>
<td>507.0 (11.7 to 3615.0)</td>
<td>9.8 (-0.2 to 174.4)</td>
</tr>
<tr>
<td>Trunk/extremity (N=4)</td>
<td>177.6 (77.4 to 724.0)</td>
<td>77.9 (16.8 to 180.5)</td>
</tr>
<tr>
<td>Extremity (N=6)</td>
<td>70.3 (3.7 to 285.0)</td>
<td>22.6 (10.6 to 40.6)</td>
</tr>
<tr>
<td>Whole body (N=3)</td>
<td>1979.0 (1727.0 to 6931.0)</td>
<td>0.6 (-4.1 to 13.3)</td>
</tr>
</tbody>
</table>
OVARIAN SEX CORD STROMAL TUMORS IN CHILDREN AND YOUNG ADULTS: A SINGLE INSTITUTION EXPERIENCE
Elizabeth Alva, Britt Erickson, Joseph Pressey. University of Alabama at Birmingham, Birmingham, Alabama, United States of America

Background: Ovarian sex cord stromal tumors (OSCSTs) are a rare heterogeneous group of tumors that account for 5-10% of all ovarian neoplasms in children. These tumors arise from non-germinative component of the ovary such as granulosa, Sertoli, or Leydig cells. To date, minimal literature exists describing the clinical characteristics and treatment of this group of tumors.

Objectives: To retrospectively describe the clinical and treatment characteristics of children and young adults diagnosed with OSCSTs at Children’s of Alabama (COA) and the University of Alabama at Birmingham (UAB) between the years 2000 and 2013.

Design/Method: Institutional databases were queried for all histologic subtypes of OSCSTs identified in patients between the ages of 1 and 25 years.

Results: Fourteen patients were identified that met inclusion criteria. Mean age at diagnosis was 15.1 years (range 7-24). Granulosa cell tumors accounted for 71% (10/14) and Sertoli-Leydig cell tumors 21% (3/14) of cases. Abdominal pain was the most common presenting symptom (57%), followed by abdominal distension and virilization with each occurring in 36% of patients. Secondary amenorrhea (29%) and dysfunctional uterine bleeding (21%) were also present. Tumor markers were available for 8 patients, with CA-125, testosterone and AFP each being elevated in 3 patients. Ten patients (71%) were FIGO stage IA, with the remaining patients diagnosed at stage IC. All patients underwent gross total resection. The extent of surgery differed based on treatment center, with 100% of patients undergoing salpingo-oophorectomy at UAB versus only 29% of patients undergoing salpingo-oophorectomy at COA (p=0.02). Treatment with platinum-based chemotherapy was pursued in 3 patients (23%). Overall survival and EFS were 100%, with a mean follow-up time of 40.5 months.

Conclusion: This cohort of patients confirms previously published data that OSCSTs in children and young adults typically present in low stages and have excellent survival. Treatment with surgical resection alone is curative in almost all patients with low stage tumors. In this cohort, patients treated at an adult facility were more likely to undergo more extensive surgical resection than patients treated at a pediatric facility, although there was no difference in outcomes between the two centers.
SECOND MALIGNANCIES IN PATIENTS WITH NEUROBLASTOMA: THE EFFECTS OF RISK-BASED THERAPY

Mark Applebaum, Tara Henderson, Sang Mee Lee, Navin Pinto, Samuel Volchenboum, Susan Cohn.
University of Chicago, Chicago, Illinois, United States of America

Background: During the past 4 decades, high-risk patients with neuroblastoma have been treated with increasingly intensive, multi-modality approaches, whereas patients classified as non-high-risk have received reduced therapy. Although it is well established that neuroblastoma survivors are at increased risk of developing second malignant neoplasms (SMN) compared to the general population, the impact of the changes in risk-based treatment approaches on SMN rates remains unclear.

Objectives: To investigate if treatment modifications over the past 40 years for patients with neuroblastoma have influenced the incidence of SMN, we analyzed patients from the SEER database according to 3 treatment eras (1: 1973-1989, 2: 1990-1996, 3: 1997-2006) corresponding to the introduction of multi-agent chemotherapy, risk-based treatment, and stem cell transplant, respectively.

Design/Method: The SEER database was mined for all patients with neuroblastoma or ganglioneuroblastoma. Cumulative incidence rates of second malignancy were estimated with all-cause mortality as a competing event. The Mann-Whitney U test compared median latency from the primary neuroblastoma diagnosis to the development of a second cancer between eras.

Results: The analytic cohort included 2,801 patients. Thirty-four patients developed a SMN, accounting for 1.2% of all patients with a cumulative incidence at 35 years of 6.8% (95% CI: 3.6%-9.4%) at 35 years. While patient characteristics were similar between these two groups, those developing a SMN received radiation more frequently for their neuroblastoma (47.1% vs 25.1%; p=0.008). Although the incidence of SMN did not differ between treatment eras (p=0.5), the time to develop SMN was significantly shorter for patients treated in Era 3. Median latency from initial diagnosis to SMN for patients in Era 3 was 50 months compared to 158 and 214 months for patients diagnosed in Era 2 (p=0.007) and Era 1 (p=0.0003) respectively. Of the SMN, carcinomas (n=10) were more frequent in Eras 1 and 2 (p=0.017), whereas acute myelogenous leukemia (AML, n=6) was more frequent in patients treated in Era 3 (p=0.04).

Conclusion: In neuroblastoma patients, SMN often arise decades after diagnosis. Children treated after 1996 with intensive, multi-modality approaches, developed second cancers earlier, with a higher incidence of secondary AML. Further research investigating treatment exposures and other causative factors is needed.
CARDIOVASCULAR RISK FACTORS IN CHILDHOOD CANCER SURVIVORS
Joann Ater, Colette Badeaux, Angela Yarbrough, Sung Kim. The Children’s Cancer Hospital at MD Anderson, Houston, Texas, United States of America

**Background:** Survivors of childhood cancer are at increased risk of cardiovascular disease (CV) and metabolic syndrome due to their treatments, lifestyle, and genetic predisposition. However, little information is known about the interaction of anthracycline exposure with other risk factors for CV disease.

**Objectives:** This study was performed to evaluate interactions of risk factors for cardiovascular disease within our patient population of childhood cancer survivors.

**Design/Method:** We performed a review of patients seen the last 3 years in our Childhood Cancer Survivor Clinic and collected patient cancer characteristics, demographics, blood pressure (BP), body mass index (BMI), fasting glucose, lipid panels, total cumulative anthracycline dose, medications, and echocardiograms. All patients had BMI measurements, but not all patients had all other parameters documented. Lowest ejection fraction (EF) and shortening fraction (SF) were determined.

**Results:** We reviewed 303 patients (160 females). Median age at diagnosis of cancer was 6.0 (range 0.1-22.9) years. Median follow-up was 17.5 (range 5.1 to 51.2) years. The cancer diagnoses included 60 sarcomas, 57 other solid tumors, 73 CNS tumors, 63 leukemia, 35 lymphoma, 7 retinoblastoma, and 8 hematologic diseases with stem cell transplant. In the children < 20 years (n=97), 45.3% were > 85th % for BMI% for age (overweight/obese). For adults (n=206), 56.3% were overweight or obese. The % patients by age group (<20, >20 respectively) on medications for the following conditions were: hypertension (5.2, 21.6)%, cardiomyopathy (1.0, 12.2)%, hyperlipidemia (0, 18.6)%, diabetes type 2 (2.1, 2.9)%. Lowest EF correlated significantly with total anthracyclines dose (r= -0.26, p=0.0026), but BMI did not. In adults exposed to anthracyclines, 21.1% were on cardiac meds. Overweight and obese patients were more likely to be on cardiac medications (0% underweight, 15.1% average weight, 29.2% overweight) and medication for hyperlipidemia (0% underweight, 14.3% average weight, 24.1% overweight).

**Conclusion:** 1. The interaction of therapy-based and cardiac risk factors applicable to the general population need further investigation, especially in adult survivors of childhood cancer. 2. Based on this preliminary data, we plan to investigate other interactions of cardiac risk factors with treatment exposures in our survivors. The interaction of body mass index and cardiomyopathy with anthracycline exposure is of particular interest.
HEALTH DISPARITIES IMPACT STAGE AT DIAGNOSIS AND OUTCOME IN CHILDREN AND ADOLESCENTS WITH MELANOMA
Mary Austin, Hoang Nguyen, Jan Eberth, Dennis Hughes, Andras Heczey, Janice Cormier, Linda Elting. University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Health disparities in the presentation and outcome for adult melanoma are well established. Low socioeconomic status (SES) has repeatedly been associated with more advanced melanoma at diagnosis and increased mortality in adult populations. It is unclear if similar disparities exist for children and adolescents with melanoma.

Objectives: To identify barriers to health care in children and adolescents with melanoma and examine their impact on disease presentation and outcome.

Design/Method: We examined all persons age < 18 years diagnosed with melanoma and enrolled in the Texas Cancer Registry between 1995 and 2009 (n=239). Geocoded information was used to calculate the driving distance between a patient’s home address and the nearest pediatric cancer treatment center. Socioeconomic status (SES) was determined using the Agency for Healthcare Research and Quality (AHRQ) formula and 2007-2011 US Census block group data. Logistic regression was used to determine factors associated with advanced-stage disease. Life table methods and Cox regression were used to estimate survival probability and hazard ratios. Statistical significance was defined as p<0.05 and results are reported as odds ratios or hazard ratios with 95% confidence intervals (CI).

Results: 189 adolescents (age > 10 years) and 50 children (< 10 years) were identified. The majority were non-Hispanic White (n=180, 75%); however, 27 (11%) were Hispanic. The adjusted odds ratios of presenting with advanced disease were higher in children compared to adolescents (OR 2.36, 95% CI 1.15, 4.88), and in Hispanics compared to non-Hispanic Whites (OR 3.28, 95% CI 1.29, 8.35). Distance to treatment and SES did not impact stage of disease at presentation. In the unadjusted survival model, Hispanics had a significantly increased odds of death compared to non-Hispanic Whites (HR 3.0, 95% CI 1.2, 7.8). However, in the adjusted survival model, only low SES and advanced disease were predictive of mortality (all p<0.05).

Conclusion: In pediatric melanoma, Hispanics and young children are more likely to present with advanced disease; however, SES plays an important role in overall survival.
MEDICAL TREATMENT OF PLEXIFORM TUMORS IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 1 USING CELECOXIB AND PEGINTRON
Albert Cornelius, David Dickens, Emily Gleason, Thomas Symington, Helen Devos Children's Hospital/Spectrum Health, Grand Rapids, Michigan, United States of America

**Background:** Plexiform tumors are a significant cause of disability in patients with neurofibromatosis type 1 with no effective medical treatment. We report the preliminary response and toxicity data using celecoxib and PegIntron as treatment for highly symptomatic neurofibromas in children with neurofibromatosis type 1.

**Objectives:** Assess the efficacy and toxicity of celecoxib and PegIntron for the treatment of high-risk plexiform tumors in children with NF-1.

**Design/Method:** This is a prospective single arm trial wherein after voluntary informed consent, children with a confirmed diagnosis of neurofibromatosis type 1 and high-risk symptomatic neurofibromas are receive celecoxib 10mg/kg/day orally and PegIntron 1mg/kg/week subcutaneous injection. If patients demonstrate a response after six months, they continue study treatment for 2 years.

**Results:** Seven patients’ ages two - 17 years old were entered on this clinical trial to date. All patients have shown improvement in their chronic pain and Lansky play scale measurements. One patient demonstrated complete resolution of vocal cord paralysis from tumor infiltration within 2 months of starting treatment. Toxicity included worsening of immune neutropenia (one patient), reactivation of depression requiring inpatient treatment (one patient), and fatigue requiring a temporary reduction in PegIntron dose (one patient). One patient chose to discontinue treatment after one year of treatment, three patients have completed two years of treatment, and three patients remain on active treatment.

**Conclusion:** We found celecoxib and PegIntron to be effective treatment for symptomatic neurofibromas in young patients with neurofibromatosis type 1. No unexpected treatment toxicity was observed, but all patients in this trial had a pre-treatment history of depression or psychological problems and need careful monitoring while on celecoxib and PegIntron treatment. We are continuing this trial to determine the maximum response and duration of response to celecoxib and PegIntron therapy.
ROLE FOR SIRTUINS IN CHEMORESISTANCE IN NEUROBLASTOMA
Branko Cuglievan, Fiorela Hernandez, Guillermo De Angulo, Regina Graham. Miami Children's Hospital, Miami, Florida, United States of America

Background: Chemoresistance is a major obstacle in the successful treatment of high-risk neuroblastoma (NB). Mechanisms of chemoresistance include the activation of survival pathways such as the unfolded protein response (UPR), an adaptive mechanism in response to endoplasmic reticulum (ER) stress, and the PI3K/AKT/MTOR pathway. AKT pathway promotes UPR and contributes to cell survival in response to chemotherapy. At the intersection of these pathways are sirtuins (SIRTs), which are NAD+ dependent deacetylases, which are activated during periods of stress leading to cellular protection.

Objectives: Determine the therapeutic potential of SIRT inhibition as a novel method to increase NB chemosensitivity to ER stressors and AKT pathway inhibition.

Design/Method: Cell viability was determined by MTS assay and cell signaling pathways were evaluated by western blot analysis. NB cells were treated with celecoxib and velcade to induce ER stress, and perifosine and everolimus to inhibit the PI3K/AKT/MTOR pathway. Sirtinol was used as Sirtuin inhibitor.

Results: Treatment of NB cells with the SIRT1 and 2 inhibitor, sirtinol, induced NB cell death (IC50 : 67μM, and 44μM for NB1691 and SK-N-BE2C, respectively). Sirtinol blocked expression of GRP78, an UPR survival protein, increased expression of the pro-death protein CHOP and significantly increased NB1691 cell death (viability; vehicle=100±2.3%, sirtinol=63±1.6%, celecoxib=67±1.1%, celecoxib+sirtinol=10±0.6%, velcade=68±2.0%, velcade+sirtinol=28±1.3%). Combined SIRT and AKT pathway inhibition induced PARP cleavage and NB1691 cell death (viability; vehicle=100±1.9%, sirtinol=70±1.9%, perifosine=76±1.9%, sirtinol+perifosine=28±0.9%, everolimus=87±3.2%, sirtinol+everolimus=23±2.2%).

Conclusion: Our data indicates that SIRTs regulate UPR and cell survival following chemotherapeutic insult. Most SIRT inhibitors are in pre-clinical trials, however NAMPT, needed to generate NAD+, inhibitors are in clinical trials and could potentially be used to inhibit SIRTs thereby enhancing the therapeutic effect of AKT and UPR targeting agents. Here we provide novel insights in role of SIRTs in NB and suggest a new therapeutic regimen for a cancer with minimal survival.
B7-H3-SPECIFIC ENGAGER T CELLS FOR THE IMMUNOTHERAPY OF PEDIATRIC SOLID TUMORS
Christopher Derenzo, Kota Iwahori, Mireya Paulina Velasquez, Xiao-Tong Song, Stephen Gottschalk.
Center for Cell and Gene Therapy, Houston, Texas, United States of America

**Background:** B7-H3 positive tumors, including osteosarcoma, neuroblastoma, and high grade glioma, cause significant morbidity and mortality in pediatric patients despite aggressive management with multimodality therapy. Current B7-H3-targeted immune-therapies take advantage of the monoclonal antibody (MAb) 8H9, which is actively being evaluated in Phase I clinical trials. We now propose to develop a T-cell therapy approach targeting B7-H3 using Engager (ENG) T cells. ENG T cells, which secrete bispecific engager molecules consisting of single chain variable fragments (scFvs) specific for CD3 and a tumor antigen, are a new class of antigen-specific T cells, with the unique ability to redirect bystander T cells to tumor cells, amplifying antitumor effects.

**Objectives:** To generate B7-H3-specific Engager (B7-H3-ENG) T cells, and pre-clinically evaluate their effector function in vitro and in vivo.

**Design/Method:** B7-H3-ENG T cells were created by synthesizing a mini gene consisting of a leader sequence and a B7-H3-specific scFv derived from MAb 8H9. The mini gene was cloned into a SFG retroviral vector containing a CD3-specific scFv and mOrange separated by an internal ribosomal entry site. RD114-pseudotyped retroviral vectors were used to transduce CD3/CD28-activated human T cells. The effector function of B7-H3-ENG T cells was evaluated in vitro by performing coculture and cytotoxicity assays with B7-H3-positive osteosarcoma (LM7), neuroblastoma (CHLA255), and glioma (U373) cell lines, and a B7-H3-negative lung cancer (HTB-119) cell line.

**Results:** Post transduction 30 to 60% of T cells were genetically modified as judged by mOrange expression. In coculture assay B7-H3-ENG T cells recognized B7-H3-positive target cells (LM7, CHLA255, U373) as judged by IFNγ production and cytolytic activity, in contrast to B7-H3-negative cells (HTB-119). T cells secreting an engager molecule specific for an irrelevant antigen (CD19) did not recognize or kill any of the target cells.

**Conclusion:** We have successfully generated B7-H3-ENG T cells and shown that these cells recognize and kill B7-H3-positive tumor cells in an antigen-dependent manner. In the future, we plan to extend our in vitro studies, and also evaluate antitumor activity in relevant preclinical animal models of pediatric solid tumors.
FUSOGENIC-OLIGOARGININE PEPTIDE-MEDIATED DELIVERY OF siRNAs TARGETING THE CIP2A ONCOGENE IN VIVO
Anca Dumitriu, Christopher Attaway, Andrew Jakymiw. MUSC, Charleston, South Carolina, United States of America

Background: One of the single greatest challenges of RNA interference (RNAi)-based therapeutics is delivery of functional small interfering RNAs (siRNAs). In particular, endosomal entrapment remains a major hurdle for RNAi therapeutics, resulting in inefficient gene silencing. Recently, we demonstrated that a chimeric peptide we synthesized, termed 599 that comprised an endosome-disruptive and cationic peptide sequence, could enhance the intracellular delivery and bioavailability of siRNAs via its direct complexation with these molecules. More specifically, the 599 peptide was demonstrated to effectively deliver siRNAs designed to target the CIP2A oncoprotein (siCIP2A) into oral cancer cells, mediate it’s silencing, and consequently inhibit oral cancer cell invasiveness and anchorage-independent growth in vitro.

Objectives: To demonstrate the feasibility of utilizing the 599 peptide to mediate delivery of siRNAs into oral cancer tissues in vivo.

Design/Method: Oral cancer cell lines were used to generate xenograft oral tumors in NOD/Scid mice. After tumor generation, the mice were either untreated or treated via intratumoral injections with either vehicle alone, DY547-labeled siCIP2A (D-siCIP2A) alone, 599+siNT, or 599+D-siCIP2A. 48 hours post-treatment, the mice were sacrificed and a histopathological examination was performed on the extracted tumors to ensure that the treatments did not induce any acute toxicities and/or inflammation. Subsequently, the tissues were also examined with a fluorescence microscope to visualize the presence of fluorescently-labeled siCIP2A. A Western blot analysis was performed to examine the degree of CIP2A knockdown in the tissues. In a second experiment, similar treatments were performed except that total RNA was harvested 72 hours post-treatment from the tumor tissues, after which CIP2A mRNA and siCIP2A levels were quantified by qPCR.

Results: Upon examination of the tissues, it was observed that the treatment group (599+D-siCIP2A) showed increased amounts of siRNA compared with the control group (D-siCIP2A alone). Upon examination of CIP2A knockdown at the mRNA and protein levels, the 599+siCIP2A complex promoted significant silencing compared with siCIP2A alone.

Conclusion: Our in vivo data demonstrate that intratumoral injection of the 599+siRNA complex can effectively deliver siRNAs into cancer cells, induce the silencing of the target oncogene, and potentially offer a new therapeutic strategy for cancer treatment.
GLIA MATURATION FACTOR BETA (GMFb) PROMOTES NERVOUS SYSTEM TUMOR DIFFERENTIATION THROUGH ITS INTERACTION WITH THE ACTIN CYTOSKELETON
Xiaohua Song, Epsita Shome, David Eisenstat. University of Alberta, Edmonton, Alberta, Canada

Background: Glia maturation factor beta (GMFb) is a 17 kDa phosphorylated protein highly expressed in the central and peripheral nervous systems (CNS and PNS, respectively) that promotes cell process outgrowth when added to glioma cell cultures in vitro.

Objectives: Our goal was to identify the mechanisms by which GMF exerts its biological function during development and in pediatric nervous system tumors, such as gliomas and neuroblastoma.

Design/Method: We generated specific anti-peptide antibodies after bioinformatic analysis. The cytoskeleton was disrupted using colchicine (microtubules) or cytochalasin D (actin). Lambda alkaline phosphatase was used for dephosphorylation. GMFb expression was assessed in primary embryonic forebrain cultures, mouse embryos, human brain, neuroblastoma and glioma tissue sections using immunohistochemistry, in situ hybridization and/or Western blotting. Differentiation (retinoic acid), gain (transfection) and loss-of-function (deletion mutants, siRNA) assays were performed using tumor cell lines. Green fluorescence-based constructs permitted cell sorting by FACS.

Results: GMFB protein is homologous to coflin, a member of the actin depolymerization factor family, and is localized to the cell soma, axons and growth cones in embryonic forebrain cultures and RA-treated cells. Treatment with cytochalasin D but not colchicine disrupts GMFb's subcellular localization. Co-immunoprecipitation (co-IP) assays confirm that GMFb and actin form protein-protein complexes in vivo. The GMFP02 antibody recognizes the C-terminal actin binding domain (ABD) and deletion of the ABD abrogates cell process outgrowth. The GMFP01 antibody recognizes phosphorylated and hypophosphorylated forms of the protein. GMFb is phosphorylated in adult brain and pilocytic astrocytomas, whereas this protein is hypophosphorylated in embryonic brain and high grade gliomas.

Conclusion: GMFb activity during differentiation requires binding directly to the actin cytoskeleton. Phosphorylated GMFb (pGMFb) is more highly expressed in differentiated adult brain and pilocytic astrocytoma. Future studies using the GMFb knockout mouse, which is viable postnatally, will explore the role of GMFb in glioma tumor invasion and in cell signaling pathways. We hypothesize that by inducing GMFb phosphorylation, there will be increased differentiation. We will also determine whether pGMFb expression correlates with improved survival in glioma and neuroblastoma patient cohorts.
ADRENOCORTICAL CARCINOMA IN THE PEDIATRIC AGE GROUP; EXPERIENCE AT CHILDREN CANCER HOSPITAL OF EGYPT (CCHE)

Wael Zekri, Mahmoud Hammad, Yasser Elborai, Hala Taha, Amal Refaat, Ahmed Alfaar, Badr Abdalla, Alaa Younis. Children Cancer Hospital of Egypt (CCHE), Cairo, Cairo, Egypt

Background: Adrenocortical cancer (ACC) is a rare but aggressive childhood endocrine neoplasm. Its incidence in children is extremely low (0.2% of pediatric cancers). Little is known about this malignancy and most available information has been learned from its more frequent adult counterpart. An exceptionally high annual incidence of ACC has been reported for children in southern Brazil, with 3.4–4.2 affected patients per 1 million children versus an estimated worldwide incidence of 0.3 per 1 million children younger than 15 years.

Objectives: Evaluate the incidence, demographic data, clinical presentation, endocrinal symptoms and survival outcome for patients with ACC in CCHE.

Design/Method: Data from CCHE registry, for pediatric ACC patients from July 2007 to December 2012, were analyzed regarding preoperative radiological and hormonal assessment and histopathological reporting. The patients were followed till December 2013.

Results: Seven cases were analyzed, 8-156 months old (median 36), 5 females and two males. One was nonfunctioning, while six were functioning; two of them showed only virulizing symptoms, one case showed hyperestrogenism, three cases were mixed. Three cases had Hypertension. According to ACC staging system, stages I, II, III and IV were 2,1,2 and 2 cases respectively. Stage IV cases had chest metastases and one of them had also liver metastases. Four cases did upfront adrenalectomy and Lymph node dissection, one case did surgery after three courses of chemotherapy, two cases were irresectable. Cases with stage I and II had no adjuvant chemotherapy, while stage III and IV received Doxorubicin, Etoposide, Cisplatinum and Mitotane with no treatment related mortality. Stage I and II are alive in CR, while stage III and IV died due to progressive disease. Overall survival 47.6% (median survival time 31 months). Progression free survival 42.9% (Median follow up 29 months).

Conclusion: Adrenocortical carcinoma in children is a very rare disease. Patients with ACC suffer not only from the malignant mass itself but also from the consequences of excess hormones. The prognosis is essentially dependent on complete resection of the tumor and thus on the initial tumor stage. The adrenotoxic mitotane and various chemotherapy protocols may only control tumor growth in the advanced stages for only short periods.
IMPACT OF 1p and 16q LOH ON THE OUTCOME OF FAVORABLE HISTOLOGY WILMS TUMOR
Fawzy, Hanafy Hafiz, Abeer Bahnassy, Amr Samir. National Cancer Institute-Egypt, Cairo, Egypt

Background: Wilms tumor (WT) represents 6.5% of childhood cancers accounting for 87% of pediatric renal tumors. According to the fifth National Wilms Tumor Study (NWTS-5), tumor-specific loss of heterozygosity (LOH) for chromosomes 1p and 16q identifies a subset of WT patients with favorable histology (FH) who have a significantly increased risk of relapse and death.

Objectives: the aim of this study was to find out 1p and 16q LOH frequencies in FH-WT patients as well as its correlation to survival outcome, epidemiologic and clinical characteristics.

Design/Method: data of FH-WT patients presented to the National Cancer Institute, Egypt (NCI) during the period from January 2005 to December 2009 was retrospectively analyzed. Clinical and demographic data were reviewed and paraffin blocks were tested for 1p and 16q LOH using polymorphic loci that span the minimal regions of LOH at this area as described in earlier studies.

Results: study included 100 patients with a median age of 5 years (8 months-15 years) and male to female ratio was 1:0.75. 39/100 patients showed LOH at 1p (n=14), 16q (n=13), or both (n=12). LOH was most frequently encountered in patients above 10 years of age (5/5), advanced stages disease (80% of stage V and 50% of each stage IV and III patients). All patients with progressive disease during chemotherapy (n=5) were positive for LOH. The 3 years OS and EFS were significantly lower in patients with double LOH (56% & 50%) followed by 16q (59% & 55%) in comparison to 1p (93% each) and negative LOH cases (98% each) respectively (p=0.001).

Conclusion: combined LOH (1p+16q) followed by 16q LOH alone are predictive of poor outcome and are associated with lower OS and EFS in FH-WT. Our data indicated a higher risk disease that would suggest the need for a different approach of therapy in aforementioned patients.
MOLECULAR PROFILING OF ADULT PATIENTS WITH PEDIATRIC-TYPE MALIGNANCIES IDENTIFIES NOVEL SOMATIC ABERRETIONS

Jorge Galvez Silva, Fernando Corrales-Medina, Vivek Subbiah. The University of Texas - MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Many common pediatric oncologic diseases such as medulloblastoma, Wilm’s tumor and Ewing’s sarcoma, are infrequently found in the adult population. Pediatric malignancies in adults are clinically aggressive, with higher risk of relapse, and more resistance to chemotherapeutics. Thus, they are very challenging to manage. Molecular profiling has recently become available for more detailed molecular analysis of these entities. These may provide insights into the aggressive biology of the disease.

Objectives: To describe molecular/genomic abnormalities present in adult patients diagnosed with cancers that are more frequently encountered in pediatric patients.

Design/Method: We conducted a retrospective chart review of adult patients diagnosed with pediatric malignancies referred to The Center for Targeted Therapy and/or Department of Pediatrics at MD Anderson Cancer Center. The archival tumors were analyzed using the CLIA certified exome next-generation sequencing at Foundation Medicine, Boston, MA, or MD Anderson Cancer Center, Houston, TX.

Results: Five patients had genomic profiling for review. Median age at presentation was 28.8 years (23 – 38 years). All of the encountered malignancies were solid tumors. The genetic aberrations identified in the two patients with history of medulloblastoma were BRCA1 (splice site 4987-1), PTCH-1 (N97fs*43 and K163fs*6). One case of Wilm’s tumor in a 36-year old male showed CTNNB1, IGF1R, FAM123B and SPEN Q1122 alterations in the absence of WT1 and WTX mutations whereas another patient with Wilm’s tumor harbored WT1 mutation. One patient with Ewing’s sarcoma harbored with CDKN2A/B loss, and BCL2L2 and c17orf39 amplification.

Conclusion: Identification of somatic aberrations in adult patients with pediatric type malignancies using CLIA certified clinical next generation sequencing is feasible. Although it is unfeasible to perform clinical trials in this population, establishment of a rare disease registry is warranted. In addition further larger analysis of these types of patients along with clinical correlation is needed.
PERIVASCULAR LEUKOCYTE AGGREGATES FORM IN TUMORS AFTER CHEMOTHERAPY
Denise Gamble, Minghui Li, Aaron Bolduc, Anna Bolduc, Theodore Johnson. Georgia Regents University, Augusta, Georgia, United States of America

**Background:** Evidence is mounting to support the hypothesis that immune processes play a critical role in tumor clearance after standard treatment such as chemotherapy. In spite of this, anti-tumor immunity is often less robust than expected. One of the major problems with immunologic therapy for tumors is that immune cells fail to traffic to the tumor and often cannot cross the vascular endothelium to enter the tumor parenchyma.

**Objectives:** To test the hypothesis that standard chemotherapy treatment leads to immune activation.

**Design/Method:** We used syngeneic murine tumor models of glioblastoma (intracranial orthotopic GL261 implantation) and melanoma (subcutaneous B16F10 implantation) to study the effect of chemotherapy (temozolomide or cyclophosphamide) on immune cells within the tumors.

**Results:** In both glioblastoma and melanoma, leukocytes aggregated in perivascular locations after chemotherapy. These perivascular immune cell “cuffs” became more prominent and frequent over time, but were confined to the tumor and peritumoral tissue. Despite the proximity to intratumoral vascular structures, analysis of endothelial integrin expression showed no upregulation of cell-surface ICAM or VCAM after chemotherapy. Immunohistochemical analysis showed a preponderance of macrophage lineage cells with a less prominent CD4 T cell component, and very few CD8 T cells. Only a very small number of T cells were in cell cycle by Ki67 staining, and a high proportion of the CD4 T cells were found to be regulatory T cells. When tumor-specific CD8 T cells were transferred into tumor-bearing mice, they did not traffic to the tumors. Finally, perivascular cuffs failed to form in Rag1-deficient host mice that lack T cells.

**Conclusion:** Our data demonstrate that chemotherapy treatment results in large immune cell aggregates around tumor vessels which are composed primarily of macrophage-lineage cells. Despite these prominent perivascular leukocyte cuffs, the vascular endothelium failed to demonstrate an activated phenotype. Interestingly, T cells were mechanistically critical for cuff formation, even though they were less frequent in the cuff architecture. Based on the histiocytic nature of the perivascular cuffs, we speculate that they are made up of tumor-associated macrophages/microglia that sense tumor tissue damage and migrate to perivascular locations, where they can protect the tumor from immune attack.
CENTRAL LINE-ASSOCIATED BLOODSTREAM INFECTION RATES IN HOSPITALIZED AND AMBULATORY PEDIATRIC HEMATOLOGY/ONCOLOGY PATIENTS BY CENTRAL LINE TYPE

Jeffrey Hord, John Lawlor: Children's Hospital Association, Alexandria, Virginia, United States of America

Background: Central line-associated bloodstream infections (CLABSI) are a significant cause of morbidity and mortality in the pediatric hematology/oncology (PHO) population and it has been suggested in prior small studies that the CLABSI risk varies by line type. Three types of permanent central venous catheters (CVC) are commonly inserted in children for easy vascular access: totally implantable catheters (ports), single or multi-lumen tunneled externalized catheters (SL TEC or ML TEC), and peripherally-inserted central catheters (PICC).

Objectives: To determine CLABSI rates for different types of CVC’s in PHO patients, both hospitalized and ambulatory, by analyzing a large dataset built by the participants of the Children’s Hospital Association Hematology/Oncology Quality Transformation Network (CHA QTN).

Design/Method: Since November 2009, 40 PHO/transplant units have joined the CHA QTN to reduce CLABSI among PHO patients. All centers report CLABSI events and central line days among hospitalized and ambulatory PHO patients monthly. A subset of 16 centers voluntarily submitted line days by line type from May 2012 through October 2013.

Results: The number of CLABSI’s, the central line days, and the CLABSI rates (infections per 1000 central line days) are reported by line subtype and setting in Table 1.

Conclusion: CLABSI rates for all line types are significantly higher for hospitalized PHO patients compared to ambulatory patients. Ports have the lowest CLABSI rate among CVC types in both settings. CLABSI rates are similar in PICC and TEC lines. The CLABSI risk appears to increase with number of lumens. This information should be considered when the type of CVC is being decided.

<table>
<thead>
<tr>
<th></th>
<th>Port</th>
<th>SL TEC</th>
<th>ML TEC</th>
<th>PICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>81/57,236</td>
<td>5/2098</td>
<td>118/26,207</td>
<td>37/13,338</td>
</tr>
<tr>
<td></td>
<td>1.42</td>
<td>2.38</td>
<td>4.5</td>
<td>2.77</td>
</tr>
<tr>
<td>Ambulatory</td>
<td>240/1,480,834</td>
<td>30/33,394</td>
<td>109/79,757</td>
<td>36/25,638</td>
</tr>
<tr>
<td></td>
<td>0.16</td>
<td>0.9</td>
<td>1.37</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Parinda Mehta, Mary Eapen, Mei-Jie Zhang, Wensheng He, Adriana Seber, Carrie Kitko, Gregory Hale, Stella Davies. Cincinnati Children's Hospital Medical Center and CIBMTR, Cincinnati, Ohio, United States of America

Background: Children with hypodiploid ALL have inferior outcomes despite risk adapted intensive chemotherapy. In large case series, patients with fewer than 44 chromosomes fared significantly worse than those with 44 chromosomes (EFS of 30% vs. 52%, p=0.01)1 and those with 25-39 chromosomes did worse compared to patients with 42-45 chromosomes (3 year survival of 29% vs. 66%)2.

Objectives: To determine whether outcomes for hypodiploid ALL might be improved with transplant.

Design/Method: Retrospective study of 78 children with hypodiploid ALL who underwent HSCT between 1990 and 2010 (reported to CIBMTR).

Results: Median age at HSCT was 10 years (range 3-18). Thirty nine patients had ≤ 43 chromosomes, 12 had 44 and 27 had 45 chromosomes. Forty three patients were transplanted in CR1 and 35 in ≥CR2. Twenty nine patients received a related donor graft, 34 an unrelated donor and 15 had cord blood. All patients received a myeloablative conditioning regimen. Multivariate analysis confirmed both disease status and number of chromosomes were independently associated with mortality; mortality risks were higher for transplants in CR2 (HR 2.16, p=0.05) and when chromosomes were <=43 (HR 2.15, p=0.05). See Table 1 for additional results.

Conclusion: Despite the obvious limitation of small numbers of patients and the retrospective nature of our study, our results suggest that compared to historical results from chemotherapy only treatment, pediatric patients with hypodiploid ALL, may have improved outcomes when transplanted in CR1, and benefit may be most notable in those with ≤43 chromosomes.1 Nachman et al; Blood 20072 Harrison et al, Br J Haematol 2004

**Table 1. HSCT outcomes in children with hypodiploid ALL at 5 years**

<table>
<thead>
<tr>
<th></th>
<th>DFS % (range)</th>
<th>OS % (range)</th>
<th>Relapse% (range)</th>
<th>TRM% (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>51 (40-62)</td>
<td>56 (44-67)</td>
<td>27 (18-38)</td>
<td>22 (14-32)</td>
</tr>
<tr>
<td>Patients in CR1</td>
<td>55 (40-70)</td>
<td>58 (43-72)</td>
<td>26 (14-40)</td>
<td>20 (9-33)</td>
</tr>
<tr>
<td>CR1 patients with ≤43 chromosomes</td>
<td>47 (29-66)</td>
<td>50 (32-69)</td>
<td>30 (15-47)</td>
<td>23 (9-41)</td>
</tr>
</tbody>
</table>

129
IMPACT OF ETHNICITY ON DONOR SEARCH RESULTS FOR CHILDREN REQUIRING STEM CELL TRANSPLANTATION

Julia DiLabio, John Doyle, Sarah Alexander, Sumit Gupta, Angela Punnett. SickKids Hospital, Toronto, Canada

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) can be curative for children with a variety of malignant and non-malignant conditions. Access to stem cells from suitable unrelated donors (URDs) or umbilical cord blood (CB) may be limited for children of certain ethnic backgrounds lacking related donors.

Objectives: We sought to determine the impact of ethnicity upon donor availability in a pediatric cohort.

Design/Method: We conducted a retrospective database and chart review of children referred to SickKids Hospital (Toronto, Canada) for allogeneic HSCT between January 2009 and August 2012. Patient demographics, self-reported ethnicity, suitable related donors, and results of combined URD and CB searches were assessed. We evaluated the proportion of children within different ethnic groups with suitable stem cell sources and compared the combined URD and CB search results between White and non-White patients.

Results: Among 252 eligible patients, 58 (23%) had a suitable related donor. Of the 161 patients with combined URD and CB searches, 78 (48%) had a suitable URD, 65 (83%) of which were fully HLA-matched. Comparatively, 143 (89%) had suitable CB, 61 (43%) of which were fully-HLA matched. The probability of finding a suitable URD differed significantly by ethnicity (p=0.007). No suitable URDs were identified for any Black children lacking family donors (n=5). Overall, non-White patients were significantly less likely to have a suitable URD than White patients (odds ratio [OR] 0.35, 95% confidence interval [CI] 0.17-0.69; p=0.003) but were equally likely to have a suitable CB source (OR 1.02, 95% CI 0.36-2.89; p=0.97).

Conclusion: Though ethnic disparities exist among pediatric patients in their likelihood of finding an URD for HSCT, they are partially mitigated by the ability to search international CB registries. These results will inform family counseling and may influence treatment planning. Given the superior outcomes traditionally associated with HLA-matched URD as compared to CB, the targeted recruitment of individuals of non-White ethnicities to donor registries remains crucial.
CD27 NEGATIVE T-CELLS PROVIDE IMMUNE RECONSTITUTION WITH LOW RISK OF GVHD IN DONOR LYMPHOCYTE INFUSIONS
Aimee Talleur. St. Jude Children's Research Hospital, Memphis, Tennessee, United States of America

Background: Viral infections and reactivation during pediatric allogeneic hematopoietic stem cell transplant (HSCT) are a common occurrence and significantly contribute to post-transplant morbidity and mortality. The most definitive treatment for viral infections is the host’s cellular defenses. However, HSCT patients experience prolonged periods of immune deficiency while awaiting immune reconstitution. Standard therapy includes antiviral medications which are often toxic, not very effective and are targeted against few viruses. Donor lymphocyte infusions (DLI) can provide a patient with antiviral immunity through the transfer of memory T-cells that have been previously primed via a donor viral infection. Unmanipulated DLI products contain memory and naïve T-cells. Naïve allogeneic T-cells can cause GVHD, and the risk of developing GVHD from a DLI often outweighs the potential antiviral benefit. Comparatively, allogeneic effector memory T-cells should not cause GVHD, but should confer immunologic memory against infectious antigens. Naïve and memory T-cells can be distinguished by surface markers, including CD27. CD27 negative T-cells are effector memory and terminal effector RA+ T-cells. If CD27 negative T-cells provide immunologic memory and are less alloreactive, manipulating a DLI product to contain only this subset of T-cells may be a potential antiviral therapy.

Objectives: To determine if allogeneic CD27 negative T-cells provide superior immunologic memory and have decreased alloreactivity potential compared to CD27 positive T-cells.

Design/Method: CD27 negative and CD27 positive cells were isolated from donor apheresis rings using CD27 microbead cell separation. To evaluate immunologic memory, lymphocyte proliferation assays were performed with viral antigen and mitogen stimuli. Alloreactivity potential was tested using one-way mixed lymphocyte reactions with irradiated stimulator cells.

Results: Comparison of the stimulation indices of the CD27 cell populations in the lymphocyte proliferation assays demonstrated that CD27 negative cells have a stronger, specific immunologic memory. Results from the mixed lymphocyte reactions showed that CD27 negative cells are less alloreactive compared to CD27 positive cells, suggesting that CD27 negative T-cells will be less likely to cause GVHD.

Conclusion: CD27 negative allogeneic T-cells provide superior immunologic memory and have decreased alloreactivity potential compared to CD27 positive allogeneic T-cells, making this subset of T-cells a promising population to be used for DLI in the post-HSCT setting.
A SIMPLE METHOD FOR AUGMENTING CORD BLOOD STEM CELL COLLECTIONS
Robert Dracker. Summerwood Pediatrics, Syracuse, New York, United States of America

**Background:** The usefulness of cord blood derived stem cells has been limited by the stem cell number constraints of a typical Cord Blood Stem Cell (CBSC) collection, as compared to other standard stem cell sources such as bone marrow and peripheral blood. Methodologies to increase volume and cell yield have included placental expression, perfusion and placental and cord tissue maceration. The potential for routine use of an abundant, low cost stem cell source such as cord blood for either hematopoietic reconstitution or other stem cell applications is obvious. The routine collection an invaluable stem cell resource having sufficient cellular content is obvious but the methodology needs to be reliable, reproducible and simplistic, ideally avoiding specialized equipment, facilities or expertise.

**Objectives:** The intent of this research was to develop a modification of the standard cord blood collection procedure which would result in significantly increased stem cell yields to increase the therapeutic usefulness and minimize the incidence of low volume collections which would otherwise be unusable.

**Design/Method:** We have developed a procedure which consistently results in the collection of a two part stem cell product which can provide sufficient mononuclear cells for the cellular needs of potential recipients beyond 30kg weight and which might also serve as a biologic resource for other stem cell applications. The methodology utilizes a standard cord blood collection procedure followed by the administration of a vasodilator and stem cell releasing agent in a cell supportive media, subsequently followed by a second collection utilizing the same phlebotomy access.

**Results:** The combined and increased stem cell volume yields 1.5 to 2 times the typical mononuclear cell number, having >95% viability. The percent mononuclear cell and CD34+ cell population is significantly elevated in the second collection volume, demonstrating selective mobilization of marginating CBSC’s. CFU cultures demonstrated comparable data for both cord blood and placental collections in Total, GM and GEMM colony types.

**Conclusion:** This improved methodology for cord blood stem cell procurement is an important, simple and reproducible technology, requiring minor modifications in the standard cord blood collection procedure, resulting in marked increases in functional CBSC yields.
HEMATOLOGICAL COMPLICATIONS OF VARICELLA INFECTION IN THE VARICELLA VACCINATION ERA

Obada Subei, Karen Fernandez, Akua Asante, Reuben Antony. Childrens Hospital of Illinois, Peoria, Illinois, United States of America

**Background:** Autoimmune hemolytic anemia and immune thrombocytopenia (ITP) are complications of varicella infection which have become rare since 1995. To our knowledge auto-immune hemolytic anemia has not been described in the context of breakthrough varicella infection (BTV, >42 days post vaccination).

**Objectives:** We describe two children who had hematological complications of chicken pox. One patient had BTV associated autoimmune hemolytic anemia and the second patient (unimmunized) presented with post varicella ITP.

**Design/Method:** Case Report

**Results:**

Patient 1: 11 year old boy presented with 24 pruritic papular, vesicular and crusted skin lesions typical of varicella, macrocytic anemia, jaundice and scleral icterus. Family history was positive for hereditary spherocytosis (HS). Labs: Hemoglobin 9.7 g/dl, MCV 92 FL, Reticulocytes 7.7%, Haptoglobin <8 mg/dl, Bilirubin (total/direct) 4.3/0.0 mg/dl, Lactate Dehydrogenase 957 IU/l. No spherocytes on peripheral blood smear. Day 3: Hb 11.1 g/dl and Reticulocytes 13%. Four weeks after presentation Hb 12.5 g/dl, MCV 86 FL, Reticulocytes 2.0% and total bilirubin 1.4 mg/dl. DCT (Direct Coomb’s Test) was negative. Varicella IgG was 3.5 (positive) and IgM was <0.9 (negative). Osmotic fragility testing confirmed HS. In BTV skin involvement may not progress beyond the papule stage and production of acute phase anti-varicella IgG and IgM (and so hemolysis) may be short lived and so not detected. Our patient’s skin lesions were most helpful in making the diagnosis. Hemolysis was likely mediated by anti I/anti P IgM antibodies and hence the negative DCT with polyspecific Coomb’s reagent (IgG and C3d) at room temperature in our patient. It is possible that in patients with HS hemolysis is induced by alteration of splenic function induced by the varicella infection. Patient 2: 13 year old unimmunized boy presented with resolving varicella lesions and severe ecchymosis on his torso and extremities. Complete blood count and peripheral smear was normal except platelet count was 9000/ul. Anti-Varicella IgG and IgM were positive, DCT/ANA were negative. For religious reasons our patient opted for no treatment. At Day 7 platelets were 24000/ul and his ecchymosis had significantly improved.

**Conclusion:** Though now very rare the hematological complications of varicella infection continue into the post varicella vaccination era. Through this report we hope to encourage early recognition of these problems.
ECULIZUMAB TREATMENT OF THROMBOTIC MICROANGIOPATHY (TMA) IN SICKLE CELL DISEASE
Satheesh Chonat, Shanmuganathan Chandrakasan, KarenAnn Kalinyak, David Ingala, Ralph Gruppo, Theodosia Kalfa. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

Background: TMA is an uncommon complication of SCD characterized by microvascular thrombosis associated with ischemic organ failure (Shome et al, Ann Hematol 2013). The diagnosis of TMA is supported by a combination of clinical and laboratory features, including microangiopathic hemolytic anemia, thrombocytopenia and organ involvement including pulmonary infiltrates, neurologic involvement and renal failure. Management has included plasma exchange.

Objectives: To describe the occurrence of TMA in a patient with SCD with evidence of complement activation. Eculizumab therapy was associated with rapid clinical improvement.

Design/Method: Chart review and analysis of plasma levels of membrane-attack-complex (SC5b-9).

Results: A nineteen year-old African-American female with SCD (SS genotype) presented with vasoocclusive crisis. After initial improvement, she developed acute exacerbation of generalized pain associated with the development of acute chest (ACS) requiring erythrocytapheresis. Respiratory symptoms improved but thrombocytopenia (31x10^3/μL) and renal failure developed rapidly over 12-hours. Schistocytes were present on blood smear. Laboratory findings included an elevated BUN and creatinine, 90 and 6.2mg/dL, respectively. DAT was negative. LDH was >4,000 IU/L. ADAMTS13 activity was normal (80%). CNS involvement was associated with seizure with a normal brain MRI. Initiation of plasmapheresis was followed by clinical improvement, but persistent renal failure. Eculizumab, a monoclonal antibody to C5, was initiated at 900 mg per week for 4 weeks, intravenously (she was already immunized against meningococcus due to her SCD status). Normalization of LDH, BUN and creatinine occurred over the following 7 days. Prior to plasma therapy, complement factor H level was decreased at 18.4mg/dL (normal 37-68 mg/dL) with no CFH antibodies. CFI and CFB levels were normal. Genetic sequencing of CFH was normal. Sequencing for MCF, CFI, CFB, C3 and THBD genes is in progress. Plasma levels of SC5b-9 demonstrated an elevated peak level prior to Eculizumab with return to normal levels with initiation of plasmapheresis and Eculizumab. The patient is currently alive with no evidence of relapse after 7-months.

Conclusion: TMA associated with SCD is a potential life threatening complication, leading to multi-organ failure. Treatment with Eculizumab may be associated with clinical improvement and reversal of organ damage. This is the first report of the use of Eculizumab for TMA in SCD.
A DIAGNOSTIC DILEMMA: SIMILARITY OF NEURORADIOLOGICAL FINDINGS IN CENTRAL NERVOUS SYSTEM HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND ASPERGILLOSIS

Jessica Foley, Heather Borders, Beth Kurt, Helen DeVos Children's Hospital, Grand Rapids, Michigan, United States of America

Background: Central nervous system (CNS) involvement in hemophagocytic lymphohistiocytosis (HLH) is not uncommon. Because HLH therapy is immunosuppressive, infectious complications also occur. Magnetic resonance imaging (MRI) findings are well described for CNS HLH and fungal infections, but have not been comprehensively compared.

Objectives: We describe a boy with acute neurological decline and abnormal brain MRI findings during therapy for HLH. To differentiate CNS aspergillosis from HLH, we reviewed available medical literature to ascertain unique neuroradiological features for both diseases.

Design/Method: A 9 year-old male with HLH and no neurological involvement at presentation was treated according to the HLH-94 protocol. Weeks into therapy, the patient seized and became encephalopathic. Brain MRI demonstrated multiple variably-sized lesions in the cerebral hemispheres, many in perforating artery territories. Areas with ring and nodular enhancement were present, but most lesions had minimal or no enhancement. Patchy (and ring shaped) areas of restricted diffusion were apparent. With an inability to distinguish CNS HLH versus aspergillosis, brain biopsies were performed, confirming Aspergillus.

Results: In the medical literature, the following MRI brain findings have been reported for HLH or aspergillosis: ischemia and hemorrhage in the distribution of small perforating/end arteries; restricted diffusion relating to ischemia; ring or nodular enhancing lesions; and laminated (target) lesions, characterized by high central T2 signal surrounded by a low T2 rim and peripheral T2 hypersignal edema. Findings more frequently reported in Aspergillus include: prominent multifocal regions of low T2/gradient echo (GRE) signal intensity; multifocal ischemia; corpus callosum involvement; and target lesions characterized by a peripheral rim of low T2/GRE signal with restricted diffusion in the low signal rim. Features more often reported in HLH include leptomeningeal enhancement and confluent white matter hyperintensity with mild or absent enhancement. Diffuse white matter atrophy is unique to CNS HLH.

Conclusion: Both Aspergillus and HLH have a predilection for brain vasculature, which results in overlapping imaging features. Certainly, early cerebral infarction in immunocompromised patients may be an indication for aggressive antifungal therapy. Given imaging overlap, a diagnosis may remain elusive and brain biopsy may be warranted, as treatment of fungal disease and CNS HLH are diametrically opposed.
EFFECTIVE USE OF PHILANTHROPIC FUNDS FOR CLINICAL RESEARCH: A SINGLE INSTITUTION EXPERIENCE USING A BUSINESS INCUBATOR MODEL
Winston Huh, Karen Broussard, Eugenie Kleinerman. University of Texas MD Anderson Cancer Center, Houston, TX, United States of America

**Background:** With funding for clinical research becoming more competitive, there is an increasing reliance on philanthropic sources of funding. Yet there is not an established model in pediatric academic centers on how best to utilize philanthropic funds that maximizes the balance between producing results and fiscal responsibility. Business incubators are institutions that provide seed funding and specialized resources to entrepreneurs in order to develop a product within a short time period that leads to larger funding from venture capitalists. Our group attempted to determine if this model could be used to support clinical projects.

**Objectives:** To report our institutional experience of using a “business incubator model” to identify 3 clinical projects and provide “seed funding” from philanthropic funds, and then use a “Board of Directors” to assess future funding needs based on the progress of the clinical projects.

**Design/Method:** Single institution experience

**Results:** In September 2012 The University of Texas MD Anderson Children’s Cancer Hospital held a retreat for investigators to present their novel, investigator-initiated clinical trial concepts – similar to business entrepreneurs giving presentations to venture capitalists. Criteria for the trial selection were: 1) The proposed trial is unique to the institution; 2) there is a clinical need and adequate patient population at the institution; 3) the trial can be completed in 5 years; and 4) there was no other source of funding. Three clinical projects were voted by peer faculty to be given “seed funding” from pooled philanthropic sources. A “Board of Directors” consisting of faculty and staff was created and has reviewed the progress of each study quarterly to ensure that the projects were attaining timeline goals, patient accrual goals, provide troubleshooting support for project delays, and reviewing expenditures. To date, two of the supported projects have been activated and are attaining patient accrual goals within the first 12 months. Also, due to the fiscal oversight, enough funding is available to support a fourth clinical project.

**Conclusion:** A business incubator and other similar corporate-based models can be employed to support clinical research projects and also ensure fiduciary responsibility of philanthropic funds.
EXTRAOSSEOUS CHORDOMA OF THE PHARYNX IN A PEDIATRIC PATIENT: CASE REPORT AND REVIEW OF LITERATURE
Fiorella Iglesias, Carole Brathwaite, Martha Ballesteros, Ziad Khatib. Miami Children's Hospital, Miami, Florida, United States of America

**Background:** Chordomas are neoplasms of bone that arise from the notochord. They typically occur in the axial skeleton and have a proclivity for the sphen-ooccipital region and sacral regions. Craniocervical chordomas involve the dorsum sella, clivus and nasopharynx. To our knowledge there have been few cases of extraosseous chordomas located in the pharyngeal space in the pediatric population.

**Objectives:** To describe a pediatric patient with extraosseous chordoma of the pharynx found incidentally during an adenoidectomy.

**Design/Method:** Case report and review of literature. The medical record, radiological studies and pathology were reviewed.

**Results:** An 11 year old boy with history of headaches, mouth breathing, and chronic rhinorrhea was evaluated for adenoid hypertrophy, physical exam was normal. During adenoidectomy, a midline mass was identified in the posterior pharynx. Excisional biopsy and aspiration of the cyst fluid was performed, histologic evaluation revealed “physaliferous cells”, consistent with chondroid chordoma. On spiral CT no clivus involvement was seen. A second surgical intervention was performed and the entire tumor was removed. Follow up MRI after 6 months showed no evidence of tumor, however the adenoid hypertrophy persisted. Patient remains asymptomatic more than 2 years after surgery. In our literature review 12 pediatric patients were identified, osseous involvement was found in 5 out of 12 cases (including scalloping of the clivus). The clinical presentation of the patients correlated with presence or absence of osseous involvement. The symptoms of nasopharyngeal chordoma with osseous involvement included diplopia, hoarseness, and headache according to our review. The patients underwent a gross total resection and 3 of them were treated with radiotherapy. The outcome was good in cases with complete resection. The best results for treatment of chordomas have being studied only for osseous chordomas and are obtained through radical surgical resection followed by radiotherapy (with high doses of photons or protons). Further studies need to be done on extraosseous chordomas, but likely complete removal of the soft-tissue tumor and the clival sinus tract is the treatment of choice in such cases.

**Conclusion:** Extraosseous chordoma should be considered in the differential diagnosis of oropharyngeal masses. The prognosis appears to be favorable in patients with complete resection.
NOT JUST YOUR AVERAGE PINWORMS:
A CASE OF A 10-YEAR-OLD GIRL WITH AXENFELD-RIEGER SYNDROME WITH A PROFOUND ISOLATED MICROCYTIC ANEMIA AND ENTEROBIUS VERMICULARIS
Torrey Parker, Karen Mandel, Donna Johnston. Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

**Background:** Anemia occurs in approximately 20 percent of children in the United States (US) at some point during childhood. The common causes of microcytic anemia in children are well described and include: iron deficiency, hemoglobinopathies, lead toxicity, sideroblastic anemia, or anemia of chronic disease. Enterobius vermicularis is a nematode or roundworm parasitic infection otherwise known as pinworms. It occurs worldwide and is the most prevalent nematode infection in the US with ~200 million cases per year, with more than 30 percent affecting children. Indeed, the highest prevalence occurs in children of preschool and school age. Interestingly, hookworm infections have been associated with microcytic anemia secondary to blood loss.

**Objectives:** To describe a case of significant microcytic anemia likely secondary to a common parasitic infection, Enterobius vermicularis.

**Design/Method:** We discuss a case of a 10-year-old girl with Axenfeld-Rieger syndrome who presented to the Emergency Department at the Children’s Hospital of Eastern Ontario with a 4-month history of shortness of breath on exertion, pallor, and decreased energy. She was subsequently found to have a profound isolated microcytic anemia with hemoglobin of 29 G/L MCV of 73.4fl with no evidence of hemolysis. She was admitted to hospital for work-up of her anemia. Further investigations revealed iron deficiency anemia and a positive fecal occult blood. On day four of her hospital admission she was found to have Enterobius vermicularis.

**Results:** To our knowledge, we report the first case of Enterobius vermicularis associated with a severe isolated iron deficiency anemia. Parasitic infections, specifically, hookworm infections have been found to be associated with microcytic anemia secondary to blood loss. Presumably the same pathophyslogic mechanisms would explain the blood loss in our patient.

**Conclusion:** This case of isolated profound microcytic anemia associated with Enterobius vermicularis is a unique clinical presentation that, to our knowledge, has not been previously reported. It is an excellent exercise in working through the differential diagnosis of microcytic anemia in a child and highlights the importance of thorough investigations to explain a clinical presentation. 1. Janus, Am Fam Phys, 2010. 2. Kucik, Am Fam Phys, 2004
A NEW VARIANT IN THE hMUNC 13-4 GENE ASSOCIATED WITH FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A FAMILY FROM YEMEN
Shipra Kaicker, Apurvi Patel, David Steffin, Kejian Zhang. Maimonides Medical Center, Brooklyn, New York, United States of America

Background: Mutations in the MUNC 13-4 gene have been previously described in familial hemophagocytic lymphohistiocytosis type 3 (FHL3). This gene is critical in the regulated secretion of cytotoxic granules by lysosomes during target cell apoptosis. Decreased expression of CD107a (LAMP-1) on the surface of activated effector cells has been shown to be a good functional correlate of abnormal MUNC 13-4 activity.

Objectives: Expanding the database of already existing mutations linked with familial HLH will allow for earlier disease recognition and timely treatment. By reporting a novel mutation in the MUNC 13-4 gene we hope to add to this existing database.

Design/Method: A retrospective chart review of inpatient and outpatient medical records for two affected siblings seen at an urban community based children’s hospital in Brooklyn, New York. Institutional IRB approval, as well as family consent was obtained. Genetic analysis for the two affected and one unaffected brother was performed at Cincinnati Children’s Hospital.

Results: The two affected siblings presented with signs and symptoms of HLH in the second decade of life. Their presentation was within a year and a half of each other. Clinical and lab criteria for HLH were met in both affected siblings. Further work up showed a decreased expression of CD107a in the two affected siblings but not in the unaffected brother. Genetic testing revealed a new variant c.194A>G in the MUNC 13-4 gene leading to the substitution of arginine for histidine at amino acid 65. This variant was present in a homozygous state in the affected siblings and in a heterozygous state in the unaffected brother. Homozygosity of other SNPs in this gene suggested parental consanguinity and this was confirmed by history. The parents belonged to a small tribe in Yemen and were distantly related but could not receive genetic testing due to insurance reasons.

Conclusion: We conclude that this newly described MUNC 13-4 variant may be pathogenic and in its homozygous state may lead to a decreased expression of CD107a and the development of late onset familial HLH.
HODGKIN DISEASE (HD) AS TORTICOLLIS - 3 CASE REPORTS OF ASYMPTOMATIC SKELETAL HD
Megan Khariton, Dominder Kaur, Jeremy Neuman, Sarah Vaiselbuh. Staten Island University Hospital, Staten Island, New York, United States of America

Background: Skeletal involvement as the initial presentation of HD is rare. Most reported cases are patients presenting with bone pain, prompting further investigations. We report three cases of asymptomatic, painless osseous lesions, where biopsy revealed the unexpected pathology of nodular sclerosis (NS)-HD.

Objectives: To report rare atypical clinical presentations of Hodgkin disease with torticollis (n=1) and painless skeletal disease (n=2).

Design/Method: Case reports and PubMed search.

Results: Three HD patients presented with a common factor of painless skeletal manifestations in the absence of B-symptoms. The presentation of each patient with an unexpected diagnosis of HD was unique. A 17-year old boy had a chief complaint of a painless unexplained torticollis. Imaging revealed near-total destruction of cervical vertebrae (C4-C7) consistent with osteomyelitis and epidural soft tissue collections. Pathology confirmed NS-HD. The second patient, a 19-year old male, presented with an enlarged supraclavicular lymph node with biopsy proven NS-HD. Further staging with bone scan demonstrated a diffuse pattern of skeletal lesions in the absence of adjacent lymph node involvement in an otherwise pain-free patient. The third patient was in first remission of NS-HD when imaging studies at three months off therapy demonstrated extensive skeletal relapse of HD in a clinically asymptomatic patient. All three patients showed chemosensitive response (ABVD or BEACOPP).

Conclusion: Skeletal HD needs to be kept in the differential diagnosis of painless lytic bone lesions, even in totally asymptomatic patients without B-symptoms. Modified BEACOPP therapy for skeletal HD might be a valid treatment alternative.

<table>
<thead>
<tr>
<th>Presentation time</th>
<th>At Initial Diagnosis- 19 year old male</th>
<th>At Initial Diagnosis- 19 year old male</th>
<th>Relapsed HD- 17 year old male</th>
</tr>
</thead>
</table>
| Presenting features | Torticollis  
No pain | 6 month H/O dry cough, wheezing and shortness of breath  
No pain | Asymptomatic  
No pain |
| Sites of skeletal Manifestation | Osteomyelitis C4-C7 | Left Distal Humerus, Right 4th posterior rib | C4,C5, T8 & L2 vertebrae, Right iliac bone, acetabulum and B/L iliac crests |
| Staging/ Imaging | Neck X-Ray, CT chest then MRI neck | CT chest, abdomen Bone scan | PET CT for surveillance |
| Pathology | Nodular sclerosing | Nodular sclerosing | Nodular sclerosing |
| Site of Biopsy | Cervical Spine | Cervical LNs | Liver lesion |
| Lymphoid System /Nodal Involvement (at staging after biopsy proven HD) | Rt. supraclavicular, Mediastinal, Hilar and Bronchopulmonary LN | Mediastinal mass, Rt. supraclavicular LN | Foci in liver as well as portacaval, peri-pancreatic and peri-aortic LNs |
| Treatment | ABVD | BEACOPP | Modified BEACOPP with Stem cell harvest |
RECURRENT/REFRACTORY METASTATIC OSTEOSARCOMA RESPONDS TO TRAIL THERAPY

Monica Khurana, Bindu Kanathezhath, James Feusner. Children’s Hospital and Research Center Oakland, Oakland, California, United States of America

**Background:** Patient survival with recurrent/refractory metastatic osteosarcoma (OS) remains dismal with 3yr survival rates <20%. We need better understanding of chemoresistance mechanisms and immunomodulators like lexatumumab. Lexatumumab mimics tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and stimulates apoptosis when bound to its receptors TR1/TR2. This recombinant human antibody appears to bind specifically to TR2, which is overexpressed in other solid cancers.1 Clinical trials attempt to delineate its effect in pediatric patients with chemoresistant OS.

**Objectives:** To report the first patient to achieve stable metastatic OS disease with lexatumumab. To encourage exploration of synergy between lexatumumab and other treatment modalities.

**Design/Method:** Case report.

**Results:** Evaluation of a 16yo female with right leg pain revealed high-grade OS in the distal femur with three pulmonary nodules <3mm deemed surgically resectable. After two cycles of MAP per AOST0331, local control with limb salvage showed poor response (65% necrosis) and resulted in therapy with IE. Concurrent staging revealed disease progression with eight new pulmonary nodules, the largest 5mm in diameter. These lesions were excised, rending her in remission. Relapse occurred <1yr with three pulmonary nodules. Proximity of the nodules to the aorta precluded resection. Surveillance in 2-3 months revealed growth of the previous nodules, now >5cm in diameter, and a new nodule (0.7cm). Imaging after palliative chemotherapy with gemcitabine and taxotere showed persistent nodular growth with left main pulmonary artery obstruction and left 6th-7th rib destruction; pain and respiratory symptoms prompted palliative radiation (3000cGy) to ribs. She enrolled on Pediatric Oncology Branch protocol 07-C-0040 with phase I lexatumumab infusions q2weeks and completed 44 infusions. Disease stabilization per chest CT and PET scan normalization occurred one and two years later, respectively. She has not only survived for >3yrs with stable disease, but also conceived and delivered a healthy baby.

**Conclusion:** Achievement of >3yr of stable recurrent metastatic OS disease is unique and attributable to lexatumumab in this patient. Immunotherapy has the potential to improve survival rates in pediatric patients with OS and possibly other solid tumors. Completion of palliative radiation five weeks prior to lexatumumab initiation suggests chemosensitization and encourages exploration of synergy between lexatumumab and other treatment modalities.1Merchant M, JCO, 2012
NON-TOXIGENIC CORYNEBACTERIUM DIPHTHERIAE AS AN EMERGING PATHOGEN: CASE REPORT OF NECROTIZING EPIGLOTTITIS AND TONSILLITIS IN A CHILD WITH UNDIAGNOSED ACUTE LYMPHOBLASTIC LEUKEMIA

Jessica Lake, Matthew Ehrhardt, Mariko Suchi, Robert Chun, Rodney Willoughby. Children's Hospital of Wisconsin, Milwaukee, Wisconsin, United States of America

**Background:** Diphtheria is rare in highly vaccinated populations and may not be recognized by modern clinicians. Infection by non-toxigenic Corynebacterium diphtheriae is not prevented by current vaccines and may be emerging as a pathogen.

**Objectives:** We present a girl with necrotizing epiglottitis secondary to non-toxigenic C. diphtheriae and undiagnosed acute lymphoblastic leukemia (ALL).

**Design/Method:** Case report and literature review.

**Results:** A 3 year-old previously healthy female developed fever, poor oral intake, fatigue and sore throat. There were no recent travel exposures. Examination was notable for cervical adenopathy. Streptococcal antigen and Monospot tested negative. The following day she developed tender submandibular swelling, drooling, halitosis, and a high-pitched voice. Laboratory evaluation revealed WBC 280, hemoglobin 8.0 and platelets 125,000. Cervical x-rays identified prevertebral soft tissue prominence. Repeat examination was significant for an afebrile, ill-appearing child with prominent, erythematous neck swelling, conjunctival erythema, cracked, red lips, bilateral tonsillar exudates, and plantar desquamation. Cervical nodes were tender and not fluctuant. There was no stridor, respiratory distress, cardiac murmur, or organomegaly. Vancomycin and cefotaxime were started. On hospital day 2, the patient developed progressive hypoxemia, drooling, and stertor. She was electively intubated in the operating room. White membranes compatible with necrosis were debrided from the left tonsil and the laryngeal surface of the epiglottis. Histology revealed extensive coagulative necrosis and invading bacteria without evidence of a pseudomembrane. A bone marrow biopsy diagnosed ALL. The patient began 3-drug induction chemotherapy. Nasopharyngeal cultures grew C. diphtheriae. She continued to require cardiopulmonary support and an echocardiogram demonstrated reduced cardiac function. She was treated with penicillin and diphtheria antitoxin, prior to confirmation of non-toxigenic C. diphtheriae. The patient was extubated after 2 weeks and discharged home after a 1 month hospitalization. She continues to do well 4 months from diagnosis.

**Conclusion:** Necrotizing epiglottitis predominantly occurs in the immunocompromised host such as this fully immunized patient with new onset ALL. Diphtheria vaccines do not protect against colonization by non-toxigenic C. diphtheriae, an emerging pathogen in countries independent of national vaccine uptake.
TREATMENT OF AN ATYPICAL CASE OF HYALINE VASCULAR VARIANT MULTICENTRIC CASTLEMAN'S DISEASE
Cathy Lee-Miller, Christiana Smith, Carreye Cost, Michael Wang. Children's Hospital of Colorado, Aurora, Colorado, United States of America

Background: Castleman's disease is a rare disorder of lymph node hyperplasia. The unicentric form is typically benign and often has histopathology consistent with the hyaline vascular variant. The multicentric form is characterized by more aggressive symptoms and can progress to multi-system organ failure, lymphoma and death; these patients usually present with plasma cell variant. There are no reported cases of hyaline vascular variant multicentric Castleman’s disease in children in the English language literature.

Objectives: To describe the diagnosis and treatment of a rare case of hyaline vascular variant multicentric Castleman's disease.

Design/Method: A previously healthy 21 month old boy of Ashkenazi Jewish descent presented with fever, irritability, bruising and lymphadenopathy. Initial CBC revealed WBC 9500 (36.6% neutrophils, 47.9% lymphocytes), hemoglobin 9.7 g/dL, platelets 25,000. His ESR was 128mm/Hr and CRP 17.2mg/dL (normal < 1.0). He quickly developed worsening anemia, thrombocytopenia, lymphadenopathy and anasarca. Bone marrow biopsy showed hypocellularity without malignancy or hemophagocytosis. An extensive infectious disease panel was negative, including testing for HIV, EBV, CMV and HHV-8. Interleukin 6 (IL-6) in serum was significantly elevated at 246 pg/mL (normal 0-5). Lymph node biopsy was performed and histopathology was consistent with the hyaline vascular variant of Castleman’s disease.

Results: Treatment was initiated with intravenous methylprednisolone (1mg/kg every 6 hours) with limited improvement. Therefore, therapy with tocilizumab was started, leading to eventual extubation, gradual regression of anasarca and hospital discharge. Tocilizumab is a humanized monoclonal antibody directed against the IL-6 receptor. Anaphylaxis occurred during the patient’s fourth dose of tocilizumab, followed by relapse of symptoms and multi-system organ failure. Repeat lymph node biopsy revealed hyaline vascular Castleman’s disease, identical to the first biopsy. He was induced on cytotoxic chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), which produced rapid clinical improvement, and near return to his baseline of health after the first cycle.

Conclusion: He remains in complete remission following six cycles of R-CHOP chemotherapy with resolution of diffuse lymphadenopathy as seen on CT and normalization of inflammatory markers, including ESR, CRP and IL-6. Multicentric Castleman’s disease is rarely seen in young children and cytotoxic chemotherapy regimens can offer curative therapy, particularly in cases of refractory disease.
A NOVEL CANDIDATE GENE IN SPORADIC MULTICENTRIC VISCERAL INFANTILE MYOFIBROMATOSIS: A CASE REPORT
John Legall, Vivian Chang, Noah Federman. Department of Pediatrics, Hematology/Oncology, UCLA, Los Angeles, California, United States of America

**Background:** Infantile myofibromatosis (IMF) although rare is the most common infant fibrous tumor. This mesenchymal tumor can affect skin, bone, muscle, and viscera. The worse prognosis is seen in multicentric visceral IMF. While ultimately lesions are likely to regress, early stage visceral myofibromas grow steadily with high mortality, 60-80% at 4 months. Low dose vinblastine (VBL) and methotrexate (MTX) chemotherapy, a standard regimen in unresectable desmoid tumors, has had success treating multicentric IMF. Recently, two genes have been identified as causative agents in familial autosomal dominant IMF: PDGFRB and NOTCH-3. However, there are no known candidate genes for sporadic IMF.

**Objectives:** We report a case of a newborn girl with aggressive multicentric visceral IMF, successful treatment with low dose VBL and MTX, and the results of whole exome sequencing revealing a novel candidate gene for the development of sporadic IMF.

**Design/Method:** Exome sequencing was performed on the patient and her parents using the Agilent SureSelect Human All Exon 50 Mb XT kit and an Illumina HiSeq 2500.

**Results:** The patient presented shortly after birth with small bowel obstruction. An ileal resection and biopsy of an incidental liver nodule were performed. Pathology showed a low grade spindle cell neoplasm in the specimens consistent with IMF. Imaging showed multivisceral disease with involvement of the liver, soft tissue infratemporal fossa, and bone (rib). She was treated with weekly 2 mg/kg MTX and 0.15 mg/kg VBL for six weeks and then 1 mg/kg MTX and 0.15 mg/kg VBL every other week for 22 weeks. Imaging has shown partial response with residual stable disease in the liver. She is now 3 years old and developing normally. Germline exome sequencing was performed, and showed no mutation in PDGFRB and NOTCH3, however a deleterious heterozygous de novo mutation in PTPMT1 c.271G>A was isolated.

**Conclusion:** Low dose VBL/MTX can be safe and effective in cases of multivisceral IMF. Furthermore, we identified a germline heterozygous mutation in PTPMT1 c.271G>A, which is a new candidate gene for IMF. Recent studies in murine models show that PTPMT1 has a role in mesenchymal differentiation. We are currently exploring the role of PTPMT1 in the development of neoplasia.
Vinblastine and Methotrexate in an Infant with Congenital Lipofibromatosis of the Gluteal Muscles

Zachary Lonjers, Aruna Vade, Dariusz Borys, Ricarchito Manera. Stritch School of Medicine - Loyola University Chicago, Maywood, Illinois, United States of America

**Background:** Lipofibromatosis is a rare fibrofatty tumor of infancy and childhood. The tumor has a predilection for the hands and feet, but is also rarely found in the thigh, trunk, head, and neck. The tumor exhibits slow growth and displays no metastatic potential. While complete surgical resection is the treatment of choice, the tumor demonstrates high rates of local recurrence. The use of chemotherapy has never been described before in the literature.

**Objectives:** The authors report an unusual case of unresectable, left gluteal lipofibromatosis diagnosed at birth in a male infant. The use of low-dose vinblastine and methotrexate for tumor stabilization is described.

**Design/Method:** A male infant was diagnosed with lipofibromatosis following the discovery of a 6x4 cm subcutaneous mass of the left buttock at birth. The tumor involved major portions of the left gluteus maximus and medius muscles and encroached upon the sacroiliac neurovascular bundle. Due to the tumor’s intimate involvement with the gluteal muscles, surgical resection would have rendered severe functional impairment to the infant. Vinblastine (5 mg/m²) and methotrexate (1 mg/m²) were prescribed with the dose adjusted for body surface area less than 0.6 m². The drugs were given weekly and later biweekly as per protocol. A total of 44 cycles were administered over a period of 14 months (age 1-15 months). The treatment was well tolerated except for episodes of neutropenia requiring dose adjustments and the administration of granulocyte colony-stimulating factor. Quarterly MR imaging studies were used to monitor tumor progress.

**Results:** The size of the tumor remained unchanged from the initiation of chemotherapy to the end of treatment. During this period, the patient underwent normal growth, with appropriate development of the tissues surrounding the lesion.

**Conclusion:** While complete surgical resection is the treatment of choice for lipofibromatosis, it is not feasible in all cases. Vinblastine and methotrexate were used to stabilize a gluteal lipofibromatosis while the infant developed normally, providing for the possibility of future resection with less functional impairment.
FACTOR X DEFICIENCY PRESENTING AS NEONATAL INTRACRANIAL HEMORRHAGE: SHORTER FACTOR HALF LIFE LEADING TO A CHALLENGING TREATMENT COURSE

Pillai Pallavi Madhusoodhan, Elizabeth Roman, Michael Nardi, Teena Bhatla. NYU Langone Medical Center, New York, New York, United States of America

**Background:** Factor X deficiency is a rare autosomal recessive bleeding disorder, with an incidence of 1:1000,000. Physiological half-life of Factor X in adults is about 48 hours, while infused products have a shorter half-life. Management can be very challenging in neonatal age group, given scarcity of data with respect to coagulation factors metabolism. We present the case of a newborn with non-traumatic intracranial hemorrhage, diagnosed with Factor X deficiency and the challenges faced during management.

**Objectives:**

**Design/Method:** Case: A full term female infant, born to parents of south-east Asian origin and consanguineous marriage, by normal spontaneous vaginal delivery, was admitted to the Neonatal ICU for suspected sepsis. On day 2 of life, she developed melena, anemia (Hb 5 gm/dL) and thrombocytopenia (platelets 80,000/µL). Coagulation screen revealed INR 9.4, PTT 200s, PT 100s. Head Ultrasound showed a significant left parieto-occipital hemorrhage. All coagulation factor levels were within normal range for newborns, except for Factor X antigen being undetectable, suggestive of severe factor X deficiency. Father’s and mother’s factor X levels were 67% and 86% respectively. After initial empirical treatment with twice daily fresh frozen plasma, she was started on Prothrombin Complex Concentrate, BebulinTM (140 U of Factor X for every 100 U of Factor IX). Despite a relatively higher dose of 40 U/Kg daily, 12 hour trough levels remained low at 12-16%, suggestive of half-life less than 12 hours. Mixing studies revealed no inhibitors. Treatment was continued for 14 days, under close monitoring. No further bleeding symptoms were noticed and she improved clinically. Upon discharge, she is being successfully prophylaxed with Bebulin 75 U/kg, twice a week, with trough levels between 3-5%. Molecular analysis is currently underway to correlate genotype with phenotypic presentation.

**Results:** n/a

**Conclusion:** Discussion and Conclusion Rare coagulation disorders can present significant treatment challenges especially when they present in the neonatal period with severe manifestations. As demonstrated in our patient, coagulation factor metabolism in neonates is different from those in older children and adults, necessitating higher and/or more frequent dosing. Larger multicenter studies are necessary for the development of evidence based guidelines for management of such rare but potentially life threatening disorders.
BACKGROUND: Invasive fungal infections are concerning cause of morbidity and mortality in children receiving treatment for malignancies. Candida and Aspergillus species are the most frequent pathogens. Common sites include skin, sinuses, lungs or central nervous system (CNS). We report a rare case of a 14 year old with T-cell ALL who developed cryptococcal osteomyelitis of the talus.

OBJECTIVES: n/a

DESIGN/METHOD: A 14 year old male, with T-cell ALL, who was in remission and receiving the last scheduled week of standard maintenance chemotherapy presented with a 2 day history of left ankle swelling and pain. He was neutropenic and profoundly lymphopenic (absolute lymphocyte count 200-500/µL), with elevated inflammatory markers. An MRI of left foot confirmed osteomyelitis in the talus with an intraosseous abscess. He underwent surgical debridement and initiated empiric treatment with vancomycin. Three bone aspirate cultures were negative for infection. While receiving a protracted course of antibiotic therapy, he developed worsening ankle pain and subsequent imaging studies demonstrated reaccumulation of an abscess in the talus. He underwent 2 subsequent debridement procedures, with 9 cultures and 1 of these cultures grew Cryptococcus neoformans, after 8 days. A confirmatory serum cryptococcal antigen titer was elevated at 1:64. There was no evidence of disseminated blood, CSF, lung or ocular disease. He was treated with an initial course of liposomal amphotericin B and flucytosine, followed by a protracted course of high dose fluconazole for 6 weeks and his infection gradually resolved.

RESULTS: Cryptococcal infections in children have a reported incidence of 6.2 per million with approximately 22% occurring in children with malignancies. Cryptococcal osteomyelitis is typically seen within the context of a disseminated infection and isolated cryptococcal osteomyelitis is very rare, with only 14 reported pediatric cases. Risk factors in this patient included lymphopenia from his protracted chemotherapy regimen and steroid-induced diabetes.

CONCLUSION: To the best of our knowledge, this is the first reported case of isolated cryptococcal osteomyelitis in a pediatric patient with T-cell ALL. This case underscores the importance of maintaining a broad differential for infection in children with malignancies and considering invasive fungal infections as possible etiologies during all phases of therapy.
SUCCESSFUL TREATMENT OF A YOUNG INFANT WITH REFRACTORY AUTOIMMUNE HEMOLYTIC ANEMIA WITH RITUXIMAB
Fae Majlessipour, Shivani Upadhyay, Alan Chin. Cedars-Sinai Medical Center, Los Angeles, California, United States of America

Background: Autoimmune Hemolytic Anemia (AIHA) is a rare disease in infancy. Steroid therapy is the mainstay of treatment. However, some patients are resistant to steroids or need long-term treatment. The use of steroids in infants carries long term side effects including growth impairment. Rituximab is a chimeric humanized anti-CD20 monoclonal antibody used in conditions such as autoimmune disorders and B-cell malignancies. Its use in infants has thus far been limited due to concerns of immunosuppression.

Objectives: To discuss the management of a unique case of Autoimmune Hemolytic Anemia, refractory to standard treatment in a young infant.

Design/Method: We describe the case and the treatment of an infant with Autoimmune Hemolytic Anemia (AIHA) who was refractory to steroid and IVIG therapy but exhibited a sustained response to Rituximab.

Results: A 5-month old, previously healthy infant presented with decreasing PO intake, lethargy, tachypnea, and pallor. There was no family history of anemia. The infant’s exam was significant for tachycardia, pallor, and a systolic murmur without hepatosplenomegaly or lymphadenopathy. Her hemoglobin was 3.6 g/dL, with relative reticulocytopenia (2.5%). Direct coombs was positive for IgG and complement, consistent with warm antibody she received packed red blood cells (pRBCs), prednisolone and IVIG. She was readmitted 2 weeks later with hemoglobin of 4.9 g/dL and reticulocyte count of 0.9%. She again received pRBCs, higher doses of prednisolone and higher doses of IVIG without response. Two months after her diagnosis she remained transfusion-dependent. She was then started on Rituximab weekly for 4 doses with excellent response with increase in hemoglobin and reticulocyte count. Due to expected B cell depletion she received IVIG every 4 weeks at a dose of 400 mg/kg/dose and PCP prophylaxis for six more months. Her immunization was resumed six months after the last dose of Rituximab. At 12-month visit her hemoglobin was 13 g/DL.

Conclusion: There has been only a handful of case reports published on the use of Rituximab for AIHA during infancy. Interestingly, our patient presented with AIHA associated with reticulocytopenia presumably due to autoantibodies against early erythroid precursors and hence the raise in reticulocyte count is thought to be indicative of a decrease in autoantibody production.
Poster # 2017

SUSTAINED THIRD COMPLETE REMISSION IN A CHILD WITH A SECOND RELAPSE OF AN EXTREMITY ALVEOLAR Rhabdomyosarcoma UTILIZING Vinorelbine AND CONTINUOUS ORAL Cyclophosphamide

Ricarchito Manera, Marie-Ellen Sarvisa, Loyola University Medical Center, Maywood, Illinois, United States of America

Background: Outcome of patients after recurrence of rhabdomyosarcoma is poor with a 5-year survival from first recurrence of 17%. This is even worse for those who suffer from a second relapse or those with tumors arising from an extremity or with alveolar histology.

Objectives: The authors report a case of a child with alveolar rhabdomyosarcoma of the left leg complicated by two successive recurrences in the regional lymph nodes treated with vinorelbine and low dose continuous daily cyclophosphamide resulting in a prolonged third remission.

Design/Method: A male child with left gastrocnemius rhabdomyosarcoma suffered two lymph node recurrences at 3 years and 5 years respectively after finishing treatment. He was heavily pretreated including amputation, radiation therapy and multiple combination chemotherapy. The second recurrence was treated with radiation therapy and chemotherapy with vinorelbine 20 mg/m2 on days 1,8 and 15 of a 28-day cycle and daily oral cyclophosphamide at 25 mg/m2/day. He received this regimen for 43 months.

Results: Resolution of the lymphadenopathy was noted at 4 months from initiation of therapy. He continues to remain disease-free at 86 months from relapse and 43 months after stopping treatment.

Conclusion: Vinorelbine and continuous low dose oral cyclophosphamide resulted in prolonged third remission in this child with heavily pretreated relapsed rhabdomyosarcoma. This regimen may represent an alternate treatment for relapsed or high risk rhabdomyosarcoma.
SUSTAINED COMPLETE REMISSION WITH IMATINIB MESYLATE IN A CHILD WITH MALIGNANT PERIPHERAL NERVE SHEATH TUMOR OF THE CHEST WALL AFTER TREATMENT WITH SURGERY, RADIOTHERAPY AND CHEMOTHERAPY
Ricarchito Manera, Mona Nourani, Jimmy Nguyen. Loyola University Medical Center, Maywood, Illinois, United States of America

Background: Malignant peripheral nerve sheath tumor (MPNST) is a highly aggressive tumor with the highest recurrence rate of any sarcomas (40-50%) and is associated with poor prognosis despite aggressive treatment (5-year survival rate of about 30%). Novel approaches are needed during the initial treatment to prevent local and distant relapse.

Objectives: The authors wish to investigate the utility of imatinib mesylate in preventing recurrence of MPNST after multimodal therapy given that platelet-derived growth factor (PDGF) acts as a cell invasion-inducing factor in MPNST and that imatinib inhibits cell invasion of MPNST induced by PDGF in in vitro studies.

Design/Method: Interventional case report

Results: A 13-year old male presented with low grade fever, cough and a huge chest wall mass. Imaging revealed a large mass in the right anterior upper chest with extrathoracic extension as well as a mass in the right lower lobe. He was treated with neoadjuvant chemotherapy doxorubicin and ifosfamide followed by radiation therapy due to unresectability of the mass. There was no significant change in the size and patient underwent surgical resection of the chest wall mass. Pathology was consistent with MPNST with minimal necrosis hence proceeded to receive more chemotherapy. This was followed by a second surgery to remove the extrathoracic component of the tumor. The mass showed viable tumor and positive margins and hence patient received more radiotherapy to the tumor bed. He was also started on imatinib 400 mg daily which he takes to the present time. He has remained in complete remission with no disease recurrence for the past 5.5 years after finishing treatment.

Conclusion: There may be a utility of imatinib mesylate in the setting of minimal residual disease after multimodal therapy in MPNST to prevent recurrence of the disease.
A COMMON PRESENTATION OF AN UNCOMMON PEDIATRIC ENTITY: CASTLEMAN'S DISEASE
Lauren McLaughlin, Violet Fernandes, Leigh Marcus. Children's National Medical Center, Washington, District of Columbia, United States of America

Background: Castleman’s disease (CD) is a rare lymphoproliferative disorder with a variable presentation and clinical course. Dr. Benjamin Castleman first reported CD in the literature in 1954 as a case report of a man with a mediastinal mass and several years of fever and weakness. Almost sixty years later, the etiology of CD remains uncertain. CD may be classified as unicentric or multicentric with two main histological subtypes: hyaline vascular and plasma cell. The unicentric, hyaline-vascular variant is the most common overall but with a peak incidence in the third to fourth decade of life.

Objectives: We report two pediatric patients diagnosed with unicentric, hyaline-vascular variant CD. Due to its infrequent presentation in the pediatric population, CD is often omitted from clinician’s differential diagnosis for pediatric masses.

Design/Method: Case Series

Results: Patient 1 is a 12-year-old female who presented with a right submandibular neck mass. The patient had a previous non-diagnostic biopsy and was treated with six months of antibiotics without effect. She then underwent an excisional biopsy of a 4.5 x 3.6 x 2.1 cm mass. Pathology revealed hyaline-vascular variant CD. She remains asymptomatic without recurrence of lymphadenopathy 18 months after resection. Patient 2 is a 9-year-old male with an incidental finding of a mediastinal mass on a chest x-ray obtained to evaluate a boney rib anomaly. He had no systemic or respiratory symptoms. Physical examination and laboratory evaluation were unremarkable. Initial core biopsy was non-diagnostic. The patient underwent complete surgical resection of a 5.5 x 4.4 x 3.6 cm mass with pathology consistent with hyaline-vascular variant CD. He has been symptom free for three months since surgery and will be followed closely.

Conclusion: Castleman’s disease is a rare condition, particularly in children. However, clinicians should consider unicentric CD in patients with asymptomatic localized lymphadenopathy. As seen in our case series, an incisional biopsy may not reveal a diagnosis of CD. Thus, an excisional biopsy is often needed, which is generally not only diagnostic but also curative for unicentric CD.
Tacrolimus Immune Suppressive Therapy for Severe Aplastic Anemia, Case Series
Matthew Miller, Ibrahim Ahmed. University of New Mexico, Albuquerque, New Mexico, United States of America

Background: Severe Aplastic Anemia (SAA) is a serious condition that would otherwise be fatal if it were not for treatment options including hematopoietic stem cell transplantation (HSCT) and immunosuppressive therapy. For pediatric patients without a matched related donor for HSCT an immunosuppressive regimen including antithymocyte globulin (ATG) and cyclosporine (CSA) have traditionally been used as a mainstay of treatment. Very few studies and case reports have evaluated the role of using tacrolimus based immune suppressive therapy.

Objectives: To evaluate if the use of tacrolimus as part of the immunosuppressive regimen for the treatment of SAA leads to counts stabilization.

Design/Method: Retrospective chart review of 3 patients between the ages of 4 and 15 years of age diagnosed between February 2011 and November 2012 with SAA at the University of New Mexico and treated with an immunosuppressive regimen consisting of Tacrolimus, ATG, and methylprednisolone.

Results: Sustained absolute neutrophil count (ANC) above 500 cells/μL for Patient A and Patient B was 45 days and 38 days, respectively. Patient C had an ANC of 540 at time of start of tacrolimus. Platelet and packed red blood cell transfusion dependence resolved soon after the initiation of Tacrolimus. Review Figure 1. After these three patients received an immunosuppressive regimen including tacrolimus count stabilization was observed with no to minimal side effects.

Conclusion: Tacrolimus may be an excellent alternative in place of cyclosporine for use as part of the immunosuppressive regimen for the treatment of SAA in pediatric patients.

Figure 1. Hemoglobin and platelet recovery in correlation with initiation of Tacrolimus containing immune therapy and transfusions
NOT-SO DOUBLE-TROUBLE: GANGLIONEUROMA MASQUERADING AS METASTATIC EWING SARCOMA
Caleb Nannes, Ashley Munchel. University of Maryland Medical Center, Baltimore, Maryland, United States of America

**Background:** Detecting a new malignancy while treating an existing cancer is usually ominous news to the pediatric oncologist – unless that malignancy is actually a benign second primary lesion.

**Objectives:** We present the case of a man with Ewing sarcoma whose treatment team was pleased to learn that instead of resistant metastatic disease, he had a simple ganglioneuroma.

**Design/Method:** Case report

**Results:** A 22-year-old male presented to his pediatrician with a three-year-history of worsening right arm swelling and a 50-pound weight loss over six months. After failing to improve on IV antibiotics, MRI of the arm showed a solid cystic mass. PET/CT revealed FDG uptake in the arm mass and an additional right adrenal mass with enlarged jugulodigastric nodes, all FDG-avid. FISH demonstrated EWS/FLI-1 rearrangement, confirming Ewing sarcoma. He subsequently underwent surgical resection with negative margins, followed by chemotherapy per AEWS0031 regimen A3. Restaging showed stable disease in the adrenal gland, but no abnormal uptake in the jugulodigastric nodes or at his surgical site. He underwent right adrenalectomy. Pathology revealed ganglioneuroma without evidence of malignancy. Follow-up PET/CT demonstrated no evidence of local recurrence or new metastatic disease.

**Conclusion:** Metastatic Ewing sarcoma refractory to initial chemotherapy carries a poor prognosis. Treatment may include additional chemotherapy and radiation. Ganglioneuroma itself is a rare diagnosis, but its co-incidence with Ewing sarcoma has never been previously described. The discovery of this benign primary lesion spared this patient unnecessary toxic therapy, and its resection proved curative. Still, this case underscores the importance of considering a second primary lesion when it is detected. While this patient’s arm lesion and lymph nodes responded to chemotherapy, neither the size nor the SUV of the adrenal mass changed over three PET/CT scans. In this case, resection proved to be diagnostic and therapeutic, but failure to quickly diagnose a second primary lesion could be harmful in other cases. While metastatic disease is the more common cause of a remote lesion in patients with a known primary cancer, pediatric oncologists must also consider an incidental second primary malignancy, especially if it does not respond to appropriate therapy.
Poster # 2022

ALPHA-THALASSEMIA MAJOR: CHALLENGES SURROUNDING EARLY IDENTIFICATION, TREATMENT AND CURE
Lydia Pecker, Ross Fasano, Michael Guerrera, Brett Loechelt, Emily Meier. Children's National Medical Center, Washington, District of Columbia, United States of America

Background: Alpha-thalassemia major is a fatal disease of increasingly heterogeneous outcomes. Intrauterine transfusions (IUT) reduce adverse fetal events and pregnancy complications. For affected newborns, short-term complications include cardiac and respiratory failure, neurologic compromise and death. Long-term sequelae include developmental delay, cardiac dysfunction, and transfusional iron overload. Bone marrow transplant (BMT) is curative.

Objectives: We report 3 boys of Vietnamese descent with alpha-thalassemia major caused by Southeast Asian double (cis) α-globin gene deletion (--SEA, --SEA).

Design/Method: Case series

Results: Patient 1 was born via emergent c-section at 34 weeks to a G3P0 mother with two prior spontaneous abortions from placental abruption and congenital anomalies. He was hydropic and coagulopathic with hepatosplenomgaly, critical coarctation of the Aorta and hypospadias. Labs on DOL1 showed hemoglobin (Hgb) 9.8gm/dL, MCV 98.0 fL and Hgb electrophoresis showed the presence of Hgb Bart’s after multiple transfusions. He died of multi-organ failure on DOL9. Patient 2 was born at 34 weeks and suffered cardiac arrest with respiratory failure, severe anemia and sepsis shortly after birth. Genetic testing confirmed alpha-thalassemia major. He required chronic transfusions, hypospadias repair, had neurocognitive impairment and suffered multiple post-splenectomy thrombotic complications. After many years of declining BMT, family chose to proceed with reduced toxicity matched unrelated donor (MUD) BMT at 9 years old. His pre-transplant ferritin was 710 ng/dL, with hepatomegaly, and focal bridging fibrosis on liver biopsy (Pesaro Class II). He died of grade IV skin and gastrointestinal graft-versus-host-disease (GVHD) and fungemia at age 13 years. Patient 3, patient 2’s younger brother, was identified on pre-natal testing. Born at 37 weeks, he received IUT and was maintained on chronic transfusions shortly after birth. He required hypospadias repair and chelation therapy. Pre-transplant evaluation showed a ferritin of 512 ng/dL (no biopsy performed). He is now 4 years post-reduced toxicity MUD BMT and doing well without GVHD.

Conclusion: Without intervention, alpha-thalassemia major is almost universally fatal. Our cases highlight challenges in treating this disorder, and demonstrate the need to recognize at-risk couples so that genetic counseling and lifesaving IUT can be implemented. Early BMT referral reduces the duration of hepatotoxic iron exposure from chronic transfusions.
LYMPHOPROLIFERATIVE DISORDER IN A CHILD WITH CROHN’S DISEASE AND THIOPURINE USE.

Amanda Messer, Chittalsinh Raulji, Matthew Fletcher, Brent Keith, Maria Velez. LSUHSC/Children's Hospital of New Orleans, New Orleans, Louisiana, United States of America

Background: Thiopurines are widely used in the treatment of patients with inflammatory bowel disease (IBD). Concern for associated lymphoproliferative disorders (LPD) must be addressed when deciding appropriate treatment. Multiple large studies have showed a strong association of increased risk of LPD in IBD patients receiving thiopurines for treatment. However, this association is not frequently described in the pediatric population and pediatric data are limited.

Objectives: To describe possibly the youngest case of LPD in association with IBD and thiopurine use.

Design/Method: An 11-year-old African-American female with one-year history of Crohn’s Disease (CD) presented with fever, respiratory distress and seizure activity. Prior to admission, she had URI symptoms for one month and intermittent fevers for two weeks. Her CD treatment consisted of 6-mercaptopurine; however, it was discontinued ten days earlier due to neutropenia. On admission, CBC showed pancytopenia with WBC 1.66 x 10^3 with ANC 460, hemoglobin 7.7 g/dL, and platelets 36,000. Ferritin level was elevated at 1823ng/ml. EBV PCR was positive in plasma (24,700 copies), bone marrow (19,900 copies) and CSF (400 copies). A head CT and MRI showed multifocal, subcortical white matter lesions, although neurological exam remained normal. Bone marrow aspirate and biopsy revealed hypocellular marrow with focal hemophagocytosis. Upon further evaluation CT scans showed multiple pulmonary nodules, an 8x5cm anterior mediastinal mass, and enlarged adenoids and tonsils. Biopsy of the anterior mediastinal mass was consistent with LPD.

Results: The patient’s treatment consisted of high dose methylprednisolone, which was later changed to dexamethasone for better CNS penetrance, and rituximab. End of treatment demonstrated normal CBC and ferritin, negative EBV PCR with improvement of brain lesions.

Conclusion: This patient is among the youngest documented to have EBV-associated LPD due to thiopurine use for CD. Her new-onset seizures and CNS lesions made her case at first puzzling. The development of LPD in children with CD can occur as a complication of the treatment, due to the immunosuppression associated with thiopurine.
A NOVEL PMS2 GENE MUTATION LEADING TO CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY IN A PATIENT WITH 3 DISTINCT ONCOLOGIC DIAGNOSES
Haneen Shalabi, Joyce Turner, Leslie Doros, Michael Guerrera, Brian Rood, Reuven Schore.
Children's National Medical Center, Washington, District of Columbia, United States of America

Background: Normal cells have highly efficient means of correcting errors that occur during DNA replication. Defects in mismatch repair (MMR) genes result in the accumulation of DNA mutations and leads to oncogenesis. Biallelic mutations in MMR genes cause constitutional mismatch repair deficiency (CMMRD) with mutations in PMS2 occurring in a minority. CMMRD is associated with hematologic, brain, and Lynch-syndrome related cancers in childhood.

Objectives: We present a case of a 14-year-old female with three distinct malignancies found to have CMMRD caused by PMS2 missense and novel splice site mutations.

Design/Method: Case report

Results: Our patient presented at the age of 7 years with intussusception with a lead point diagnosed as DLBCL; she was treated with 2 cycles of COPAD, with no evidence of recurrence. At 9 years of age, she presented with headache, neck pain, and neurological deficits and was found to have a parietal-occipital mass. Biopsy showed atypical high-grade glioma with features of a PNET. She underwent gross total resection, and was treated with vincristine, cisplatin, and cyclophosphamide, craniospinal XRT with a boost to the tumor site followed by metronomic therapy with temozolomide, isotretinoin, cyclophosphamide, and etoposide. At 12 years of age, she presented with headaches, fatigue, and pancytopenia with peripheral blasts. Brain imaging showed no recurrence of tumor and bone marrow revealed acute myelogenous leukemia with monosomy 7. During therapy, she developed headaches, vomiting, and gait disturbances, and imaging showed a cerebellar mass. The patient and her family opted for palliative care. On autopsy, the cerebellar mass was consistent with a recurrence. Germline genetic testing revealed missense and a novel splice site PMS2 mutation, c.137 G to T and c.2445+1 G to T.

Conclusion: CMMRD causes multiple malignancies in children including brain tumors, colon cancers, and hematologic malignancies. MMR gene analysis should be considered in these patients even in the absence of a familial cancer history. We identified a previously unreported mutation in PMS2. Identification of MMR gene mutations may be helpful with identifying at-risk patients and initiating proper surveillance; thus, allowing for early cancer detection. A diagnosis of CMMRD may require altered treatment including dose-reducing chemotherapeutics or radiation therapy.
PATTERNS OF EMERGENCY DEPARTMENT CARE FOR NEWLY DIAGNOSED ITP IN U.S. CHILDREN’S HOSPITALS
Laquita Jones, Terah Koch, Sarah O'Brien. Nationwide Children's Hospital, Columbus, Ohio, United States of America

Background: There has been a wide variation in the management of acute immune thrombocytopenia (ITP), including the decision to admit, and when to utilize observation alone, steroids, or immunologic therapy. The majority of children with acute ITP experience no, or mild (skin manifestations alone), bleeding symptoms regardless of therapeutic approach. In 2011, the American Society of Hematology published guidelines recommending observation alone for children with no, or mild, bleeding symptoms.

Objectives: To characterize the therapeutic approach to ITP in patients presenting to U.S. pediatric emergency departments (EDs).

Design/Method: Using the Pediatric Health Information System database, we identified patients presenting to pediatric EDs from July 2010-June 2013, with ITP (ICD-9 287.31) as either their first or second diagnosis. We examined admission rates and implemented therapies. To limit our population to new patients, we required that patients had not been seen in the 12 months prior for ITP. Therapy types included: steroids, intravenous immunoglobulin (IVIG), rho D immune globulin (anti-D), combination therapy, and no identified therapy.

Results: A total of 2,655 unique, acute ITP patients were evaluated in the ED; 1,721 (64.8%) were admitted to the hospital. IVIG was the most commonly used therapy, being administered in 44.5% of patients (62% of hospitalized patients). The second most common therapeutic approach was observation alone, utilized in nearly 75% of outpatient cases.

Conclusion: Despite current guidelines on ITP, approximately 2/3 of new ITP patients presenting to pediatric EDs are admitted to the hospital. Over 40% of new patients receive IVIG, the most expensive therapy.
LATE VITAMIN K DEFICIENCY BLEEDING IN INFANTS NOT RECEIVING PROPHYLAXIS
Lauren Marcewicz, Joshua Clayton, Matthew Maenner, Althea Grant, Erika Odom, Ekwutosi Okoroh, Alyson Goodman, Deborah Christensen, Julie Traylor, Angela Miller, Michael Warren. Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

Background: Late vitamin K deficiency bleeding (VKDB) is a severe coagulopathy occurring in infants older than two weeks. Intramuscular vitamin K prophylaxis prevents VKDB; without it, incidence in European populations ranges from 4-7/100,000 infants. In 2013, five infants with hemorrhage and laboratory evidence of vitamin K deficiency presented to Hospital X in Tennessee; by parental choice, none had received vitamin K at birth.

Objectives: We conducted an epidemiologic investigation in order to estimate incidence of VKDB in 2013 as compared to previous years, and identify risk factors contributing to bleeding in infants not receiving prophylaxis.

Design/Method: We determined the proportion of infants not receiving vitamin K using medical record review of a sample of births from hospitals in Hospital X’s metropolitan area. We queried Tennessee hospital discharge data from 2007–2012 for discharges with diagnoses of VKDB. We conducted a case-control study, with cases defined as infants with VKDB in the absence of prophylaxis and predisposing medical conditions. Controls were healthy breastfed infants who had not received prophylaxis. Medical histories were obtained through chart review and structured interviews. Parents were also interviewed about their reasons for opting out of prophylaxis.

Results: Two point nine percent of infants did not have documentation of vitamin K administration or had documentation of parental opt-out of prophylaxis. A single case of VKDB was found in hospital discharge data from 2007–2012. All case (n=4) but no control (n=12) mothers reported a history of easy bruising, heavy periods, or both (p <0.01). No other factors were significantly associated with VKDB. Parents (n=16) cited a number of concerns about vitamin K, including preservatives (n=7), dosage (n=5), and cancer risk (n=5); 44% thought prophylaxis was unnecessary.

Conclusion: The incidence of VKDB in Tennessee in 2013 was higher than observed in previous years. Undiagnosed bleeding disorders may have contributed to VKDB among infants; however, small sample size limits this interpretation. These findings underscore the importance of intramuscular vitamin K for prevention of VKDB. Parents of cases and controls commonly cited non-evidence-based concerns about vitamin K. Reliable information for parents addressing concerns and the risks of opting out of prophylaxis is needed.
ECHOCARDIOGRAPHIC EVALUATION OF CARDIAC ANATOMY AND LEFT VENTRICULAR SYSTOLIC FUNCTION IN PATIENTS WITH SHWACHMAN-DIAMOND SYNDROME

Thomas Ryan, John Jeffries, Parinda Mehta, Richard Harris, Joan Mooer, Audrey Anna Bolyard, Barbara Otto, Amanda Jones, Akiko Shimamura, Stella Davies, Kasiani Myers. Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, United States of America

Background: Shwachman–Diamond Syndrome (SDS) is an autosomal recessive condition characterized by bone marrow failure and exocrine pancreatic dysfunction. Other organ systems, including the heart, may be affected. Dilated cardiomyopathy and heart failure have been described in SDS patients, as has decreased myocardial reserve in exercise. Circumferential strain (εcc) is a measure of systolic performance that identifies dysfunction in at-risk patients when standard measures are normal.

Objectives: Here we characterize systolic function in SDS patients, including a subset post bone marrow transplant (BMT), using shortening fraction (SF) and εcc.

Design/Method: Patients with SDS were identified and the echocardiographic database was queried. In patients post-BMT, the last study prior to transplant and most recent study post-transplant were identified. Cardiac anatomy and function, including SF, were recorded. Feature tracking analysis software (Image Arena, TomTec) was used to measure εcc based on a modified American Society of Echocardiography 16-segment model.

Results: From 1995-2013 there were 34 patients with SDS cared for at our institution, 15 of whom had at least one echocardiogram available for review; 11 patients underwent BMT, with echocardiograms available in 9. One echocardiogram showed dilated left ventricle, while two had dilated aortic root including one with bicuspid aortic valve. SF was normal in all 14 patients evaluated; however strain was decreased compared to published norms in 8 of 13 studies prior to BMT, and in 6 of 8 after BMT. Echocardiogram reports were also available for another 6 patients in the SDS registry, with normal SF reported in all studies.

Conclusion: While SF was normal in all SDS patients evaluated, εcc was abnormal in 62% prior to BMT, and 75% of those who had undergone BMT. These results suggest that SDS alone is associated with systolic dysfunction, while patients with SDS who have undergone BMT are at even greater risk. Further studies are needed to define the incidence of dysfunction in this group, and the progression to symptomatic heart failure.
EFFECT OF MATERNAL CIGARETTE SMOKING ON NEWBORN IRON STORES
Irina Pateva, Elizabeth Kerling, Susan Carlson, Manju Reddy, dan Chen, Jakica Tanacabelic.
University of Kansas Medical Center, Kansas City, Kansas, United States of America

Background: Previous small-scale studies suggest that maternal smoking lowers neonatal body iron.
Objectives: To study and compare the relationship between maternal and infants’ body iron in smokers and non-smokers in a large matched-pair cohort.

Design/Method: This was a prospective cohort study involving 144 mothers – 72 smokers and 72 non-smokers and their respective infants. Samples were obtained from maternal blood and infants’ cord blood at delivery for serum transferrin receptor (sTfR) and ferritin levels. Serum TfR and ferritin levels were measured by RAMCO ELISA and RIA assays. The total body iron (TBI) was calculated using the sTfR/ferritin ratio.

Results: Women who smoked compared to nonsmoking women had lower sTfR (mg/L) 5.02± 2.64 vs 6.24± 3.67, higher ferritin (u/L) 36.2± 27.6 vs 30.3± 26.5 and higher body iron (mg/kg) 4.9 ± 4.09 vs 3.8± 4.27. In contrast to their respective mothers, we found that the number of days and packs per day (PPD) smoked during pregnancy was negatively correlated with infants’ ferritin and total body iron and positively correlated with infants’ sTfR. Birth weight was lower in babies of smokers compared to nonsmokers (mean +/- SD =3270 +/- 475 vs. 3393 g +/- 475 g, p=0.03). Correlation studies revealed also that birth weight in infants of smokers was negatively correlated with PPD smoked and number of days smoked. We found a positive correlation between maternal education and maternal body iron – it significantly increased for both smokers and non-smokers. Additionally, there was a negative correlation between smoking and breastfeeding- if mothers smoked before and during pregnancy, they breastfed less.

Conclusion: Mothers who smoked during pregnancy had higher iron stores but their newborn infants had lower iron stores than those of non-smoking mothers. There may be a negative dose-dependent response between fetal smoke exposure and infant iron stores. Mothers who smoke tend to breastfeed babies less than non-smokers.
TREATMENT OF IRON DEFICIENCY ANEMIA: A SURVEY OF PEDIATRIC HEMATOLOGY-ONCOLOGY PHYSICIANS
Jacquelyn Powers, Timothy McCavit, George Buchanan. University of Texas Southwestern Medical Center, Dallas, Texas, United States of America

Background: Iron deficiency anemia (IDA) is the most common hematologic condition affecting children and adolescents in the United States (US). Research on IDA management is lacking, and no prior reports have described the treatment of IDA among pediatric hematology-oncology specialists.

Objectives: We sought to describe the self-reported management of IDA by US pediatric hematology-oncology specialists.

Design/Method: We designed a 20-question survey that included two typical IDA scenarios. In October 2013 individual emails were sent to active US members of the American Society of Pediatric Hematology Oncology (ASPHO). Surveys were emailed on weeks 0, 2, and 6. Physicians not routinely treating IDA could opt out of the survey.

Results: Of 1217 recipients, 398 (32.7%) completed the first case and were included in the analysis. In a toddler with nutritional IDA, 15% (N=61) reported performing no diagnostic testing beyond a complete blood count. Otherwise, wide variability in diagnostic testing was reported. The mostly commonly ordered combination of iron-specific tests included ferritin, iron, and total iron binding capacity (TIBC) (N=93, 23%). For treatment of toddlers, most respondents recommended ferrous sulfate (N=335, 84%) at a dose of 6 mg/kg/day (N=248, 62%) divided twice daily (N=272, 68%). Most respondents would not have changed dosing recommendations for higher or lower hemoglobin at presentation. The recommended duration of iron treatment after correction of anemia was widely variable (33% - no further treatment; 45% - 1-2 additional months; and 20% - three or more additional months). In the second case of an adolescent female with heavy menstrual bleeding and IDA, most respondents again recommended ferrous sulfate (N=327, 83%) based on the number of tablets (versus weight-based dosing). For IDA refractory to initial oral treatment, 13% (N=52) chose to continue oral iron therapy whereas 48% (N=188) opted for parenteral treatment with Venofer®, 17% (n=68) with Ferrlecit®, and 15% (N=60) with Infed®.

Conclusion: With few exceptions, the approach to diagnosis and treatment of IDA in childhood is widely variable among ASPHO members in the US. More research into IDA management in childhood is needed.
SAFETY AND EFFICACY OF LONG-TERM OPEN-LABEL DOSING OF ROMIPLOSTIM, A THROMBOPOIETIN (TPO)-RECEPTOR-AGONIST, IN THROMBOCYTOPENIC PEDIATRIC PATIENTS WITH IMMUNE THROMBOCYTOPENIA (ITP) IN AN EXTENSION STUDY

Michael Tarantino, James Bussel, Amy Geddis, Michael Guerrera, Alan Ikeda, Kun Nie, Melissa Eisen. Amgen Inc., Thousand Oaks, California, United States of America

Background: Romiplostim increased platelet counts in children with ITP in a phase 1/2 study. Patients completing that study or an ongoing phase 3 study could enter this extension study.

Objectives: Evaluate romiplostim’s long-term safety and efficacy in pediatric ITP.

Design/Method: Weekly subcutaneous romiplostim adjusted ≤10 µg/kg to target platelets 50-200x10^9/L.

Results: Twenty-two patients (from phase 1/2, n=12, phase 3, n=10), median age 12.0 years (range 3–16), 18.2% splenectomized, received romiplostim ≤172 weeks (3.3 years, median 89.0 weeks, 6 patients ≥3 years). Median average weekly dose was 4.0 µg/kg (range 1–10), including ramp-up. Four patients discontinued the study (withdrew consent, n=3; noncompliant, n=1). From Week 2 on, median platelets were above 50x10^9/L (Figure). Median romiplostim dose (Q1, Q3) was 6.0 (2.0, 8.0) µg/kg at Week 1 and declined to 3.5 (0.0, 7.0) µg/kg at Week 168. Eight patients received rescue medications (for platelets <10x10^9/L, bleeding/wet purpura, or investigator decision), including immunoglobulins (n=3), tranexamic acid (n=3), platelet transfusion, aminocaproic acid, and prednisone (n=1 each). Four patients had nonfatal serious adverse events [AEs] (asthma, hemangioma, hypotension, infection, thrombocytopenia, and transfusion reaction) and 1 had 2 nonfatal life-threatening AEs (infection and thrombocytopenia), none treatment-related. Twelve patients had bleeding events: epistaxis (n=4), petechiae (n=3), gingival bleeding (n=2), hemorrhage (n=2), and bleeding from the anus, injection site, lip, and mouth (n=1 each); gingival bleeding and petechiae were deemed treatment-related. Bone marrow biopsies were not performed.

Conclusion: In this ongoing long-term extension study, romiplostim maintained platelets in pediatric patients with ITP without significant toxicity.

Supported by Amgen Inc.
HOSPITALIZATIONS IN PEDIATRIC PATIENTS WITH IMMUNE THROMBOCYTOPENIA (ITP) IN THE UNITED STATES (US) IN THE 2009 KIDS’ INPATIENT DATABASE (KID)
Michael Tarantino, Mark Danese, Robert Klaassen, Jennifer Duryea, Melissa Eisen, James Bussel.
Amgen Inc., Thousand Oaks, California, United States of America

Background: ITP can lead to resource-intensive hospitalization in children.
Objectives: To examine resource utilization, costs, and outcomes in pediatric hospitalizations with ITP diagnoses.

Design/Method: The ICD-9 code 287.31 was used to identify hospitalizations in patients with ITP in the 2009 KID, an all-payer sample of pediatric hospitalizations from US community hospitals. A patient could be represented more than once if more than one hospitalization occurred in 2009. Hospitalizations related to birth, secondary thrombocytopenia, and in children <6 months were excluded. We used diagnosis and procedure codes to estimate national utilization rates of ITP-related procedures, prevalence of selected comorbid conditions, cost of care (using cost-to-charge ratios), length of stay (LOS), and mortality. Whether comorbid conditions began before or during the hospitalization could not be distinguished.

Results: In 2009, there were 4,512 (95%CI:3,995-5,028) hospitalizations in children age 6 months-17 years with an ITP diagnosis code; 43% occurred in children age 1-5. Emergency department utilization was associated with 47% of hospitalizations with ITP. The average cost of a hospitalization with ITP was $5,420, average LOS 2.0 days, and mortality rate was 0.3% (n=13, 95%CI:5-21). With any bleeding diagnosis [prevalence 15.2%, n=688, 95%CI:584-791, including gastrointestinal 2.1%, hematuria 1.3%, intracranial hemorrhage (ICH) 0.6%], average cost was $7,231, LOS was 2.5 days, and mortality rate was 1.50%. Specifically, for ICH (prevalence 0.6%, n=27, 95%CI:12-42), average cost was $40,209, LOS 8.5 days, and mortality rate was 21%. Infections occurred in 15% of all hospitalizations (including upper respiratory infections 5.2%, viral infections 4.8%, bacterial infections 2.0%, urinary tract infections 1.3%, skin infections 1.2%, septicemia 1.0%, hepatitis 0.6%, and mycoses 0.4%); average cost was $7,076, LOS 2.9 days, and mortality rate was 0.89%. Septic shock occurred in 0.3% of hospitalizations. Immunoglobulins were administered in 37.5% of hospitalizations, and splenectomies were performed in 2.3% (n=105, 95%CI:77-133). Factors significantly (p<0.05) associated with higher costs in hospitalizations with ITP included age>6, ICH, transfusion, splenectomy, and bone marrow evaluations.

Conclusion: Hospitalizations of children with ITP with clinically significant bleeding and procedures were associated with higher costs. Analysis of the forthcoming 2012 KID may show effects of more recent ITP guidelines.

Supported by Amgen Inc.
COMBINATION OF SIROLIMUS AND PROPRANOLOL SAFE AND EFFECTIVE IN RAPIDLY PROLIFERATING VASCULAR ANOMALIES WITH IMPENDING AIRWAY OBSTRUCTION

Tishi Shah, Stanley Calderwood, Leonard Bodner, Christopher Gribbin, Karen Kestenbaum, Matthew Kaufman, Thomas McPartland, Nibal Zaghloul, Ionela Iacobas. Saint Peter's University Hospital, New Brunswick, New Jersey, United States of America

**Background:** Rapidly proliferating vascular anomalies on the neck and lips have a high potential for airway compromise, thus a diagnosis has to be achieved fast and acute management cannot be delayed.

**Objectives:** We present the case of a baby Nigerian girl who was evaluated initially at 6 weeks-old for a 7x6x0.5 cm bluish mass on the neck that has appeared and grown in only a few days. No bleeding, no tenderness, no ulceration. Mother related a history of stridor for the baby. She was admitted and an MRI was obtained urgently. The images revealed a submental lobulated mass, not infiltrative and minimally enhancing suggestive of a stable veno-lymphatic malformation and the child was discharged on no medication. Seven days later the lesion has enlarged significantly measuring 10x9x1cm, very firm with blue-purplish color. On the midline of lower lip few new pink nodules were now noted affecting both cutaneous and buccal mucosa part of the lip.

**Design/Method:** There are 2 vascular tumors that can present with this dramatic growth early in infancy: infantile hemangioma and Kaposiform hemangioendothelioma. As the cutaneous component and the MRI images were not specific for either, the child was scheduled for biopsy. Due to the rapid enlargement of the lesion and concern for impending airway compromise, she was started on propranolol and sirolimus targeting both possible diagnoses. Within 48h the lesion not only has stopped growing, but has actually significantly reduced in size, and continued to improve. Pathology revealed infantile hemangioma GLUT-1 positive.

**Results:** After one week of double therapy, the lip nodules were almost completely flat and the neck mass became softer. Sirolimus was discontinued and the baby continued treatment on Propranolol with no rebound growth.

**Conclusion:** Classically, the airway vascular anomalies are addressed with high-dose steroids regardless of etiology. This is the first report to our knowledge of targeted therapy using the combination of two anti-angiogenic agents. The result was high efficiency, no complications (avoiding the steroid-induced side effects), no wean-off period. This combination should be strongly considered in rapidly proliferating vascular anomalies with impending airway obstruction and deserves a comparative study with the current standard of care.
A NOVEL MUTATION IN THE GP Ib ALPHA SUBUNIT IN A NEWBORN WITH BERNARD SOULIER SYNDROME
Thomas Moulton, Harini Racherla. Bronx Lebanon Hospital Center, Bronx, New York, United States of America

Background: Bernard Soulier Syndrome (BSS) is a rare congenital autosomal recessive bleeding disorder. It is characterized by a macrothrombocytopenia ranging from 20-140,000. Clinical symptoms are the result of genetic defects in the GP Ib/IX/V complex.

Objectives: To describe a case of a novel mutation in the GPIb alpha subunit

Design/Method: A newborn male from a consanguineous marriage was noted in the NICU to have severe macrothrombocytopenia of 15,000 as an incidental finding. Subsequently he had platelet counts as low as 8,000 and consistently <20,000 but responded normally to an initial platelet transfusion. There was a history of two male cousins with thrombocytopenia and severe bleeding with circumcision. The child also had other hematologic (ABO/Rh incompatibilities) and congenital abnormalities (bilateral hip dislocation). There was no intraventricular hemorrhage noted in the NICU. The child subsequently developed hematochezia which was felt to be due to milk protein allergy.

Results: X-linked thrombocytopenia was initially considered, but GATA-1 and SCALA-35 gene analysis were normal. Subsequent GPIb subunit/IX gene sequencing revealed a novel homozygous duplication causing a frame shift mutation in the alpha subunit resulting in the elimination of GPIb expression on the platelet surface.

Conclusion: Thrombocytopenia in this neonate raised the consideration of several differential diagnoses, including neonatal alloimmune thrombocytopenia (ruled out with a normal platelet response to transfusion), hypersplenism was also considered due to the possible splenic activation from his ABO/Rh incompatibility and X-linked thrombocytopenia, with 3 affected male members of the family. BSS was not initially considered because of the extremely low platelet count. BSS was considered the diagnosis when the medical record of one of the affected cousins was obtained noting a diagnosis of BSS. Because of the severely low platelet count, gene sequencing was done which revealed the novel mutation. It is possible to utilize this mutation to prenatally diagnose BSS in this family. His diagnosis of BSS proved to be a challenge in correcting his congenital bilateral hip dislocations.
DOSING AND SAFETY WITH DALTEPARIN USE IN PEDIATRIC PATIENTS: A SINGLE INSTITUTION EXPERIENCE
Trey Mullikin, Deepti Warad, Kevin Graner, Shakila Khan, Amulya Nageswara Rao, Vilmarie Rodriguez, Mayo Clinic, Rochester, Minnesota, United States of America

Background: The use of low molecular weight heparin (LMWH) in pediatric patients for anticoagulation has increasingly become prevalent due to absence of interference with other drugs or diet, minimal monitoring requirements, reduced incidence of heparin-induced thrombocytopenia and osteopenia, largely based on Enoxaparin studies. The other commonly used and FDA approved LMWH is Dalteparin, with extensive safety data in adults. Dalteparin also offers once daily dosing and relative safety in renal impairment; however, similar data in children is lacking.

Objectives: We report our 15 year institutional experience with use of dalteparin in children for treatment of venous thromboembolic events (VTE).

Design/Method: Retrospective chart review was performed on 37 children (23 males, 14 females) aged 0-18 years with VTE and anti-Xa levels drawn between 4-6 hours after dalteparin dose.

Results: Median age was 13.3 years (Range 0.04–17.9 years). Eleven patients received q24 hour and 26 patients received q12 hour dosing. Upon age-based subgrouping, the mean dose required to achieve therapeutic anti-Xa levels (0.5-1 IU/ml) was significantly higher in infants [infants <1 year, mean=457.3 units/kg/day (SD=108.7, n=7); 1-9.99 years, mean=271.4 units/kg/day (SD=73.7, n=7); 10-18 years, mean=200.9 units/kg/day (SD=67.8, n=23)] (p<0.0001). Outcomes of 36 patients included complete/partial clot resolution (72.2%), stable clot (25%), and clot extension (2.8%). One was lost to follow-up. No association between dosing frequency and response to anticoagulation was noted. Three patients had ongoing acute renal dysfunction and received adjusted renal dosing resulting in complete clot resolution n=1, stable clot n=1 and loss to follow-up n=1.

Conclusion: The safety and efficacy of dalteparin has been well-documented in adults with a reported 3-14% bleeding complications. In our cohort, no complications, including bleeding, were attributable to dalteparin. The recommended adult dose of 200 units/kg/day to achieve therapeutic anti-Xa levels cannot be directly extrapolated to pediatric population due to their unique physiology and metabolic capacity. Though our study sample is limited, the findings suggest that dalteparin dosing is age dependent with significantly larger doses required in younger children to achieve therapeutic levels. Notably, these high doses were well tolerated. We conclude that larger studies with pharmacokinetic analysis are required to better understand dalteparin dosing requirements in children.
UNUSUAL VASCULAR ABNORMALITIES OF THE NEONATE (PUZZLING PRESENTATIONS AND DIAGNOSIS)
Ashok Raj, Scott Myers, Arun Panigrahi, Anita Gupta, Denise Adams. University of Louisville, Louisville, Kentucky, United States of America

**Background:** Pediatric vascular tumors and malformations, comprising a broad category of lesions often referred to as vascular anomalies. The most common anomaly in the newborn period is the infantile hemangioma. Other vascular tumors are rare and require a multidisciplinary approach to diagnosis and management. Here we report several atypical presentations of vascular anomalies and describe diagnosis and treatment.

**Objectives:** Evaluating the role of accurate histopathologic description and knowledgeable clinical and radiologic evaluation as absolute prerequisites for study and meaningful diagnosis of vascular anomalies.

**Design/Method:** Case reports: A full term Caucasian female infant born via spontaneous vaginal delivery was noted to have extensive bruising after birth. Initial work up revealed thrombocytopenia. Immune disorder and infectious disease workup was negative. She subsequently developed new skin lesions with thrombocytopenia, hypofibrinogenemia and D-dimer elevation. Imaging studies showed bony disease in the pelvis and vertebrae with compression fractures, lung nodules and multiple skin lesions. Biopsy of skin lesions and bone marrow aspirate and biopsy were done. A full term Caucasian male was born via C section delivery with extensive bruising, severe anemia and thrombocytopenia, splenomegaly and left frontoparietal and right parietal acute intracranial bleeding. He also had D-dimer elevation but with normal fibrinogen levels. Additional imaging studies showed a large irregular hypodense/poorly enhancing lesion within the spleen with nearly contiguous hypodense soft tissue noted in the root of the mesentery/behind the pancreas as well as along the left para-aortic region. Biopsy of mesenteric lesions and bone marrow aspiration were done.

**Results:** The pathologic findings were consistent with Kaposiform lymphangiomatosis (KLA), a rare lymphatic anomaly recently reported, which is associated with coagulopathy. The patients were treated with the mTOR inhibitor sirolimus with therapeutic monitoring, which lead to significant clinical improvement without side effects.

**Conclusion:** In this case series, we emphasize the unusual presentation of neonatal vascular anomalies, and the need for a multidisciplinary approach to uncover a rare diagnosis rarely reported in the newborn period. Sirolimus appears to be effective in KLA as reported here at a very young age.
HYPERAMMONEMIC ENCEPHALOPATHY SECONDARY TO PEGYLATED ASPARAGINASE TREATED WITH ORAL LACTOLUSE SOLUTION AND INTRAVENOUS SODIUM BENZOATE/SODIUM PHENYLACETATE
Muaz Alrazzak, Barbara Bambach, Denise Rokitka, Matthew Barth. Roswell Park Cancer Institute, Buffalo, New York, United States of America

**Background:** Pegylated Asparaginase (PEG-ASP) is a mainstay of treatment of childhood acute lymphoblastic leukemia (ALL). It has a longer biological half-life than the previously used asparaginase which could be contributed to the higher incidence of some side effects. Those include anaphylaxis, thrombosis, pancreatitis, hyperammonemia and hyperglycemia. Hyperammonemic encephalopathy is a rare side effect of asparaginase and has been increasingly recognized after the introduction of PEG-ASP. The clinical presentations vary from mild anorexia and nausea to headache, vomiting, dizziness, lethargy and altered mental status. The treatments include hydration with glucose containing fluid, arginine replacement, protein restriction and ammonia trapping agents. Hemodialysis could be indicated in some cases.

**Objectives:** To report a case of hyperammonemic encephalopathy secondary to PEG-ASP, we will discuss the clinical presentation and the treatment options of hyperammonemic encephalopathy in patients receiving chemotherapy.

**Design/Method:** The medical record including clinical presentation, laboratory data and radiologic study were reviewed.

**Results:** A 9 year-old girl with ALL presented with headache, tremor and altered mental status 10 days after receiving PEG-ASP as a part of her consolidation chemotherapy. Her initial laboratory workup showed very high plasma ammonia level with normal liver and renal function tests, her head MRI was normal as well. She was treated successfully with oral lactulose solution (0.4mg/kg every 8 hours) and intravenous sodium benzoate/sodium phenylacetate (an ammonia-trapping agents’) with loading dose of 2ml/kg over 2 hours, followed by maintenance dose of 2 ml/kg continuous infusion over 24 hours. The patient had significant clinical and laboratory improvement within 24-36 hours of presentation. It was difficult to distinguish whether the improvement was due to the lactulose or the sodium benzoate/sodium phenylacetate. The patient is currently doing well; she continued to receive Erwinia asparaginase during her subsequent courses of chemotherapy without adverse effects.

**Conclusion:** Hyperammonemic encephalopathy is a rare side effect of PEG-ASP and this could be fatal. The critical step is the early recognition of the syndromes by measurement of the plasma ammonia levels in patients with neurologic symptoms, leading to accurate diagnosis and early treatment intervention.
ANALYSIS OF REDOX AND APOPTOTIC EFFECTS OF ANTHRACYCLINES TO DELINEATE A CARDIOPROTECTIVE STRATEGY
Daniela Egas Bejar, Joy Fulbright, Mary Irwin, Fernando Corrales-Medina, Blake Johnson, Joya Chandra. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Anthracyclines are essential antileukemic drugs, however their use has been associated with cardiotoxicity. Their cardiotoxic action involves generation of reactive oxygen species (ROS) which are counteracted by intracellular antioxidants, such as glutathione (GSH). Given that basal levels of antioxidants vary greatly between different cell types anthracyclines may exert distinct effects on oxidative stress and consequent apoptosis induction in leukemia cells and nontransformed hematopoietic cells (PBMC) relative to cardiomyocytes.

Objectives: To evaluate the mechanism of cell death induction and regulation of ROS levels after anthracycline exposure and the effect of use of antioxidants on cytotoxicity of anthracyclines in leukemia cells versus cardiomyocytes.

Design/Method: Acute leukemia cell lines Jurkat (T-cell ALL) and ML-1 (AML), cardiomyocyte cell line H9C2 and PBMC were treated with anthracyclines with or without pretreatment with antioxidants. Viability, DNA fragmentation and caspase 3 activation were measured. GSH levels were obtained as an indirect measure of ROS levels. Loss of mitochondrial membrane potential was determined using TMRE. Antioxidants used included N-acetylcysteine (NAC, GSH precursor and amino acid source), GSH ethyl ester (cell permeable form of GSH), trolox (water soluble form of vitamin E) and tiron (free radical scavenger).

Results: Acute leukemia cells were more sensitive than H9C2 cells to anthracyclines, showing greater loss of viability at 24 hours treatment with equimolar doses. In acute leukemia cells, caspase activation preceded DNA fragmentation and viability loss. GSH levels decreased after caspase activation in leukemia cells and cardiomyocytes. Use of caspase inhibitors showed that GSH regulation was independent of caspase activation. Neither antioxidant interfered with anthracycline cytotoxicity in Jurkat cells but trolox significantly protected ML-1 cells from daunorubicin cytotoxicity. No antioxidant protected the PBMC but NAC protected H9C2 cells from anthracycline cytotoxicity.

Conclusion: NAC can protect cardiomyocytes without interfering with anthracycline cytotoxicity in acute leukemia cells. In humans, one RCT tested the chronic administration of NAC during doxorubicin therapy, detecting no evidence of cardioprotection. However, trial design may not have been optimal, including schedule for NAC administration and lack of incorporation of oxidative stress markers. A strategy that incorporates pretreatment NAC prior to anthracycline administration may prove beneficial if markers of oxidative stress are used as endpoints.
CRITICAL CONTRIBUTIONS OF CRM1 TO CALM- AF10 LEUKEMOGENESIS
Jessica Heath, Amanda Conway, Catherine Lavau, Daniel Wechsler. Duke University, Durham, North Carolina, United States of America

**Background:** CALM-AF10 leukemias are associated with overexpression of HOXA genes, which are critical effectors of oncogenic transformation. While the OMLZ region of AF10 is known to recruit the Dot1L histone methyltransferase to the HOXA locus, the contribution of CALM has been unclear. Our lab has recently identified a Nuclear Export Signal (NES) within CALM that is both necessary and sufficient for CALM-AF10 mediated HOXA cluster upregulation and leukemogenesis. The CALM NES is recognized by and interacts with the nuclear export protein CRM1.

**Objectives:** Since the CALM NES is critical for CALM-AF10 leukemogenesis, we hypothesize that CRM1 participates in HOXA gene upregulation and may functionally substitute for CALM in leukemogenic fusions with AF10.

**Design/Method:** Murine CALM-AF10 leukemia cells and the human CALM-AF10 leukemia cell lines U937 and P31/Fuji were treated with the CRM1 inhibitor Leptomycin B (LMB) which blocks the interaction of CRM1 with NES proteins. HOXA gene expression was measured by real time PCR. Murine hematopoietic progenitors were retrovirally transduced with CALM-AF10, CRM1-AF10, or CRM1-OMLZ and then transplanted into irradiated recipients to generate primary leukemias. Bone marrow cells harvested from these mice at terminal illness were then injected into irradiated recipients to generate secondary leukemias.

**Results:** Murine and human CALM-AF10 leukemia cells show a reduction in HOXA9 and HOXA10 expression following brief exposure to LMB (0.7 nM, 2 hours), suggesting that CALM-AF10 mediated HOXA overexpression depends on the interaction between CALM and CRM1. The CRM1-AF10 fusion causes acute myeloid leukemia in vivo. This leukemia has a low penetrance and long latency but is transplantable into secondary recipients with 100% penetrance.

**Conclusion:** The interaction of CRM1 with CALM-AF10 is necessary and sufficient for leukemogenesis and mediates upregulation of the HOXA gene cluster. Furthermore, fusing CRM1 to AF10 recapitulates the leukemogenic properties of CALM-AF10. These findings indicate that CALM’s primary role in CALM-AF10 mediated transformation is to tether AF10 to CRM1. This critical role for CRM1 in leukemogenesis suggests that CRM1 inhibitors – currently in clinical trials – should be considered as rational therapeutic agents for CALM-AF10 leukemias.
TARGETING OF CALM-AF10 LEUKEMIAS BY IRON DEPRIVATION
Jessica Heath, Catherine Lavau, Joshua Weiss, Daniel Wechsler. Duke University, Durham, North Carolina, United States of America

**Background:** The CALM-AF10 fusion protein that arises from the t(10;11) chromosomal translocation is found in AML and 8-10% of T-cell ALL and is associated with a poor outcome in both pediatric and adult patients. The Clathrin Assembly Lymphoid Myeloid leukemia (CALM) protein is necessary for clathrin-mediated endocytosis, which is essential for cellular uptake of iron-bound transferrin. We have previously shown that Calm-heterozygous fibroblasts are iron deficient, and are more sensitive to the effects of iron deprivation than Calm-wildtype controls.

**Objectives:** Since CALM-AF10 leukemia cells are haploinsufficient for CALM, we hypothesize that their reduced levels of CALM result in relative iron deficiency and sensitivity to iron deprivation.

**Design/Method:** Hematopoietic progenitors derived from Calm+/- fit1 mice were retrovirally transduced with CALM-AF10, and then transplanted into irradiated recipients to generate leukemias. Calm+/- CALM-AF10 leukemia cell lines were generated and exposed to an iron chelator (deferoxamine (DFO)) with and without cytarabine to assess the effect of iron deprivation in vitro. To examine the impact of iron deprivation in vivo, mice transplanted with Calm+/- CALM-AF10 leukemia cells were maintained on a low-iron diet, and/or given deferasirox (33mg/kg/dose, 5 days/week) (DFX). This was tested alone and in combination with cytarabine and doxorubicin.

**Results:** In vitro, Calm+/- CALM-AF10 cell lines were sensitive to DFO, and combination with cytarabine had an additive effect. In vivo, following secondary transplantation of Calm+/- CALM-AF10 leukemia cells, iron-deprived mice consistently exhibited reduced splenomegaly, suggesting a negative effect on tumor burden. However, the survival of iron deprived mice was not reproducibly prolonged compared with matched iron replete controls.

**Conclusion:** Our in vitro results suggested that iron deprivation might be effective in treating CALM-AF10 leukemias alone and in combination with cytarabine. Furthermore, early in vivo results held promise that iron deprivation results in decreased tumor burden in a mouse model of CALM-AF10 leukemia. However, iron depletion did not result in a survival benefit either alone or in combination with chemotherapy in our mouse model. It is possible that the complex interplay of metabolism, proliferation and nutrient availability in vivo allows for variable tumor responses to iron accessibility and results in a narrow therapeutic window.
PARENTAL PERCEPTION OF VULNERABILITY IN PATIENTS ATTENDING A REGIONAL CHILDHOOD CANCER SURVIVOR CLINIC

Mary-Jane Hogan, Lyn Balsamo, Nina Kadan-Lottick. Yale University School of Medicine, New Haven, Connecticut, United States of America

Background: Parents of children undergoing treatment for cancer, who perceive their child as “vulnerable”, have been reported to exhibit overprotective behaviors associated with childhood emotional problems.1

Objectives: We sought to assess the frequency of vulnerability perception in parents of childhood cancer survivors attending Yale HEROS (Health, Education, Research Outcomes for Survivors) clinic.

Design/Method: This cohort analysis included pediatric patients in remission who were diagnosed with cancer at an age ≤21 years, were ≥3 years since diagnosis and attended HEROS clinic between 1/2010-10/2013. All HEROS attendees were screened using the Children’s Oncology Group Long-Term Follow-Up Guidelines. Their parents completed The Child Vulnerability Scale (CVS), consisting of eight items with responses ranging from 0, ‘definitely false’, to 3, ‘definitely true’. (Total score of ≥10 correlates with perceived vulnerability). Late effects identified in clinic were scored with the CTCAE v4.0 from I-V.

Results: A total of 83 survivors were eligible for analysis (median age 13.4 years, 51% female, median of 9.2 years since cancer diagnosis). Prior cancer diagnosis included leukemia (54%), non-CNS solid tumor (26%), CNS tumor (12%) and lymphoma (7%). Parents completed 107 CVS visit forms including 20 survivors with ≥2 annual visits. Parental perception of vulnerability was discovered in 19 (23%) survivors. There were a total of 171 late effects (65% grade I and 34% grade II). Vulnerable survivors were more likely to have ≥1 late effect compared to the Non-Vulnerable group (84% vs. 42%; p=0.01). Vulnerable survivors had similar Grade I (61% vs. 66%) and Grade II (37% vs. 33%) toxicities as Non-Vulnerable survivors. Gender, cancer type, age at cancer diagnosis, age at HEROS visit, years in treatment, years since cancer diagnosis, severity of late effects, insurance type, and median household income were not associated with vulnerability. Repeat attendees’ parents recorded unchanged total CVS scores between annual visits.

Conclusion: Twenty-three percent of parents of long-term survivors continue to perceive their children as vulnerable. Parental perception of vulnerability was associated with having at least one late effect but not the severity of the effect. Our data suggest the need to provide parents of childhood cancer survivors with ongoing education and supportive resources. 1.Colletti, Pediatr Blood Cancer, 2008.
Acute and Subacute Neurotoxicity of Methotrexate in Children with Cancer

Background: Neurotoxicity is a known side effect of methotrexate, a common medication used to treat pediatric malignancies. Neurotoxicity may be seen within days to weeks after administration, but there is little data on the frequency of methotrexate toxicity. In previous reports, 1-15% of patients developed neurotoxicity after receiving either high dose (HD) and/or intrathecal (IT) methotrexate.

Objectives: To determine the frequency of neurotoxicity after HD and/or IT methotrexate administration as well as risk factors and outcomes associated with the development of neurotoxicity in these patients.

Design/Method: We performed a retrospective chart review to identify oncology patients who received HD (>1g/m2) or IT methotrexate between January 2008 - June 2013 at our institution. Among these patients, we identified those that had neurologic symptoms. We excluded patients who had a history of a neurologic disorder or whose neurotoxic event could be attributed to another cause.

Results: We identified 372 patients who received HD or IT methotrexate. Among these patients, 22 met inclusion criteria. 12/22 patients were female. All 22 patients received IT methotrexate. No other IT medications were administered concurrently. 6/22 patients received at least 1 dose of HD methotrexate (5g/m2), and among those, 5/6 had received IT methotrexate and HD methotrexate on the same day prior to their neurotoxic event. The median time after receiving IT methotrexate to toxicity was 9 days, with a range of 0-43 days. The median time after receiving HD methotrexate to toxicity was 10 days, with a range of 8-73 days. 19/22 patients were re-challenged with methotrexate and 5/19 had a second episode of toxicity.

Conclusion: The incidence of methotrexate toxicity from January 2008 - June 2013 at our institution is 5.9%, consistent with what has been previously reported. All patients who developed neurotoxicity received IT methotrexate prior to the event, and 6 also received HD methotrexate. Patients who receive HD and IT methotrexate on the same day, have a higher likelihood of developing neurotoxicity if their cumulative methotrexate dose is greater than or equal to 5g/m2.
CANINES AND CHILDHOOD CANCER: MEASURING THE FEASIBILITY OF CONDUCTING ANIMAL-ASSISTED INTERACTION RESEARCH IN PEDIATRIC ONCOLOGY SETTINGS
Molly Jenkins, Amy McCullough, Ashleigh Ruehrdanz. American Humane Association, Denver, Colorado, United States of America

**Background:** Although childhood cancer has profound psychological effects for children and families, few studies have critically evaluated complementary therapies to help families cope. Increasingly, attention has focused on the roles that animals play in supporting human health. However, while animal-assisted interventions (AAIs) occur daily in children’s hospitals across the U.S., there remains a lack of rigorous research regarding their impact on patients, families, or the therapy dogs who visit them.

**Objectives:** The Canines and Childhood Cancer (CCC) Study seeks to address these research gaps by measuring the feasibility of conducting AAI research in pediatric oncology settings in preparation of a RCT to rigorously examine the well-being effects of these interactions for patients, parents/guardians, and therapy dogs.

**Design/Method:** Six children, aged 3-11 and recently diagnosed with ALL, and their parents were observed over a four month pilot at two children’s hospitals. Those randomly assigned to the AAI cohort were visited weekly by a therapy dog for 20 minutes in the outpatient clinic. Those in the control cohort received the standard-of-care for ALL. Patients in both groups had their blood pressure and heart rate variability measured at designated intervals and their videotaped behavior rated via the Observational Scale of Behavioral Distress (OSBD). Parents completed the State Trait Anxiety Inventory and the Pediatric Inventory for Parents, and had their heart rate variability measured. Therapy dog behavior was videotaped and rated via animal-handler self-reports and an ethogram. Canine salivary cortisol was also used to examine their levels of stress during sessions.

**Results:** With commitment, rigorous AAI research is feasible in pediatric oncology settings. Most instruments were useful and had good compliance, with the exception of the OSBD and heart rate variability. Preliminary data indicate that dogs tended to have a lower post-session salivary cortisol average than at baseline. Design modifications, including instrument and data collection optimization, have been made for the current 12 month clinical trial with five sites.

**Conclusion:** Lessons from the CCC pilot will advance the AAI and pediatric oncology fields through groundbreaking research, thus improving childhood cancer treatment and outcomes.

The CCC Study is supported by grant funding from Zoetis and the Pfizer Foundation.
LACK OF AWARENESS OF OBESITY RISK IN PARENTS OF CHILDHOOD SURVIVORS OF ACUTE LYMPHOBLASTIC LEUKEMIA
Gary Jones, Wendy McClellan, Ashley Sherman, Sripriya Raman, Erin Guest, Keith August.
Children's Mercy Hospitals and Clinics, Kansas City, Missouri, United States of America

Background: Obesity is a well established late effect following treatment of acute lymphoblastic leukemia (ALL) in childhood and constitutes a major source of morbidity and reduced quality of life. Unlike other late effects of therapy, obesity is potentially modifiable making it critical to ensure that patients and families are aware of these risks.

Objectives: To assess the incidence of overweight/obese in off-therapy ALL and examine parent perceptions of diet, activity and risk education provided by practitioners.

Design/Method: Off-therapy ALL patients were evaluated after completion of therapy during routine follow-up in the Hematology/Oncology clinic. Height/weight and BMI were obtained and percentiles were compared to previous measurements from the patient’s record. Parents completed a questionnaire while in clinic to evaluate their thoughts on their child’s diet, weight, activity level, and obesity education provided by practitioners.

Results: Data was collected for 70 patients. Median time from the end of therapy was 27 months [range: 2 - 138 mo]. At the time of survey, 35 patients (50%) met CDC criteria for overweight (≥85th percentile) with 18 (25.7%) meeting criteria for obese (≥95th percentile). Twenty-seven of the overweight patients (77.1%) were identified as “overweight” by their parents. Most parents felt their child was less active during therapy, but felt after completing therapy the activity level returned to baseline. Parents did not identify overweight patients as being significantly less-active than non-overweight patients. Twenty-three of the parents of overweight children (65.7%) did not recall discussing weight with their medical team. Of all the parents, only 25 (35.7%) recalled having an off-therapy discussion about diet with their physician and 45 (64.3%) did not recall a discussion regarding obesity risk in ALL survivors.

Conclusion: Despite the increased attention to the late-effects associated with ALL therapy, obesity is an area that is often under-emphasized with patients and families. Improved awareness and education of families may provide an avenue for the future prevention of obesity and its related comorbidities.
POST INDUCTION PROPHYLACTIC HOSPITALIZATION OF CHILDREN WITH NEW DIAGNOSIS OF ACUTE MYELOCYTIC LEUKEMIA (AML)

Israa Khan, Rao Mushtaq, Susumu Inoue, Nkechi Onwuzurike, Elna Saah, Jenny LaChance, Dawn Carson. Hurley Children's Hospital, Flint, Michigan, United States of America

**Background:** Patients with new diagnosis of AML develop profound pancytopenia during and following the initial induction chemotherapy with a high mortality rate due to infections. Some state that continuing preemptive hospitalization post induction chemotherapy is “standard of practice”. Some COG AML protocol recommends hospitalization post chemotherapy till absolute phagocyte counts shows increasing trend (AAML0531). We, at Hurley Children’s Hospital (HCH) have not adopted a policy of automatic hospitalization, and discharge decision has been made on case by case basis.

**Objectives:** We aimed to determine the remission and survival rates of patients who were electively discharged vs. who were kept in the hospital at our institution.

**Design/Method:** This is a retrospective medical records review of children with new diagnosis of AML who were consecutively treated at HCH between 1989 and 2011. We extracted the pertinent information whether the patient was electively discharged from the hospital after completion of Induction I chemotherapy. All patients whose records had sufficient information were included.

**Results:** There were 26 patients with new AML (APL excluded) (M: F=1:1). Fifty percent (13/26) of them were electively discharged post induction I of which 38% (5/13) were readmitted within 3 days because of complications such as febrile neutropenia, sepsis, dehydration etc. and the remainder (8/13) readmitted after ≥6 days due to similar complications. The remaining 50% of patients (13/26) continued to stay in the hospital after induction chemotherapy due to complications such as neutropenic fever or sepsis except one who was kept prophylactically because of pancytopenia. 92% achieved remission with a mean of 42 days. Of the patients who were electively discharged after induction completion, 69% (9/13) were alive at a 5 year follow up and also 69% (9/13) are alive of those who continued to stay in the hospital due to post induction complication.

**Conclusion:** We found no significant difference in survival in patients who remained hospitalized versus those who were electively discharged. Thus, we conclude that current practice of discharging patients upon completion of initial induction chemotherapy has not adversely affected the survival.
THERAPEUTIC PHLEBOTOMY FOR IRON OVERLOAD IN CHILDHOOD CANCER SURVIVORS
Julie Krystal, Jonathan Fish. Cohen Children's Medical Center, New Hyde Park, New York, United States of America

Background: Children being treated for cancer often receive many packed red blood cell transfusions, resulting in long-term iron overload. As endocrinopathies and cardiomyopathies are the most common late-effects of both iron overload and treatments for childhood cancer, the management of iron overload in childhood cancer survivors is an important area of study. Little data on therapeutic options for iron overload in childhood cancer survivors exist.

Objectives: To retrospectively review the safety and effectiveness of phlebotomy as a treatment for transfusion-related iron overload in a cohort childhood cancer survivors.

Design/Method: A retrospective chart review was conducted on childhood cancer survivors who were treated with phlebotomy for iron overload, as assessed by liver iron concentration (LIC) on hepatic R2 MRI and serum ferritin. Follow-up serum ferritin and MRI-based LIC measurements were reviewed to determine the effect of phlebotomy on iron status. Patients were monitored throughout phlebotomy procedures and assessed at each visit for any adverse events.

Results: Five childhood cancer survivors with abnormal LIC (mean initial LIC: 8.36mg/g) and abnormal ferritin (mean initial ferritin: 923.26ug/L) underwent therapeutic phlebotomy via peripheral venipuncture. The average volume phlebotomized was 55.8ml/kg of blood, and all five patients had a reduction in serum ferritin, with a mean final ferritin of 361.34ug/L. Four patients had a decrease in their LIC. One patient was noted to have an increase in LIC, however this patient’s follow-up MRI was done by a different technique at a different site making a direct comparison of MRI results difficult. In terms of adverse events, two patients had transient hypotension during blood removal that responded to intravenous fluids, permitting continued phlebotomy. No patients had long-term side effects or reported adverse events once discharged from the phlebotomy sessions.

Conclusion: Phlebotomy to treat transfusion-related iron overload was effective and well-tolerated in childhood cancer survivors and should be further studied in this population.
MALE FERTILITY, SPERM DNA DAMAGE AND ANEUPLOIDY IN MALE SURVIVORS OF PEDIATRIC HODGKIN’S LYMPHOMA

Amy Lee Chong, Keith Jarvi, Kirk Lo, Ethan Grober, Sergey Moskovtsev, Brendan Mullen, Leia Spencer, David Hodgson, Mark Greenberg, Paul Nathan. The Hospital for Sick Children, Toronto, Ontario, Canada

Background: Current survival rates for Hodgkin’s Lymphoma exceed 90% on contemporary multimodality protocols. Future fertility is a major concern for survivors. Alkylating agents are considered the primary cause of gonadal dysfunction. Treatment may also be associated with high rates of sperm DNA fragmentation.

Objectives: To assess the impact of chemotherapy on sperm quality, DNA damage and aneuploidy in survivors of pediatric Hodgkin’s Lymphoma.

Design/Method: In this cross-sectional study, male Pediatric Hodgkin’s Lymphoma survivors (aged ≥18 years and > 3 years from completion of therapy) treated between 1985-2007 at a single pediatric institution, were recruited from a survivorship clinic. Participants completed the study questionnaire, underwent a urological exam, assessment of sexual hormones and semen analysis. DNA fragmentation/sperm aneuploidy was performed in consenting non-azoospermic males. Cumulative doses of alkylator agents were expressed as tertiles and cyclophosphamide equivalent doses.

Results: Of the 38/49 (76%) Hodgkin’s lymphoma survivors contacted; 15/38 (40%) completed the study requirements. Participants ranged from 21-35 years in age (mean 26 years) with a median time from diagnosis to assessment of 12 years (range 6−20 years). Over two-thirds (10/15; 67%) had stage I/II disease; all participants were treated on alkylator containing regimens. All developed secondary sexual characteristics by 16 years of age (range 11-16 years). Almost half (46%; 7/15) reported at least one symptom on the sexual function/androgen-screening questionnaire. Seven (47%) participants had low serum testosterone levels (median 9nmol/L, range 5-9.9nmol/L); none receive testosterone replacement. On semen analysis 47% (n=7) were normozoospermic, 20% (n=3) oligozoospermic and 33% (n=5) azoospermic. Normozoospermic survivors had a lower mean cumulative alkylator score (2.4 vs. 3.3 and 3.4 for oligozoospermic and azoospermic respectively). Amongst seven samples tested, sperm DNA fragmentation index was normal (<15%) in six normozoospermic survivors and borderline (16%) in the severe oligozoospermia survivor. In four normozoospermic survivors, aneuploidy was slightly elevated (3.46% ± 0.97) but significantly higher in the severe oligozoospermia survivor (11%).

Conclusion: Infertility remains a concern for male Hodgkin’s lymphoma survivors. Of those who retain spermatogenic capacity, there appears to be no long-term risk of increased sperm DNA damage, but the observed increase in the aneuploidy rates requires further evaluation in a larger cohort.

178
CHALLENGES IN THE DIAGNOSIS OF THE ALEUKEMIC PRODROME OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA
Elaine Leung, Mylene Bassal, Luke Shier. Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

Background: Pediatric acute lymphoblastic leukemia (ALL) may present with a myriad of clinical manifestations. In 1-2% of pediatric ALL, an aleukemic prodrome of transient profound peripheral pancytopenia (pre-ALL) precedes overt leukemia. This presentation is often challenging, both from a clinical and a laboratory perspective.

Objectives: To describe the challenges encountered in the clinical and laboratory diagnosis of pediatric ALL presenting as pre-ALL, focusing on morphology and flow immunophenotyping data.

Design/Method: All cases of pre-ALL were reviewed from 2006 – 2013 at a tertiary care pediatric hospital.

Results: Out of 119 new ALL cases, 2 had a pre-ALL presentation (1.7%). Both patients were female, one was 21 months and the other 10 years old at time of presentation. The younger presented with fevers, vulvar ulcers and disseminated pseudomonas bacteremia; the older with a several month history of fatigue and weight loss. Both demonstrated a profound peripheral pancytopenia and absence of, or rare, circulating blasts. Initial bone marrow evaluation in both showed small populations of cells morphologically suspicious for blasts, although benign hematogones with atypical features could not be excluded. Dyserythropoiesis was common to both. Flow immunophenotyping also showed subtle features suspicious for leukemia, but could not definitively identify the cells as lymphoblasts or hematogones. Within weeks, both patients' peripheral blood counts gradually improved. After repeated bone marrow evaluations over the subsequent months, evolution to frank precursor-B lymphoblastic leukemia was confirmed. The time from initial presentation to overt leukemia was 2 – 3 months.

Conclusion: Pre-ALL is an uncommon aleukemic presentation for pediatric ALL and can pose diagnostic challenges. Despite the presence of only a small population of abnormal cells, clues to the diagnosis can be found on both morphology and flow immunophenotyping. Recognition of this entity should prompt close follow-up of any patient presenting with peripheral pancytopenia and even minimal morphologic or flow immunophenotyping abnormalities, to assess for evolution of disease. An improvement in peripheral blood counts may be transient and does not exclude ALL. Consideration should be given to the possibility of pre-ALL in the spectrum of diagnostic investigations that one would order on a patient presenting with unexplained pancytopenia.
INTRATHECAL CYTARABINE AS SUBSTITUTION FOR INTRATHECAL METHOTREXATE IN THE SETTING OF NEUROTOXICITY
Suzanne Lewis, Paul Thomas, Gregory Aune, Chatchawin Assanasen. University of Texas Health Science Center of San Antonio, San Antonio, Texas, United States of America

Background: Intrathecal Methotrexate is a major component of lymphoblastic leukemia therapy. Its use, however, has been associated with significant acute and chronic neurologic toxicities including progressive neurologic and cognitive deterioration. Depending on the amount of exposure the prevalence of MTX neurotoxicity has been estimated between 3-11% of treated children. Alternative intrathecal prophylaxis therapy for ALL patients with CNS toxicities thought to be attributable to IT MTX has not been well studied. One option considered in some institutions is a direct 1:1 substitution of IT Cytarabine for IT MTX utilizing the same age based dosing provided on day 1 of induction therapy.

Objectives: Our objective was to review and analyze the outcomes of patients who received IT AraC after initial toxicity related to IT MTX.

Design/Method: We performed a retrospective chart review of 400 oncology patients treated between 1997 and 2013 at the University of Texas Health Science Center at San Antonio. The medical records for each patient were searched individually for documented CNS toxicity from IT MTX and subsequent initiation of IT Ara C. The records were then reviewed for details of clinical presentation, previous neurologic disease, treatment phase, current disease status and any subsequent complications possibly attributable to AraC.

Results: 14 patients (3.5%) were identified as having experienced a CNS event attributed to IT MTX and were subsequently switched to IT AraC. 10/14 charts were able to be reviewed with none of the patients experiencing any neurotoxic events subsequent to the IT AraC substitution. Eight of the patients completed therapy with AraC as the prophylactic IT agent. Of the eight patients who have completed therapy, seven are in their first clinical remission, with an average of 3.6 years off therapy. One patient developed bone marrow relapse but no evidence of CNS recurrence was identified. Two patients are still receiving chemotherapy, including IT AraC injections without noted complications.

Conclusion: We were unable to identify any new adverse neurological events or CNS recurrence when patients received IT AraC after initial toxicity related to IT MTX. IT AraC appears to be a tolerable substitution for IT methotrexate when necessary. Further investigation regarding its long-term effects is warranted.
ASSESSMENT OF EARLY STEROID RESPONSIVENESS IN CHILDREN WITH T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA - NATIONAL CANCER INSTITUTE- CAIRO UNIVERSITY EXPERIENCE.

Ossama Maher, Ross Cleveland, Yasser Elborai, Hani Hussein, Heba Moussa, Aziza Sedrak, Alaa EL Haddad. National Cancer Institute- Cairo University, Cairo, Egypt

Background: Assessment of early treatment responsiveness is useful in differentiating low and high risk T-Cell Acute Lymphoblastic Leukemia (T-ALL) patients. Initial response to steroids is one of such predictor. Current Children’s Oncology Group (COG) protocols recommend the use of dexamethasone rather than prednisone in treatment of children with ALL based on the fact that dexamethasone has high central nervous system (CNS) penetration and lower incidence of CNS relapse.

Objectives: To assess the impact on survival of early steroid responsiveness in children with T-ALL following one Egyptian institution’s Pediatric Oncology Group (POG) study inspired protocol and to evaluate whether the use of prednisone for the whole period of therapy will be effective in prevention of CNS leukemia.

Design/Method: A prospective analysis of 67 consecutive pediatric patients with newly diagnosed T-ALL treated by the Pediatric Oncology Department at the National Cancer Institute, Cairo University (NCI-Cairo) between November 1, 2004 and August 1, 2008. All patients were treated with a protocol modeled after the POG 9404 study, Arm 4. In brief, NCI-Cairo used an intensive anthracycline-based multidrug regimen and central nervous system (CNS) irradiation (1800 cGy).

Results: Initial response to steroid was assessed in 67 cases. Peripheral blood blasts in 37 cases showed good response to steroid treatment with less than 1,000/µL after 7-day of induction, while 30 cases showed poor steroid response. There was a strong relationship between an early response to steroid and long term survival rates. The 3 years disease free survival (DFS) was 84.7% for patients with good prednisone response, 25.9 % for patients with poor prednisone response (P= 0.02). The 3 year event free survival (EFS) was 80.2% for patients with good prednisone response and 27.5% for patients with poor prednisone response (P < 0.0001). CNS relapse was recorded in 13 cases in the study (19%), 12 of which occurred after cranial irradiation.

Conclusion: Patients with T-ALL with early steroid response demonstrate a better outcome compared to non-responders. The high incidence of CNS relapse supports the use of dexamethasone rather than prednisone due to better CNS penetration. Future studies are needed to determine the preferred glucocorticoid for specific phases of treatment.
Background: Acute myeloid leukemia (AML) continues to have a poor prognosis despite intensified therapy. Considerable work is currently being done to identify novel therapeutic targets and small molecule inhibitors for the treatment of AML. Internal tandem duplication (ITD) mutations of the FLT3 tyrosine kinase have been identified as prevalent genetic changes in approximately 30% of AML patients and are associated with a poorer prognosis. Here we present novel small molecule inhibitors with high specificity to FLT3 that show pre-clinical efficacy and prolong survival in a mouse xenograft model.

Objectives: Characterize the efficacy of novel FLT3 inhibitors in cell lines expressing the FLT3-ITD mutation and in mouse xenograft models of FLT3-ITD AML.

Design/Method: Two cell lines known to express the FLT3-ITD mutation (MV4;11 and Molm13/14) were treated with the tyrosine kinase inhibitors (TKIs). Inhibition of downstream FLT3 signaling was evaluated via immunoblotting. Apoptosis was evaluated with flow cytometry after staining with Yo-Pro 1 iodide and propidium iodide. Cell proliferation was assessed using soft agar. NSG mice were injected with a FLT3-ITD AML patient sample and treated daily via oral gavage with either a TKI or vehicle (saline).

Results: Treatment of FLT3-ITD cell lines with nanomolar concentrations (25-100nM) of TKI led to decreased phosphorylation of FLT3, as well as important downstream signaling molecules, AKT, ERK1/2, and STAT5. After TKI treatment for 72 hours, these cell lines demonstrated greater than 10-fold induction of apoptosis (5.4±1.2%, treatment with vehicle, versus 83.4±7%, treatment with 100nM TKI, p <0.0001). Colony formation in soft agar was inhibited 5-10 fold after treatment with TKI for 14 days (for Molm13, mean of 17±4 CFU with vehicle, versus 1.5±0.7 with 25nM TKI; for MV4;11, mean of 31±9 CFU with vehicle, versus 2±1 with 25nM TKI, p<0.01). Additionally, once daily TKI treatment prolonged survival in a FLT3-ITD+ AML patient sample xenograft model (median survival 23 days with vehicle, versus 110 days with TKI, p<0.01).

Conclusion: We have characterized novel FLT3 inhibitors, which inhibit phosphorylation of FLT3, abrogate signaling through FLT3-dependent pathways, significantly induce apoptosis and inhibit proliferation in FLT3-ITD AML cell lines. Treatment with TKI prolongs survival in a patient sample mouse xenograft model.
CHEMOTHERAPY RESISTANT HISTIOCYTIC SARCOMA RESPONSIVE TO THALIDOMIDE AND LENALIDOMIDE
Deanna Mitchell, Matthew Steensma. Helen DeVos Children's Hospital, Grand Rapids, Michigan, United States of America

Background: Histiocytic sarcoma (HS) is an exceedingly rare malignancy in childhood and there is currently no standard approach to treatment. Most reports have utilized multi-agent chemotherapy and bone marrow transplant, albeit with poor outcomes. Three patients have been reported in the literature with partial responses to thalidomide; an agent that is better tolerated than high dose chemotherapy.

Objectives: We present a case of a patient with metastatic HS, refractory to multiple chemotherapy agents who had a dramatic response to thalidomide, followed by a sustained complete response with lenalidomide, an agent not previously reported in HS.

Design/Method: This previously healthy 13 year old male presented with a 3 month history of worsening iliac pain and weight loss. A pelvic MRI revealed a 5.5 X 4.5 cm destructive lesion of his left iliac crest. A biopsy revealed a histiocytic sarcoma with positive staining for CD68 and CD 163. A PET scan revealed metastatic disease at T1 and L4 vertebral bodies, 6th and 7th ribs, right iliac crest, femur, and left iliac crest lesion. Bone marrow biopsies were positive. The patient was treated with Ifosfamide, Carboplatin, Etoposide; followed by Vincristine, Doxorubicin, Cyclophosphamide and Prednisone, with progression of pain. PET scan showed no improvement. Therapy was changed to Vinorelbine, Ifosfamide, Bortezomib for 2 cycles with no response.

Results: Given his chemotherapy resistance, the patient was treated with thalidomide at 150 mg/day. His pain improved within one month of treatment. PET scan after 3 months revealed decreased avidity in left iliac bone and ribs with resolution at other sites. However, the patient developed significant depression. Thalidomide was held and reintroduced. Given concern about his mental health, thalidomide was discontinued after 8 months of treatment. One month later lenalidomide was started at 10 mg/day. Lenalidomide has not been previously reported in the literature as therapy for HS. Three months later the PET scan showed a complete response with no evidence of metabolically active disease. The patient remains on lenalidomide in CR with no toxicity for ten months.

Conclusion: This case confirms that thalidomide, and now lenalidomide, remain viable alternatives to conventional chemotherapies for histiocytic sarcoma.
ENSURING OPTIMAL THERAPY: MAINTAINING ANTHRACYCLINE TREATMENT AFTER DECLINE IN EJECTION FRACTION WITH SEPSIS.
April Morrison, Priscila Badia, Guillermo DeAngulo. Miami Children's Hospital, Miami, Florida, United States of America

Background: Cardiac dysfunction, as evidenced by decreased ejection fraction on echocardiogram, is a well-known complication of sepsis. Functional rather than structural heart alterations are frequently seen, causing a reversible cardiac dysfunction. It is also a well-described phenomenon that anthracyclines can induce cardiotoxicity, which may affect a patient’s survival. However, removing anthracyclines from a protocol also affects survival. It is important to recognize cardiac dysfunction that is secondary to sepsis in patients treated with cardiotoxic chemotherapy in order to prevent decreasing or discontinuing treatment that will alter prognosis.

Objectives: Describe three patients treated with anthracyclines with a decreased ejection fraction secondary to sepsis and the subsequent normalization of cardiac function after sepsis.

Design/Method: Retrospective review of three patients treated with anthracyclines and culture proven bacteremia with sepsis and concomitant decline in ejection fraction by echocardiogram, followed by continued administration of anthracyclines.

Results: Three patients ages 10, 20 and 23 years of age with leukemia treated with anthracycline had episodes of sepsis with positive blood cultures. During the episodes of sepsis, these patients were found to have cardiac dysfunction with accompanying decrease in ejection fraction from baseline, demonstrating ejection fraction (EF) ranging from 31-48%. Two patients were treated with cardiac medications including ACE inhibitors for a short period of time, with no modification to chemotherapeutic treatment. Both patients’ cardiac function normalized and ejection fraction returned to baseline. The other patient demonstrated normalization of cardiac function after sepsis, however this patient received no more anthracyclines due to maximum dose reached. Patients continue to be monitored with regularly scheduled echocardiograms. No clinical cardiac dysfunction is present with any of the three patients.

Conclusion: Anthracyclines are an important part of chemotherapy for patients with leukemia. In order to maintain optimal therapy it is important to differentiate cardiotoxicity due to anthracyclines or secondary to sepsis. We report on three patients that had a significant decline in cardiac function due to sepsis and continued with scheduled anthracycline therapy without worsening of cardiac function.
NOVEL ANTI-LEUKEMIA THERAPY WITH AN ISATIN DERIVATIVE: DUAL INHIBITION OF TUBULIN POLYMERIZATION AND AKT PATHWAY
Sunil Muthusami, Mansi Sachdev, Krishnegowda Gowdahalli, Chunhua Song, Shantu Amin, Sinisa Dovat. Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania, United States of America

Background: The currently used antitumor drugs, vinca alkaloids and taxanes, inhibit mitosis by targeting microtubules. The major drawback of these agents is their limited efficacy as single agents, prompting the quest for additional targets/agents with enhanced therapeutic potency, fewer side effects and decreased drug resistance. Recent studies have demonstrated the superiority of dibromo-isatin over other isatins in inhibiting microtubule assembly in the U937 (human leukemic monocyte lymphoma) cell line. Isatin-11, a novel dibromo-isatin created by Dr. Amin’s lab has a thiocyanate conjugation, which augments the microtubule inhibition with Akt inhibitory activity. In solid tumor cell lines, Isatin-11 demonstrated greater inhibition of tubulin polymerization compared with vinblastine, and demonstrated significant AKT inhibition. The PI3K/AKT/mTOR pathway is often abnormally activated in childhood leukemia due to constitutive activation of AKT and provides a rationale to target this pathway. Inhibition of AKT results in apoptosis of cancer cells with decreased resistance to chemotherapy. We hypothesized that by virtue of inhibiting microtubules and inhibiting the AKT pathway, Isatin-11 has considerable potential for leukemia treatment.

Objectives: We aimed to determine the potency of Isatin-11 and elucidate its mechanism of action by testing a broad panel of human leukemia and lymphoma cell lines.

Design/Method: We performed cytotoxicity assays to quantify the therapeutic effect of Isatin-11 on acute lymphoblastic leukemia, acute myeloid leukemia, T-cell ALL and lymphoma cell lines. To demonstrate apoptosis, Annexin V/7-AAD staining was done at 24 and 48 hours post treatment.

Results: Isatin-11 treated leukemia cell lines demonstrated a significant dose-dependent cytotoxicity and our observed IC50 values were: 0.2 μM for Nalm-6 (B-ALL), CEM (T-cell ALL), HL-60, NB4 (APML) and Ramos (Burkitt's lymphoma) cell lines; 0.5 μM for MOLT-4 (T-cell ALL) and 1 μM for U937 (AML). The Annexin V/7-AAD staining demonstrated significant apoptosis in all cell lines at 24 and 48 hours.

Conclusion: These results confirm the efficacy of Isatin-11 on leukemia cell lines and its potency at low micromolar concentrations. With these encouraging results demonstrating significant apoptosis, additional studies to elaborate the mechanism of action of this drug are presently underway. This data shows promise for further testing of this drug in leukemia.
EXPRESSION OF CD36 AND THE PRESENCE OF CYTOPLASMIC GRANULES IN BLASTS PREDICTS POOR PROGNOSIS IN CHILDREN WITH B-LYMPHOBLASTIC LEUKEMIA
Joanna Newton, John Horan, Todd Cooper, Michael Rossi, Sunita Park. Children's Healthcare of Atlanta, Emory University, Atlanta, Georgia, United States of America

Background: CD36, a marker expressed on monocytes and erythroid cells, is rarely expressed on blasts in childhood B-lymphoblastic leukemia (B-LL). We have observed that these CD36+ blasts often have cytoplasmic granules (CG), also a rare finding, and that patients with CD36+/CG+ B-LL seem to have a worse outcome.

Objectives: To describe the patient and disease characteristics and treatment outcomes in CD36+/CG+ B-LL.

Design/Method: We performed an IRB-approved retrospective review of B-LL cases diagnosed between September, 2008 and April, 2013 at our institution. To be eligible for this analysis, patients had to be less than 21 years old and have had a marrow aspirate at initial diagnosis demonstrating moderately bright CD36 expression on at least 5% of blasts. A pediatric hematopathologist reviewed smears for the presence of cytoplasmic granules. We abstracted data on patients, disease, and treatment from patients’ charts.

Results: We identified 20 cases of CD36+ B-LL. 14 were male, 10 Hispanic, 3 African American and 6 White. 11 were less than 10 YO. 11 patients met NCI high-risk criteria. 11 cases had cytogenetic abnormalities, but only 5 had risk defining abnormalities (1 double trisomy 4 and 10, 1 iAMP21, 3 Ph+). On average, CD36 was expressed on 26.92% (+/-19.22) of blasts. 10 patients had blasts with cytoplasmic granules. Treatment varied according to risk classification. Induction therapy failed in 5 cases; in another 10, there was minimal residual disease (≥0.01%) at day 29 of induction. 4 patients underwent hematopoietic stem cell transplantation in 1st complete remission. Outcome: With a median length of follow up 22 months, 3-year EFS was 49.45±14.01 for the entire cohort, 72±17.8 for patients whose blasts were CD36+/CG- and 24±18.85 for those whose blasts were CD36+/CG+ (p=0.033).

Conclusion: B-LL that expresses CD36 and contains cytoplasmic granules in pediatric patients appears to be associated with a poor prognosis. This needs to be confirmed in a larger sample. In addition, we are presently performing RNA sequencing on a subset of these samples to identify differences in gene expression that may account for the poor prognosis.
**TSLP-REGULATED GENE EXPRESSION SIGNATURE IN A PRECLINICAL MODEL OF CRLF2 B-ALL**

Shannalee Martinez, Olivia Francis, Ruijun Su, Ineavely Baez, Ross Fisher, Christopher Morris, Xiaobing Zhang, Valeri Filippov, Sinisa Dovat, Kimberly Payne. Loma Linda University, Loma Linda, California, United States of America

**Background:** Genetic defects leading to overexpression of CRLF2 occur in approximately half of children with high-risk “Ph-like” B cell acute lymphoblastic leukemia (B-ALL). This defect is 5 times more common in Hispanic children than others making it a significant biological component of pediatric cancer health disparities. CRLF2, together with the IL-7Rα, forms a receptor complex that is activated by the cytokine TSLP to induce JAK2-STAT5 phosphorylation in normal cells.

**Objectives:** Our goal was to identify the in vivo effects of TSLP on gene expression in a human-mouse xenograft model of CRLF2 B-ALL. However, mouse TSLP is species-specific and does not induce human CRLF2 signaling. We engineered immune-deficient NOD/SCID IL-2Rγ null (NSG) mice to express human TSLP (hTSLP+ mice), as well as control mice that lack the human TSLP cytokine (hTSLP– mice). We used this hTSLP+/– xenograft model system to evaluate the in vivo effects of TSLP on gene expression in primary CRLF2 B-ALL cells.

**Design/Method:** hTSLP+ and hTSLP– mice were transplanted with primary CRLF2 B-ALL cells from a Hispanic patient. Transplanted mice were euthanized at 10 weeks and bone marrow (BM) was harvested for whole genome microarray to evaluate in vivo effects of hTSLP on gene expression.

**Results:** We identified 280 genes that are upregulated and 281 genes that are downregulated (> 2 fold; p<.05) in vivo in leukemia cells from hTSLP+ as compared to hTSLP– mice. Ingenuity Pathway Analysis of changes in gene expression identified “Cell Death and Survival” as the “Molecular and Cellular Function” most impacted by TSLP in vivo (34 genes differentially regulated). Changes in whole genome expression following in vitro TSLP stimulation post-xenograft expansion identified ~1/3 fewer gene targets in primary CRLF2 B-ALL cells from hTSLP– mice as compared to cells from hTSLP+ mice.

**Conclusion:** These data suggest that TSLP-induced signals may contribute to leukemogenesis in vivo by upregulating genes involved in CRLF2 B-ALL cell survival. Current studies are aimed at identifying TSLP-regulated genes that can be therapeutically targeted as a part of combination therapy to successfully treat CRLF2 B-ALL and reduce the cancer health disparities for children with this disease.
GENOTYPING OF METHYLENE TETRAHYDROFOLATE REDUCTASE AND REDUCED FOLATE CARRIER GENES AND RISK OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

Nermin Raafat, Osama Elsafy, Tamer Hassan, Amal Gharib. Medical College, Zagazig University, Zagazig, Egypt

**Background:** Childhood acute lymphoblastic leukemia (ALL) is the most common malignancy affecting children, constituting about 30% of all cancers among children. It constitutes about 75% of pediatric acute leukemia with peak incidence between ages 3 and 4. Although significant improvements in both ALL diagnosis and treatment have been made over the past decades, the etiology of most cases of ALL remains unknown due to probable multifactorial mechanisms of pathogenesis. The assertion that ALL may have a genetic basis has long been pursued through association studies based on candidate genes as folate metabolism. Polymorphisms in folate pathway genes may influence the susceptibility to acute lymphoblastic leukemia. Increased risk of ALL was observed in reduced folate carrier protein (RFC1) 80GA variant carriers. A 1.4-fold reduction in ALL risk was observed for carriers of the methyl tetrahydrofolate reductase (MTHFR) 677T allele.

**Objectives:** this study was carried out to evaluate the contribution of MTHFR C677T and RFC1 80GA gene polymorphism and susceptibility of childhood acute lymphoblastic leukemia.

**Design/Method:** DNA was isolated from 100 children, divided into 2 groups, group I included 60 pediatric ALL patients and group II included 40 healthy donors as controls. Genotyping of MTHFR C677T and RFC1 G80A was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using Hinf I and HhaI restriction endonuclease respectively.

**Results:** MTHFR 677T allele carriers were significantly lower in ALL cases (45%) than healthy controls (57%). Reduction in ALL risk was observed for heterozygous (CT) or homozygous (TT) carriers of the MTHFR 677T allele (OR 0.7; 95% CI, 0.9-1.5; P < 0.002). RFC1 80A allelic carriers have an increased susceptibility to ALL. Risk was increased 1.8 times (OR 3.4; 95% CI, 1.5-4.8 ; P .02) for A-allelic carriers.

**Conclusion:** our data suggested that the MTHFR gene variants are associated with decreased ALL rate and risk. The reduced risk associated with the MTHFR C677T polymorphisms may be the result of changed intracellular folate redistribution. the results of our study also supported the suggestion that RFC1 G80A single nucleotide polymorphism contributed to increase the susceptibility and the development of pediatric ALL.
SELENIUM-CONTAINING HISTONE DEACETYLASE INHIBITORS (HDACi) – NOVEL THERAPEUTIC APPROACH FOR LEUKEMIA TREATMENT
Mansi Sachdev, Dhimant Desai, Sunil Muthusami, Chandrika Gowda, Chunhua Song, Shantu Amin, Sinisa Dovat. Penn State Hershey Medical Center, Hershey, Pennsylvania, United States of America

Background: Even though tremendous advances have been made in the treatment of leukemia that have resulted in better survival of patients with the disease, high-risk and relapsed leukemia continues to pose clinical challenge. Hence, there is a need for the development of novel, more potent therapeutic modalities.

Objectives: Targeted therapy with various types of histone deacetylase inhibitors (HDACi) have shown therapeutic efficacy in a wide range of malignancies ranging from hematologic malignancies to solid tumors, with minimal side effects. Dr. Amin’s group recently reported the development of potent, novel, selenium-containing HDACi (SelSA-1 and 2), which have shown efficacy against Hodgkin’s lymphoma, lung cancer and melanoma cell lines. We, therefore, expanded the efficacy studies of these selenium-containing HDACi to include a wide range of hematopoietic malignancies and also address the drug effects on cellular functions.

Design/Method: Therapeutic efficacy of two novel HDACi – SelSA-1 and SelSA-2 were tested on acute lymphoblastic leukemia, acute myelogenous leukemia and non-Hodgkin’s B cell lymphoma. Results: Cell proliferation assays demonstrated sharp dose-dependent cytotoxic effects in all the above cell lines at 96-hours post-treatment. Quantitative analysis showed that SelSA-1 and SelSA-2 have distinct effects in different types of hematopoietic malignancies. In non-Hodgkin’s lymphoma and in T-cell acute lymphoblastic leukemia (T-ALL), both SelSA-1 and 2 have similar therapeutic activity with IC50 of 1-2uM and 1uM, respectively. SelSA-1 has superior therapeutic activity compared to SelSA2 in B-cell acute lymphoblastic leukemia (B-ALL) with IC50 = 0.2uM vs. 1.25uM, respectively. In acute promyelocytic leukemia (APML) without t(15;17) translocation, SelSA-1 was found to be superior to SelSA-2 with an IC50 of 0.25uM and 1uM, respectively, whereas APML with t(15;17) translocation showed similar sensitivity to both the compounds (IC50 = 1-2uM). Cell cycle analysis (via flow cytometry) revealed that these compounds induce G1-cell cycle arrest in leukemia cells. Preliminary data suggests that both these selenium-containing HDACi have a synergistic effect when combined with other standard chemotherapeutic agents that induce DNA-damage.

Conclusion: This preliminary data demonstrates the effectiveness of the two selenium-containing analogs of SAHA, SelSA-1 and 2, on multiple leukemia cell lines. Additional studies to identify detailed mechanistic pathways of these drugs on cellular function are currently underway.
HYPOGAMMAGLOBULINEMIA IN PEDIATRIC PATIENTS WITH ALL
Jeffrey Schwartz, Li Xie, Eric Sandler, Nemours Children's Clinic, Pensacola, Florida, United States of America

**Background:** Pediatric oncology patients are immunocompromised during treatment and at high risk for serious infections. Previous studies have shown IgG concentrations to be low during treatment in select populations and specific vaccine antibodies to be low in patients with acute lymphoblastic leukemia (ALL). There are no reports of antibody levels in pediatric patients with cancer treated with current, more intensive therapy.

**Objectives:** The primary aim of the current study was to determine the prevalence of hypogammaglobulinemia in patients undergoing maintenance chemotherapy for ALL. The secondary aim was to identify correlations between hypogammaglobulinemia and clinical outcomes.

**Design/Method:** This study included pediatric ALL patients in maintenance therapy without a known or suspected immune disorder. For the purposes of this study, hypogammaglobulinemia was defined as a value less than 450 mg/dL based on age-based reference ranges for IgG levels and published thresholds for IVIG infusion. IVIG administration was left to the discretion of the treating physician and was not a required intervention. Demographics, lab data, and clinical events (chemotherapy interruption or hospitalization for fever/neutropenia) were collected at baseline and every three months for four total time points.

**Results:** Thirty-five patients, ages 2 – 20 years, were enrolled. There were 57 episodes of hypogammaglobulinemia with 63% of patients having at least one episode and 43% having more than one episode. There were 39 clinical events and 46% of these were preceded by an episode of hypogammaglobulinemia although this association did not reach statistical significance. IVIG was administered following 54% of hypogammaglobulinemia episodes but did not have a statistically significant effect on clinical events.

**Conclusion:** Hypogammaglobulinemia occurred in over half of the patients in this study. Due to the small numbers of the study, it was not possible to demonstrate a significant statistical association between clinical events and hypogammaglobulinemia or IVIG administration. This study suggests that IgG levels are frequently low in patients with ALL in maintenance therapy and should be monitored regularly with consideration given to IVIG repletion. Further study on a larger scale is justified.

Supported by a Hope on Wheels Hyundai Scholar Grant.
PEDIATRIC OVARIAN TISSUE REMOVED FOR CRYOPRESERVATION CONTAINS FOLLICLES IRRESPECTIVE OF AGE, DISEASE DIAGNOSIS, TREATMENT HISTORY, and SPECIMEN PROCESSING METHOD
Francesca Duncan, Sherif Badawy, Katy Ebbert, Megan Romero, Clarisa Gracia, Jill Ginsberg, Barbara Lockart, Yasmin Gosiengfiao, Teresa Woodruff. Feinberg School of Medicine, Northwestern University, Chicago, Illinois, United States of America

Background: Fertility preservation in a female pediatric population is challenging because standard assisted reproductive technologies may not be possible due to pre-menarchal status or the inability to delay cancer treatment. For these patients, ovarian tissue cryopreservation (OTC) to preserve the primordial follicles within the ovarian cortex may be the only option. This tissue can potentially be used for transplantation to restore endocrine function and/or fertility.

Objectives: In this study, we determined whether follicles were present in histological samples of ovarian tissue from 25 pediatric participants (under the age of 18) undergoing OTC. These participants represented a diverse group of patients in terms of age, disease diagnosis, treatment history, and specimen processing methods.

Design/Method: We obtained ovarian research tissue from the Oncofertility Consortium National Physicians Cooperative (NPC) under IRB-approved protocols. Eighty percent of the ovarian tissue removed was cryopreserved for future clinical use while the remaining 20% was designated for research after informed consent. A standard histological analysis was performed using the research tissue to document whether ovarian follicles were present or absent.

Results: Participants ranged in age from 2 to 17 years (mean: 12.5 ± 0.93 years) and exhibited a wide distribution of both cancer and non-cancer diagnoses, including solid tumors (24%), leukemias/lymphomas/MDS (56%), and hematological disorders (16%). Fifty two percent of the participants had received previous therapy (surgery, chemotherapy, radiation) at the time of OTC. In addition, 40% of the tissue was from a cortical biopsy whereas 60% was from a whole ovary. Twenty eight percent of the ovarian tissue was from local sites and processed immediately, whereas 72% of the tissue was removed at nationwide sites and maintained at 4°C for up to 24 hours prior to use for research. Despite these variables, preantral follicles were observed in ovarian tissue from all participants.

Conclusion: These findings are promising for fertility preservation using OTC and suggest that ovarian tissue from a pediatric population is likely to contain follicles regardless of age, disease diagnosis, treatment history, and specimen processing methods. Future studies are needed to investigate how such factors impact follicle quality and the ovarian environment.
LABORATORY ORDERING PATTERNS FOR COAGULATION TESTING IN A PEDIATRIC TEACHING HOSPITAL
Ibrahim Ghemlas, Elaine Leung, Nick Barrowman. Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

Background: The utilization of diagnostic laboratory tests has increased around the world. It constitutes approximately 5% of total health care costs. The appropriate utilization of laboratory tests is necessary for optimal patient care and to reduce unnecessary costs.

Objectives: To evaluate the clinical appropriateness and accuracy of orders for routine coagulation tests (INR, aPTT, and Fibrinogen) in a tertiary care pediatric teaching hospital.

Design/Method: Charts were reviewed retrospectively on all patients who had routine coagulation testing performed in the Emergency Room, Medical Daycare Unit, and an inpatient ward over a one-month period. We looked at the written physician order, the paper laboratory requisition, and the tests that were actually performed by the lab. Discordances between the order and requisition, and requisitions and tests performed were noted. The appropriateness of each order was then assessed based on the clinical situation and determined to be either: 1) appropriate; 2) probably appropriate; 3) not appropriate; and 4) elements of testing likely appropriate.

Results: 182 patients were included. In 38% of orders there was a discrepancy between the written physician order and the transcribed paper requisition. With respect to the appropriateness of the orders: 28% were definitely appropriate to the clinical situation, 31% were probably appropriate, and 26% were not appropriate. Of the 47 patients who had “inappropriate” testing performed, 57.4% had testing without clear indication, 27.6% had testing as a screen for a bleeding disorder without a significant personal history/family history of bleeding or when there was already an obvious reason for bleeding, and in 15% the testing was repeated unnecessarily or with duplication.

Conclusion: Our study showed that in a significant proportion of orders there is a discrepancy between the physician written order and the transcribed requisition forms. 26% of the coagulation tests were ordered inappropriately. Coagulation testing was often done as part of treatment or triage protocols (e.g. fever and neutropenia management, routine trauma blood work). Our hospital will be implementing a Physician Order Entry ordering system (CPOE) in the near future; however this will not address inappropriate orders. Increased education is required regarding appropriate test utilization.
IMPLEMENTATION AND FINDINGS OF A STANDARDIZED CLINICAL ASSESSMENT AND MANAGEMENT PLAN (SCAMP) FOR NEWLY DIAGNOSED PEDIATRIC IMMUNE THROMBOCYTOPENIA (ITP)

Rachael Grace, Wen Tao, Rose Hamershock, Dorothy Miller, Lauren Kerr, Dionne Graham, Ellis Neufeld. Boston Children's Hospital, Boston, Massachusetts, United States of America

Background: Practice variation exists in the diagnosis and management of newly diagnosed pediatric ITP. SCAMPs can be valuable to decrease practice variation and resource utilization and learn from outcomes and deviations to improve practice.

Objectives: To describe the implementation and findings from a SCAMP utilized for newly diagnosed pediatric ITP patients at Boston Children’s Hospital.

Design/Method: The SCAMP was developed by local ITP experts and included a patient management guideline and plausible outcomes for the group of patients enrolled. Deviations were encouraged. Eligibility included: ITP/Evans, platelet ≤30 kcells/μL, duration <2 weeks, no prior treatment, and age 1-16 years. Recommended initial labs include: CBC, differential, reticulocyte count, blood smear review, direct coombs, uric acid, and blood type. Bleeding grade was assigned using the Buchanan & Adix score. In patients with grade 3 or higher bleeding, the guidelines recommended outpatient management with IVIG or steroids. At each visit, clinicians completed data forms including reasons for any deviations from the guideline.

Results: Over 14 months, 32 newly diagnosed ITP patients were followed prospectively using the SCAMP. 43.8% were female; median age was 4.5 y (1.4-13.8 y). Ordered lab tests generally followed the SCAMP. 100% of patients had a bleeding score assigned at each clinical visit. 19/32 (60%) had grade 3 bleeding and pharmacologic treatment at presentation. Of 19 treated, 18 (95%) were treated with steroids; reasons for choosing steroids included: ease (100%), side effect profile (33%), and cost (28%). Of 13 patients observed at presentation, none required future treatment or had bleeding complications.

Conclusion: A SCAMP was successfully implemented within the clinical practice of pediatric ITP patients at a large academic center. Although equipoise led to the option of treatment with steroids or IVIG for bleeding, steroids were selected in almost all patients as first-line treatment. A higher than expected frequency of grade 3 bleeding was reported at diagnosis, leading to fewer patients observed. Given these findings, the SCAMP will be modified to recommend steroids as first-line pharmacologic treatment; data forms will include bleeding symptoms leading to treatment decisions and give guidance on patients with grade 3 bleeding who might be observed. (Buchanan, J Pediatr, 2002).
REDUCTION IN TIME TO ANTIBIOTICS FOR NEW FEVER IN NEUTROPENIC PEDIATRIC ONCOLOGY INPATIENTS

Adam Green, Joanna Yi, Natalie Bezler, Yana Pikman, Venee Tubman, Esther Obeng, Lisa Morrissey, Teresa O'Neil, Robert Mersereau, Amy Billett. Dana-Farber/Boston Children’s Cancer and Blood Disorders Center, Boston, Massachusetts, United States of America

Background: Fever and neutropenia in childhood cancer is a medical emergency requiring rapid administration of antibiotics to prevent morbidity and mortality from serious bacterial infections. Prior quality improvement initiatives demonstrated reduction in time to antibiotics in emergency departments, but the issue has received less attention in the inpatient setting.

Objectives: To increase the proportion of neutropenic pediatric oncology inpatients receiving antibiotics within 60 minutes of new fever.

Design/Method: Involved staff was interviewed to define steps from fever documentation to antibiotic administration. Time points for each step were collected through chart review prospectively over a three month period. Process improvements included adding fever plan documentation to the daily rounds checklist, encouraging documentation of a fever plan in the attending daily note, adding the topic to resident orientation, and increasing engagement by randomly rewarding participating unit staff in all disciplines.

Results: The proportion of patients receiving antibiotics within 60 minutes increased from 44% during the three months prior to intervention to 54% during the study period and 71% six months later. During the study, the mean time to antibiotics was significantly shorter in cases with a fever plan documented in the note the day of the fever (57 min, n=8) than in those with no plan documented (121 min, n=3) (p=0.00005).

Conclusion: Multiple process improvements, including focus on a clear antibiotic plan for new fever in neutropenic patients, correlated with a reduced time from fever measurement to antibiotic administration.
ORGANISMS RESPONSIBLE FOR CENTRAL LINE-ASSOCIATED BLOODSTREAM INFECTIONS IN HOSPITALIZED AND AMBULATORY PEDIATRIC HEMATOLOGY/ONCOLOGY PATIENTS

Jeffrey Hord, John Lawlor. Children's Hospital Association Hematology/Oncology QTN, Alexandria, Virginia, United States of America

**Background:** Central line-associated bloodstream infections (CLABSI) are a significant cause of morbidity and mortality in the pediatric hematology/oncology (PHO) population. The few published studies describing the epidemiology of CLABSI in this patient population are limited by small sample size, varying definitions of CLABSI, and lack of data from the ambulatory setting.

**Objectives:** To determine the distribution of organisms identified as causing CLABSI’s associated with temporary central lines (temp) and permanent central lines (perm) in PHO patients in both the hospital and the ambulatory setting.

**Design/Method:** The Children’s Hospital Association Hematology/Oncology Quality Transformation Network (CHA QTN) consists of 40 PHO/transplant units working together to reduce CLABSI among PHO patients through standardizing best practices in line maintenance. Data from a subset of 16 centers who voluntarily submitted line days segregated by line type (temp and perm) along with CLABSI data between May 2012 and October 2013 was analyzed.

**Results:** The distribution of infectious organisms responsible for CLABSI separated by line type (temp or perm) and by setting (inpatient=inpt or ambulatory=amb) is recorded in Table 1.

**Conclusion:** The general distribution of organisms was similar for temp and perm lines in hospitalized patients with a greater proportion of gram positive organisms isolated compared to gram negative organisms (ratio=1.64). There were approximately equal proportions of gram negative and gram positive organisms associated with CLABSI in the ambulatory setting.

<table>
<thead>
<tr>
<th></th>
<th>Gram (-)</th>
<th>Gram (+)</th>
<th>Yeast/Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpt Temp</td>
<td>18/48 (37%)</td>
<td>27/48 (56%)</td>
<td>3/48 (6%)</td>
</tr>
<tr>
<td>Inpt Perm</td>
<td>66/207 (32%)</td>
<td>111/207 (54%)</td>
<td>30/207 (14%)</td>
</tr>
<tr>
<td>Amb Temp</td>
<td>39/65 (60%)</td>
<td>20/65 (31%)</td>
<td>6/65 (10%)</td>
</tr>
<tr>
<td>Amb Perm</td>
<td>181/424 (43%)</td>
<td>200/424 (47%)</td>
<td>43/424 (11%)</td>
</tr>
</tbody>
</table>
CHEMOTHERAPY DOSING FOR PAEDIATRIC PATIENTS ON ECMO
Kathryn Hollis, Serina Patel, Donna Johnston. Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

Background: Literature exists for the pharmacokinetics and pharmacodynamics of several antibiotics, sedatives and analgesic medications being utilized during extracorporeal membrane oxygenation (ECMO); however there is minimal literature published to help with the dosing of chemotherapy for patients on ECMO.

Objectives: We report a case of dose adjustment and administration of chemotherapy in a pediatric patient diagnosed with acute myeloid leukemia (AML) requiring ECMO for acute respiratory failure.

Design/Method: Case report.

Results: A 5-year old boy was transferred to our institution after an initial presentation of symptoms associated with pneumonia. Subsequent blood work revealed anemia, thrombocytopenia, neutropenia and peripheral blasts. Peripheral blood was sent for flow cytometry concluding a diagnosis of AML, which was later confirmed with a diagnostic bone marrow aspirate. The patient was subsequently transferred to the intensive care unit due to declining clinical status. He was intubated with subsequent initiation of ECMO therapy after a bradycardic and hypoxic arrest. Pulmonary inflammation was deemed to be in part secondary to leukemic process therefore the decision was made to initiate chemotherapy for AML. Due to lack of published literature regarding the pharmacokinetics and pharmacodynamics of administration of chemotherapy with ECMO, extensive consultation with colleagues experienced with ECMO and pharmacotherapy resulted in dose adjustment to account for the ECMO circuit. The adjustment resulted in a 25% increase in chemotherapy dosing. The patient remained on ECMO and received 3 days of chemotherapy prior to removal of life-sustaining therapies due to declining neurologic status indicative of intracranial bleed and furthermore herniation.

Conclusion: More experience and published literature on the administration of chemotherapy and ECMO simultaneously are required to help with the guidance and dose adjustment for patients requiring both life saving modalities.
USING A TOKEN ECONOMY TO IMPROVE THE BMT EXPERIENCE FOR PATIENTS, FAMILIES, AND STAFF
Ronald Jones. Children's Mercy Hospital, Kansas City, Missouri, United States of America

**Background:** Research in cognitive behavioral psychology has proven the token economy as an effective method to change behavior. Cooperation by the patient and caregiver are required to minimize risk and assure successful outcome in BMT.

**Objectives:** Bone marrow transplant is a grueling, lengthy hospital experience for children and their parents. Power struggles often arise between children and parents and hospital staff. There is a need to improve patient compliance without coaxing and threats of punishment that add stress to a time-critical, tense situation.

**Design/Method:** A token economy was created using 1, 5, and 10 dollar bills personalized into BMT Bucks by replacing the president's portrait with a photo of the patient. The patient could earn BMT Bucks by cooperating with daily hospital tasks and routine: vitals, taking medicine on time, daily showers, brushing teeth, physical exams, permitting unpleasant procedures such as dressing changes, etc. A chart posted near the bed listed payments for specific tasks and documented task completion. Patients stored their BMT Bucks at the bedside to show family and staff what they had earned. Each week, Child Life staff would bring items uniquely desired by that patient for purchase using the BMT Bucks. The average cost for items purchased during a 4-8 week inpatient stay was $150.00; paid for with a grant from a children's cancer support group.

**Results:** Changes in the emotional atmosphere of the BMT Unit were immediate and dramatic. What had been a stressful environment became a positive one where the children themselves expressed pride in their accomplishments. Although initially designed as a pilot study, nursing staff and parents were insistent on continuing the BMT Bucks program.

**Conclusion:** A controlled research project could provide objective data to convince other BMT Units to set up their own token economy systems. Such research may reveal what we currently suspect, that not only is the experience enhanced, but that by improving compliance, outcomes may also be improved.
THE UTILITY OF PERIPHERAL BLOOD CULTURES IN FEBRILE PEDIATRIC ONCOLOGY PATIENTS

Dana Leblanc, Nicholas Bartel, Cruz Velasco-Gonzales, Lolie Yu. LSUHSC/Children's Hospital, New Orleans, Louisiana, United States of America

Background: The question of clinical benefit of obtaining peripheral blood cultures in the evaluation of febrile oncology and/or hematopoietic stem cell transplant (HSCT) patients with central venous lines (CVL) remains unanswered. There is limited data on this topic among the pediatric population in the scientific literature.

Objectives: Our primary objective was to examine the incidence of true blood stream infections (BSI) detected only by peripheral culture. Our secondary objectives were to document the incidence of any positive blood cultures in febrile oncology and/or HSCT patients with CVL, to assess the rate of probable contaminants detected in peripheral cultures, and to examine the relationship of bacteremia with other variables including neutropenia, patient age and type of malignancy.

Design/Method: A retrospective chart review was conducted of oncology and/or HSCT patients admitted to our institution with fever who received both CVL and peripheral blood cultures on the same day prior to the initiation of broad-spectrum antibiotics. We defined true blood stream infections in peripheral cultures due to common contaminants (e.g., coagulase negative staphlococcus) as those in which multiple cultures were positive. All positive central line cultures were considered true BSI.

Results: Between January 2012 and December 2013, 376 charts were reviewed of patients with fever and 71 episodes of blood stream infections were included, indicating an overall incidence of positive blood culture of 18.9% in febrile patients. Of these 67/71 (94.4%) of these were classified as true BSI and 4/71 (5.6%) were classified as contaminants. Importantly, 5/67 (7.5%) of true BSI were detected in peripheral blood cultures only, and 32/67 (47.8%) of BSI were detected in central blood cultures only.

Conclusion: This data indicates that 7.5% of true BSI are detected with peripheral blood culture only. This is similar to findings in previous studies in the pediatric oncology/HSCT population and supports the continued practice of obtaining peripheral blood cultures in addition to CVL cultures in the evaluation of these patients, at least at the onset of fever.
EARLY PALLIATIVE CARE CONSULTATION FOR HIGH RISK PEDIATRIC ONCOLOGY PATIENTS: A FEASIBILITY STUDY
Laila Mahmood, Ann Dozier, James Dolan, Denise Casey, Craig Mullen, David Korones. Golisano Children's Hospital at University of Rochester, Rochester, New York, United States of America

Background: While the overall cure rate for children with cancer is high, 20% of children still die from disease, and those who are cured suffer acute and chronic therapy-related toxicity. As part of a larger study evaluating the impact of early palliative care in children with high risk malignancies, we assessed the feasibility of obtaining palliative care consultations within one month of diagnosis.

Objectives: To assess the feasibility of obtaining early (at diagnosis) palliative care consultations for children with high risk malignancies.

Design/Method: Children were eligible for early palliative care consultation if they had a high risk malignancy, defined as: 1) relapsed disease, 2) need for stem cell transplantation (SCT), or 3) newly diagnosed with an estimated overall survival of < 50%. The pediatric hematology/oncology division identified eligible patients at a weekly patient-care conference. Medical charts were reviewed every two weeks to assess the status of the consultation and number of follow-up visits after initial consultation.

Results: Since implementation in March 2013, 16 of 18 eligible patients received an early palliative care consultation. No children or families declined the consult. Two patients did not participate in the study; one was a child from an outside hospital referred to our institution for autologous SCT who was discharged prior to consultation, and the other was a child with a brain tumor whose oncologist is a palliative care physician. The median time from diagnosis to consult was 9 days (2 - 51). Fifteen of 16 (94%) patients received consultation within 30 days of diagnosis. Eight of 16 (50%) were newly diagnosed, and 8/16 (50%) had relapsed/recurrent disease. Twelve of 16 (75%) had follow up palliative care visits after initial consultation; 1/12 had only one follow visit. The median number of follow up visits for the group was 4.5 visits (1-24).

Conclusion: An early palliative care consultation program for children with high risk malignancies is feasible and is well-accepted by pediatric hematologist/oncologists, children and families.
A RETROSPECTIVE STUDY OF THE MORBIDITIES SUFFERED BY SURVIVORS OF PEDIATRIC CANCER THERAPY

Lisa Mueller, Elizabeth Bell, Robert Cooper, Chun Chao, Lanfang Xu. Kaiser Permanente Medical Center, Los Angeles, California, United States of America

**Background:** 80% of children diagnosed with cancer survive. 1:640 young adults ages <40 years are cancer survivors. Retrospective studies typically conducted by questionnaire note increased treatment related complications. A CCSG study found 62% of survivors had at least one chronic condition with a higher risk for a life-threatening condition than siblings (1). These numbers are high & likely under-reported. Current treatment protocols are more toxic, so future survivors may have more late effects. Kaiser Permanente has used an electronic medical record since 2004. Most patients maintain their insurance into adulthood, allowing better care & the potential to prevent severe outcomes. We are uniquely positioned to track survivors into adulthood evaluating for late effects & developing tools to improve outcomes.

**Objectives:** The aim of this study is to determine if survivors of pediatric malignancies suffer more complications of their treatment than matched age and sex controls.

**Design/Method:** We identified survivors of pediatric cancer over a 25 year span (1985-2010). All were diagnosed, treated & remained at Kaiser during the study period. Charts were reviewed for toxic exposures including chemotherapy, radiation therapy & surgery. Only documented problems in the medical record were noted & matched to controls. Outcomes measured included mortality, secondary malignancies, & chronic comorbidities.

**Results:** A total of 652 pediatric cancer survivors, 0-18 years, were identified. All survived at least 5 years after diagnosis. Mean age at diagnosis was 9 years. 53.2% were males. 47.2% were White, 8.7% were Black, 36.5% were Hispanic & 6.6% were Asian/Pacific Islander. Leukemia (31.75%) was the most common diagnosis. Chronic health problems documented included liver, lung, heart, thyroid, vascular, bone & joint disease, dyslipidemia, hearing/vision loss, hypertension, hypogonadism, renal failure/CKD. Mortality & other co-morbid conditions for survivors were compared to controls.

**Conclusion:** In adjusted models (for race/ethnicity groups), the incident rate ratios (IRR) for mortality (IRR=14.13), secondary malignancy (IRR=9.26), cerebrovascular disease (IRR=10.01), dyslipidemia (IRR=1.92), hearing/vision loss (IRR=5.03), heart disease (IRR=4.15), hypogonadism (IRR=4.30), renal failure/CKD (IRR=13.71), thyroid disorders (IRR=6.36) were statistically significant (p-value<0.05). Medical problems were documented in the chart versus self-reported making our study unique. Survivors of pediatric cancers suffer more medical problems from their disease & treatment than controls. 1. Oeffinger, NEJM. 2006
VITAMIN D SURVEILLANCE AND SUPPLEMENTATION IN SICKLE CELL DISEASE: A QUALITY IMPROVEMENT PROJECT
Devin Muntz, Osarhiemen Omwanghe, Janice Beatty, Alexis Thompson, Robert Liem. Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, United States of America

**Background:** Vitamin D deficiency is common in children with sickle cell disease (SCD) and may be associated with chronic pain and poor bone health in this population. To counter this trend, our institution developed a standard of practice (SOP) aimed at screening and treating vitamin D deficiency in children ≥ 6 years old with SCD.

**Objectives:** The objective of this analysis was to evaluate programmatic adherence to our vitamin D SOP, defined as provider screening and treatment recommendation practices. Our secondary objective was to determine the barriers to adherence and treatment effectiveness.

**Design/Method:** We performed a data abstraction from the electronic medical record from January 2008 through July 2013 by cross-referencing SCD related ICD9 codes with serum total 25-hydroxyvitamin D (25(OH)D) levels. We examined baseline and follow-up levels collected during this time and reviewed clinic notes for provider treatment recommendations according to the SOP. Summary statistics were applied to the data using Microsoft Excel.

**Results:** A total of 549 serum 25(OH)D levels (median 18.7 ng/mL, range 3 to 91 ng/mL) were obtained from 247 children and young adults, 154 (62%) of whom had multiple levels. Screening was more effective for children ≤ 18 years when compared to > 18 years old. Levels were classified as severe deficiency (≤ 10 ng/mL) in 82/549 (15%), insufficient (10 to 30 ng/mL) in 394/549 (72%) and optimal (≥ 30 ng/mL) in 73/549 (13%). Severe deficiency was most common in the winter. Providers documented recommending over-the-counter supplementation for 267/476 (56%) children with severe and insufficient levels. Improvement in levels enough to cross categories was seen in 41/171 (24%), no change in 116/171 (68%) and worsening of levels in 14/171 (8%) patients prescribed supplementation with repeat levels obtained.

**Conclusion:** Moderate and severe vitamin D deficiency was common in our patients with SCD, affecting greater than 80% evaluated. Despite deficiency documented in the majority, provider treatment recommendations for supplementation were suboptimal. Absence of immediate results during clinic and lack of insurance coverage for supplementation may contribute to ineffective treatment. Future QI efforts using PDSA strategies will focus on addressing barriers to provider recommendations and improving patient adherence to supplementation.
IMPROVING A PEDIATRIC PHASE I TRIAL CONSENTING PROCESS
Estella Mote, Rhonda Robert. University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America

**Background:** The Phase I Trial enrollment process involves an interdisciplinary team and has the potential to be stressful for all involved. The patient has limited treatment options and time within which to act; parents anticipate the implications of disease progression and advocate; faculty physicians and investigators’ balance clinical and research interests throughout study accrual; and research nurses coordinate, organize, and lead the child and family through the enrollment process. Each of these interdisciplinary team members’ expertise varies by training background, clinical and research experience, and designated team roles.

**Objectives:** The global aim of this project was to improve the Phase I Trial consenting process.

**Design/Method:** Team members documented the established Phase I consent practice; compared current consent process with available study findings and best practice recommendations; identified future practice options; discussed and explored preferences with parent advisers, faculty physicians and investigators. Feedback was integrated by repeating the process.

**Results:** Suggested consent process improvements included: 1) defining team roles, e.g., research nurse present at the Phase I trial conference; 2) timely eligibility screening, e.g., preliminary and comprehensive; 3) minimizing disappointment, e.g., offering the patient a Phase I option and later learning of ineligibility or no study slot opening; 4) minimizing financial burden, e.g., phone interviews prior to incurring travel expenses for Phase I option; 5) optimizing the treating oncologist’s lead role (when the treating oncologist is not the PI); 6) emphasizing palliative and hospice care as alternatives or complements to Phase I participation; 7) maximizing social and environmental support; 8) utilizing educational materials, including short form consent & Phase I participation calendar that emphasizes study specific procedures, treatments, and duration; and 9) minimizing risk of study enrollment coercion by encouraging time for reflection.

**Conclusion:** The consenting process was revised in keeping with suggested improvements. We hope to further improve the Phase I consenting process by assessing patient and parent satisfaction.
COMFORT FOR ADOLESCENTS LIVING WITH ADVANCED CANCER
Riza Mauricio, Rhonda Robert. Univ of Texas MD Anderson Cancer Center, Houston, Texas, United States of America

Background: In the course of developing a pediatric palliative care program within a large tertiary institution, parents’ expertise was tapped through focus groups. Parent participants whose children were treated toward the end of their life had emphasized the need for emotional and interpersonal support; and other core components of pediatric palliative care were less dominant, including symptom management and treatment decision-making. The possible limitations of parents’ retrospective, proxy reporting highlighted our interest in patients’ self-report while living with advanced cancer.

Objectives: The study aim was to understand what most comforts adolescents living with advanced cancer.

Design/Method: Purposive sampling was used to recruit adolescents who were diagnosed with metastatic or progressive disease and were 15-21 years old. A demographic questionnaire and a semi-structured interview form were used to record participants’ primary information and to guide the audio-recorded one-on-one interview. The data was analyzed using Van Mannen’s method of combined descriptive and interpretive phenomenology.

Results: Thirteen ethnically diverse adolescents participated. Comfort was derived from interpersonal support. Particular importance was ascribed to: 1) friendly and compassionate demeanor of professional caregivers; 2) educational and developmental accommodations; and 3) presence or connection with family members and peers. Adolescents’ adaptability and resilience was largely attributed to perceived interpersonal support.

Conclusion: Adolescents living with metastatic cancer emphasized the necessity of familial and extra familial support, including professional caregiver support. Adolescent self-report and retrospective parent proxy report were quite similar, with both having emphasized the importance of interpersonal support.
CHEMOTHERAPY COMPETENCY TRAINING AND EDUCATION: A SURVEY OF
PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOWS IN TRAINING
Deepti Warad, Shakila Khan, Amulya Nageswara Rao. Mayo Clinic, Rochester, Minnesota, United
States of America

Background: As part of pediatric hematology/oncology (PDHO) training, fellows are involved in
planning, scheduling, and ordering chemotherapy. In addition to being well versed in pharmacology
fellows are required to learn and be competent in writing chemotherapy orders, processing and
preparation, safe handling and administration of chemotherapy.

Objectives: To describe the perception of PDHO fellows regarding chemotherapy training and the
educational structure at various institutions.

Design/Method: An online survey was distributed via REDCap to 367 PDHO fellows. Each trainee
received an initial request followed by a maximum of 3 reminders. A five-point Likert scale was used
for collecting responses to most questions.

Results: One forty one (38.4%) PDHO fellows responded. Ninety five percent of fellows
agreed/strongly agreed that training in safe administration of chemotherapy should be part of the
fellowship training curriculum. Fifty four percent reported use of electronic orders, 43% reported use
of paper or hand-written orders and the rest reported a combination of all three order systems. Fellows
who use paper order sets or hand-written orders agreed/strongly agreed to being more comfortable and
feeling more competent with writing chemotherapy orders by hand than those who use electronic
orders (p<0.0001). Chemotherapy sessions included formal and informal teaching sessions with
attendings (58% and 67%, respectively) and with pharmacists (50%). A smaller fraction reported small
group discussions (18%), test case scenarios/writing chemotherapy orders (16%), quiz/questionnaires
(7%), and chemotherapy/pediatric pharmacy rotation (3%).

Conclusion: Although electronic chemotherapy order sets are designed to minimize errors associated
with manual ordering and increase quality of care and patient safety, this may diminish the learning
experience of trainees. Fellows training in programs that currently use paper orders or hand-written
chemotherapy orders felt significantly more comfortable and competent in generating chemotherapy
orders without assistance of automated systems. With advancing technology and with more programs
embracing the electronic order systems the educational needs of trainees needs to be considered.
Trainees may benefit with dedicated chemotherapy training and self-assessment sessions which
include didactics and methods such as test case scenarios that require generating chemotherapy orders
which will also help with a better understanding of rationale behind dosing and protocols as well as
preventing potential serious errors.
CHEMOTHERAPY COMPETENCY TRAINING AND EDUCATION: A SURVEY OF PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOWSHIP PROGRAM DIRECTORS
Deepti Warad, Shakila Khan, Amulya Nageswara Rao. Mayo Clinic, Rochester, Minnesota, United States of America

**Background:** Pediatric Hematology/Oncology (PDHO) trainees are required to demonstrate competence in treatment planning, ordering, safe-handling and administration of chemotherapy. Many institutions have successfully implemented electronic chemotherapy order systems after rigorous quality checks that have greatly improved patient care and safety. However, for trainees, electronic orders generated by entering minimum variables can potentially eliminate the need for critical thinking and reasoning, and hinder the acquisition of knowledge required for dispensing chemotherapy orders.

**Objectives:** To describe: 1. the perception of fellowship Program Directors (PDs) regarding chemotherapy training, and 2. the educational structure at various institutions.

**Design/Method:** An online REDCap survey was distributed to 64 fellowship PDs of ACGME (Accreditation Council for Graduate Medical Education) accredited PDHO programs. Each PD received an initial request followed by a maximum of 3 reminders. A five-point Likert scale was used for collecting responses to most questions.

**Results:** Response rate was 51.5%. Majority (97%) agreed/strongly agreed that safe chemotherapy administration training is integral to fellowship curriculum. Most common training sessions included informal and formal teaching sessions with attendings (79% and 73%, respectively) and with pharmacists (64%). A minority used methods such as test case scenarios/writing chemotherapy orders (15%), quiz/questionnaires (6%), chemotherapy safety courses (6%), and chemotherapy/pediatric pharmacy rotation (3%). Forty eight percent of PDs trained using only hand-written chemotherapy orders compared to 9% of current programs. Fifty one percent agreed/strongly agreed that electronic/paper order sets generated by minimal input prevent acquisition of knowledge while 39% felt that it diminished critical thinking and reasoning. Only 27% agreed/strongly agreed that fellows are comfortable writing chemotherapy orders by hand, while 42% reported that fellows are competent doing the same. Forty five percent of PDs reported at least 1 medical error, near-miss or sentinel event in the prior 3 months.

**Conclusion:** Advancing technology and implementation of electronic order systems have increased the educational needs of trainees for chemotherapy administration. In addition to didactics, methods such as test case scenarios that require generating chemotherapy orders may enhance the learning experience of trainees by allowing in-depth self-assessment, awareness of critical focus areas, and rationale behind dosing and protocols as well as preventing potential serious errors.
RENAL TUBULAR DYSFUNCTION IN BETA THALASSEMIA MAJOR
Mohamed Badr, Tamer Hassan, Asmaa Esh, Mahmoud Metwally. Zagazig University, Zagazig, Cairo, Egypt

Background: Patients with thalassemia are known to have severe cardiopulmonary, reticuloendothelial, and other major systems dysfunction, but renal involvement has received little attention. Reports investigating renal dysfunction in thalassemics have been limited in number, mainly studying adult patients.

Objectives: We aimed to investigate renal tubular functions in beta thalassemia major patients and their relationship to epidemiological, transfusion and chelation characteristics of these patients.

Design/Method: This study included 100 patients with β-thalassemia major and 50 age and sex matched healthy children as controls. All epidemiological, transfusion and chelation data were collected. Timed (8 hours) urine samples were collected from all study participants for measurement of uric acid/creatinine ratio, sodium/creatinine ratio, potassium/creatinine ratio, calcium/creatinine ratio, phosphorus/creatinine ratio, magnesium/creatinine ratio, albumin/creatinine ratio and β2-microglobulin.

Results: Patients with beta thalassemia major had significantly higher uric acid/creatinine ratio, sodium/creatinine ratio, potassium/creatinine ratio, calcium/creatinine ratio, phosphorus/creatinine ratio, magnesium/creatinine ratio, albumin/creatinine ratio and β2-microglobulin compared to controls. There was no significant relationship between indicators of renal tubular functions and age, sex, transfusion and chelation characteristics of patients.

Conclusion: Periodic assessment of renal tubular functions should be added to the routine workup of beta thalassemia major patients. Early identification of renal tubular abnormalities is of great importance as it may allow specific measures to be undertaken that will delay the progression of renal injury and thus reduce the incidence of renal impairment.
RETROSPECTIVE ANALYSIS OF PAIN MANAGEMENT IN EMERGENCY DEPARTMENT FOR PATIENTS WITH SICKLE CELL DISEASE: A SINGLE INSTITUTION STUDY
Chantel Cacciotti, Sarah Vaiselbuh, Eleny Romanos-Sirakis. Staten Island University Hospital, Children’s Cancer Center, Staten Island, New York, United States of America

Background: Sickle Cell disease (SCD) is a chronic multisystem disorder, with painful vaso-occlusive events presenting as a major complication. A large portion of Emergency Department (ED) visits and hospitalizations are pain-related. Adequate and timely pain management improves quality of life.

Objectives: 1. Review the use of pain assessments scales before and after intervention. 2. Review the pain regimens used for patients with SCD presenting to the ED with vaso-occlusive events.

Design/Method: Retrospective chart review selected by ICD-9 codes related to SCD. 176 encounters were reviewed from 47 patients.

Results: 1. 76% of SCD patients had documented pain scales at triage; 28/167 (17%) patients reported mild pain (pain scale 1-3), 51/167 (30%) moderate pain (4-6) and 88/167 (53%) severe pain (7-10). Average time from triage to pain medication administration was 63 (+/- 46) minutes, range 10-300 minutes. Mean time to reassessment after pain medication was given was 100 (+/-63) minutes. After initial intervention, 8/137 (5.8%) reported no pain, 51/137 (37%) mild pain, 47/137 (34%) moderate pain, and 31/137 (23%) severe pain. 2. 32/168 (19%) patients received both NSAID and narcotic as initial pain medications, 81/168 (48%) patients received NSAID alone, and 55/168 (33%) received narcotics alone. Patients who received NSAIDs alone reported lower mean initial pain scales. There was a significant association between admission and higher pain scale at both triage and reassessment. However, among patients with severe pain at reassessment, 35% were discharged. 3. Further analysis of additional variables is ongoing.

Conclusion: Time to initial treatment and reassessment varied and was often prolonged. Providers were more likely to treat lower pain scales with NSAIDs alone; these patients may benefit from education regarding home pain regimens that may prevent unnecessary ED visits. Initial treatments varied; the decision to provide combination treatment to only a small proportion of patients warrants further investigation. Higher pain scales at reassessment were associated with admission, suggesting a need for further inpatient management. However a notable minority of patients with severe pain at reassessment were discharged. Comprehensive ED guidelines for assessment and treatment of SCD pain may contribute to optimal and consistent care.
PREVALENCE OF PULMONARY COMPLICATIONS IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE BASED ON VALIDATED SCREENING QUESTIONNAIRES
Fernando Corrales-Medina, Aravind Yadav, Nidra Rodriguez, Trihn Nguyen, Mary Carrol, John Stark, Deborah Brown. The University of Texas - MD Anderson Cancer Center, Houston, Texas, United States of America

**Background:** Sickle cell disease (SCD) is one of the most prevalent genetic diseases in children. Pulmonary complications including airway obstruction, acute chest syndrome (ACS) and sleep-related breathing disorders (SRBD) can result in significant morbidity and mortality in this population.

**Objectives:** To validate the use of screening questionnaires as effective tools for early detection of pulmonary complications in SCD pediatric patients.

**Design/Method:** Previously validated Pediatric Sleep Questionnaire (PSQ) and Asthma-Screening Questionnaire (ASQ) were administered to children with SCD (HbSS or HbSB0) ranging between 5-18 years of age at their routine hematology clinic visit. Spirometry was also obtained and scored by a pulmonologist who was blinded to the questionnaire responses. Documented history of pulmonary complications was taken from patients’ records.

**Results:** Twenty-four (43%) of the 56 patients who completed the PSQ scored positive for sleep disturbances. This number was significantly higher (p<0.001) than the expected proportion based on published rates of SRBD as measured by the PSQ in the general pediatric population. Within the PSQ, there were a higher proportion of positive responses to behavioral questions compared to snoring and sleepiness questions. Twenty-one (52.5%) of the 40 patients with SCD who completed the ASQ, scored positive for asthma, whereas a spirometry-based obstructive airway pattern was also detected in 21 (49.5%) of 43 patients, but the concordance between these two parameters was low (52%), suggesting low sensitivity for the ASQ. There was no significant association (P>0.05) of positive PSQ with obstructive airflow pattern by spirometry. Interestingly, patients whom scored positive on the PSQ had higher prevalence of ACS than their counterpart (42% vs. 28%). The mean platelet count was higher in children with SCD and a positive PSQ (mean: 462k, sd: 190k) compared to those with a negative PSQ (mean: 350,000, sd: 126,000; p=0.0139).

**Conclusion:** Symptoms of sleep disturbance and obstructive airway patterns are common among children with SCD. The PSQ may be helpful in identifying SRBD in children with SCD. Further evaluation by polysomnography is warranted in order to further validate the PSQ findings. Although a validated tool in the general pediatric population, the ASQ may not be a suitable screening tool in children with SCD.
OUTCOMES OF CHILDREN WITH SICKLE CELL DISEASE AND MOYAMOYA WITH AND WITHOUT CEREBRAL REVASCULARIZATION SURGERY
Erin O'Brien, Jeffrey Leonard, Kristin Guilliams, Robert Fallon, Monica Hulbert. Washington University School of Medicine, St. Louis, Missouri, United States of America

Background: Cerebral revascularization surgery (CRS) is increasingly performed on children with sickle cell disease (SCD) and cerebral vasculopathy/moyamoya. The outcomes of children with SCD and vasculopathy who do or do not undergo CRS have not been compared.

Objectives: To determine the number and type of cerebrovascular events in children with SCD and vasculopathy following CRS compared with those who do not have CRS.

Design/Method: Retrospective chart review at two academic centers. Inclusion criteria: SCD; chronic transfusions due to overt stroke, silent stroke, or abnormal transcranial Doppler ultrasonography; moderate or severe cerebral vasculopathy on two or more brain magnetic resonance imaging studies (MRIs). Exclusion criteria: insufficient medical records; no confirmation of cerebral vasculopathy.

Results: Twenty-six children met all criteria, followed for a total of 246 patient-years. Twenty-three (88%) had progressive vasculopathy/moyamoya (mean 2.4 years after identification of vasculopathy, range 0.3-7.4 years); 15 (58%) had at least one infarct (silent or overt) or TIA after initiating transfusion therapy (mean 2.4 years, range 0.05-6.9 years). Ten children underwent CRS at mean 4.5 years (range 1.4-10.9 years) following initiation of transfusion therapy, due to recurrent silent or overt infarction in 6 children (7 infarcts total), TIA in 2, and moyamoya progression in 2. Mean postoperative followup was 5.1 years (range 0.9-11 years). Two postoperative neurological complications occurred: one child had a TIA on postoperative day 1, and one had subarachnoid bleeding, headache, and fevers on postoperative day 2. Following the immediate postoperative period, 4 children had TIAs with similar symptoms as their preoperative TIAs but less frequently. None had new overt or silent infarctions, a significant difference compared to the number of preoperative infarcts (p=0.01). Five children had no immediate or later postoperative cerebrovascular events. Of the 16 children without CRS, 44% (7/16) had recurrent infarctions (median 2 events, range, 1-6 events). Six experienced one or more recurrent overt strokes, and one had a non-fatal intraventricular hemorrhage plus silent infarction.

Conclusion: In this cohort, children who underwent CRS had no postoperative infarctions and a reduction in TIA frequency, whereas nearly half of those without CRS had recurrent infarctions. CRS reduces recurrent infarctions in children with SCD and cerebral vasculopathy/moyamoya.
DEVELOPMENT OF A COMPREHENSIVE RAPID NEXT-GENERATION SEQUENCING ASSAY FOR THE DIAGNOSIS OF INHERITED HEMOLYTIC ANEMIA

Amber Hogart Begtrup, Neha Dagaonkar, Satheesh Chonat, Katie Giger, Ammar Husami, Diane Kissell, Mary Risinger, Clinton Joiner, Mehdi Keddache, Kejian Zhang, Theodosia Kalfa. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, Unites States of America

**Background:** Hereditary hemolytic anemia (HHA) is caused by defects in hemoglobin, the red blood cell (RBC) cytoskeleton proteins, or by deficiencies in RBC enzymes. Congenital dyserythropoietic anemias (CDAs) are inherited red cell lineage disorders, which occasionally, especially CDA-II, can be misdiagnosed as spherocytosis. Diagnosis of HHA not due to a hemoglobin disorder is based upon RBC morphology, functional assays like ektacytometry and osmotic fragility, and enzymatic assays. Genetic sequencing is an attractive diagnostic tool, especially in transfused patients, but its use has been limited by expense and long turn-around times.

**Objectives:** To develop a rapid, comprehensive, next-generation sequencing-based assay that evaluates 27 genes with published disease-causing mutations for RBC cytoskeletal disorders, enzymopathies, and CDAs.

**Design/Method:** The protein-coding exons plus 20 bases of exon/intron junction and promoter sequences with known relationship to clinical phenotypes were included in the design. Genomic DNA was digested with a panel of 8 restriction enzymes and oligonucleotide probes were used to enrich the target regions. Enriched samples were then sequenced on an Illumina MiSeq benchtop sequencer with 150 base pair, paired-end reads. Sequencing reads were aligned to the human genome reference sequence and analysis of coverage and variants was completed using NextGENe software.

**Results:** Initial validation included 9 affected probands, 1 affected sibling of a proband, and 6 parental samples. Two patients with transfusion dependent disease were found to have autosomal recessive HS due to combined heterozygosity of a nonsense SPTA1 mutation in trans to the low-expression SPTA1 alpha-LEPRA allele. A third patient with transfusion-dependent anemia had biallelic ANK1 mutations: T1075I (ankyrin Tubaro) in trans to a novel nonsense mutation, p.Y735*. A fourth patient and her sibling with moderate HS were found to have a novel ANK1 frameshift mutation, c.3464delG. In addition, we identified PIEZ01 mutations in two patients with xerocytosis, homozygous TPI1 mutations in a patient with triose phosphate isomerase deficiency, CDAN1 mutations in a patient with CDA-I, and SEC23B mutations in a patient with CDA-II.

**Conclusion:** This comprehensive sequencing assay is a robust and rapid diagnostic tool for patients with HHA, facilitating clinical diagnosis and management decisions.
PREDICTORS OF IN-HOSPITAL MORTALITY IN CHILDREN AND ADOLESCENTS WITH SICKLE CELL DISEASE: A PEDIATRIC HEALTH INFORMATION SYSTEM DATABASE ANALYSIS

Ram Kalpatthi, Troy Richardson, Gerald Woods, Bradley Warady, Jignesh Dalal, Children's Mercy Hospital, Kansas City, Missouri, United States of America

Background: Previous studies in adults with SCD reported various clinical and demographic predictors of mortality such as severe anemia, acute chest syndrome, hospital volume and patient socioeconomic status. However, no prior study has explored the clinical predictors of in-hospital mortality in children with SCD.

Objectives: To explore the various clinical predictors of all-cause mortality in hospitalized children with SCD.

Design/Method: Children with SCD from 44 children's hospitals in the Pediatric Health Information System database between 2004-2012 were included for analysis. We abstracted data on demographics, hospitalizations, medication use and mortality.

Results: A total of 24,429 unique children with SCD were identified. Median age was 6 years (1, 13) and 48% were males. HbSS was the most common phenotype (77%) and vaso-occlusive painful episode was the most common reason (70%) for hospitalization. Only 4181 patients (17%) had been prescribed hydroxyurea. There were a total of 175 deaths with an all-cause in-hospital mortality rate of 0.7%. Cox proportional hazards model showed that diagnosis of CKD, systemic hypertension, every year increase in age, and a history of RBC transfusion were independently associated with a greater risk of mortality, whereas hydroxyurea use was associated with a decreased mortality risk (Table 1).

Conclusion: Ours is the first study to show the clinical predictors of in-hospital mortality in children with SCD. Although the use of hydroxyurea was associated with a survival advantage, it was significantly underutilized. Further studies addressing barriers of hydroxyurea use and targeted therapy based on these predictors of mortality risk are needed to improve patient outcome.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hazard Ratio (95% Wald CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD (Yes vs. No)</td>
<td>6.194 (3.548,10.814)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Every year increase in age</td>
<td>1.064 (1.037,1.093)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Transfusion (Yes vs. No)</td>
<td>3.274 (2.310,4.641)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension (Yes vs. No)</td>
<td>2.237 (1.541,3.249)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hydroxyurea (Yes vs. No)</td>
<td>0.341 (0.227,0.514)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
IDENTIFYING RENAL MICROSTRUCTURAL AND BLOOD FLOW CHANGES IN SICKLE CELL DISEASE USING QUANTITATIVE MRI TECHNIQUES
Connie Piccone, Lan Lu, Shannon Donnola, Katherine Dell, Jane Little, Chris Flask. University Hospitals Case Medical Center, Cleveland, Ohio, United States of America

Background: Renal disease in sickle cell disease (SCD) is common and is associated with increased morbidity and mortality. To date, no large studies of functional or structural renal changes have been published. Magnetic Resonance Imaging (MRI) is safe and has been used to assess both acute and chronic kidney disease, but its utility in sensitively quantitating renal function in SCD has not yet been established.

Objectives: To test quantitative MRI for its ability to assess both structure and renal blood flow in patients with SCD.

Design/Method: Pediatric and adult patients were recruited to an IRB approved study from the Sickle Cell Anemia Centers at UH Rainbow Babies & Children’s Hospital and University Hospitals Case Medical Center. Six pediatric patients (age 12-18 years, 1 male, 5 female, eGFR 110-185 mL/min/1.73m²) have been recruited to date. Healthy controls were also recruited. Diffusion (DTI) and Arterial Spin Labeling (ASL) scans were performed to assess medullary microstructure and cortical perfusion (non-contrast), respectively. Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) maps were calculated using established methods. Mean renal T2* was measured to assess iron burden. A Student’s t-test was performed to compare the mean renal DTI and ASL results between subjects and healthy controls.

Results: In the six pediatric subjects, medullary FA values were decreased, suggesting degradation of medullary microstructure. Both cortical ADC and medullary FA were significantly reduced, indicative of microstructural changes in SCD subjects compared to controls. ASL perfusion maps, likewise, showed reduced cortical perfusion for SCD subjects in comparison to controls. Preliminary differences in blood flow and microstructure were seen between SCD subjects on hydroxyurea (HU) and those not on HU. Analysis of the T2* data showed increased renal iron deposition that did not appear to correlate with serum ferritin.

Conclusion: Our results suggest that quantitative diffusion and ASL MRI are sensitive to medullary microstructural and cortical blood flow changes in pediatric patients with SCD. Preliminarily, iron deposition in the kidney appears to relate to chronic hemolysis rather than transfusional iron. These sensitive techniques may be useful in assessing the impact of therapeutic interventions, such as HU, on renal function in children.
HOMOZYGOUS VHL (D126N) MISSENSE MUTATION IS ASSOCIATED WITH POLYCYTHEMIA WITH DRAMATIC EPO LEVELS AND EARLY ONSET SEVERE PULMONARY HYPERTENSION BUT NOT TUMORS
Susmita Sarangi, Lucie Lanikova, Katarina Kapralova, Suchitra Acharya, Lawrence Wolfe, Jeffrey Lipton, Josef Prchal. Cohen Children's Medical Center, NS-LIJ Health System, New Hyde Park, New York, United States of America

Background: Von Hippel Lindau (VHL) protein is the principal negative regulator of hypoxia sensing mediated by transcription factors (HIFs). The majority of VHL loss-of-function mutations are associated with VHL tumor predisposition syndrome that include pheochromocytoma/paraganglioma and renal carcinoma; however some distinct VHL mutations are associated with polycythemia. Mutations in the exon 3 of the VHL gene lead to Chuvash (VHLR200W) and Croatian (VHLH191D) polycythemias. These patients are predisposed to arterial and venous thrombosis and pulmonary hypertension as adults. Recently, polycythemia causing mutations in the exon 2 of the VHL gene have been described (VHLP138L and VHLD126N/S183L).

Objectives: To describe the phenotype of an infant with homozygous VHL (D126N) mutation.

Design/Method: Sensitivity of erythroid progenitors to EPO was performed with Methocult H4531 media with various concentrations of EPO.

Results: An infant of Bangladesh ethnicity presented with failure to thrive and polycythemia (hematocrit 67.9%) since birth. Propositus’ erythropoietin (EPO) levels were dramatically elevated at 2407 mIU/ml (normal <32 mIU/ml). He had multiple hepatic hemangiomas. He was started on biweekly phlebotomy (maintaining hematocrit <45%) and prophylactic anticoagulation due to high risk of thrombosis. He developed severe pulmonary hypertension which worsened after a parainfluenza virus infection at the age of 2 years which ultimately led to his demise. He had extensive cerebral infarctions at the time. In contrast to Chuvash polycythemia with VHLP138L mutations, limited studies of erythroid progenitors (BFU-E) of the propositus did not reveal a marked EPO hypersensitivity, yet his EPO was markedly higher than in these other VHL polycythemic mutations. Further, NF-E2 and RUNX1 transcripts that correlates with BFU-E EPO hypersensitivity in polycythemic mutations were not elevated.

Conclusion: Our study underlines the remarkable heterogeneity of clinical phenotypes of VHL mutations, ranging from cancer, polycythemia with and without high EPO and a propensity to thrombosis unrelated to high hematocrit. In addition in two independent studies of VHLD126N mutation (one compound heterozygote and the homozygote described in this report) there is previously unappreciated severe early onset pulmonary hypertension with a dramatic elevation in plasma EPO levels. Further studies, exploring a possible non-canonical VHL effect on HIF regulation will be needed to establish the molecular basis of the complex disease phenotype resulting from VHL mutations.
ADHERENCE TO PROMPT FEVER EVALUATION IN CHILDREN WITH SICKLE CELL DISEASE AND THE HEALTH BELIEF MODEL
Corinna Schultz, Trudy Tchume-Johnson, Renee Cecil, Kim Smith-Whitley, Angela Ellison.
Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States of America

Background: Children with sickle cell disease (SCD) are at increased risk of death from infection. Fever is a sign of a potentially serious infection and medical emergency for children with SCD. Limited data exists regarding caregiver adherence to the recommendation to seek immediate medical evaluation of fever in children with SCD.

Objectives: To determine caregiver adherence with prompt evaluation of fever in children with SCD and to assess the efficacy of the health belief model (HBM) and the abbreviated Wake Forest Trust Scales in predicting caregiver reported adherence.

Design/Method: Cross sectional survey of caregivers of children with SCD during routine hematology visits at the Children’s Hospital of Philadelphia. Surveys included four sections: (1) caregiver reported adherence to prompt evaluation of fever, (2) 15 questions based on Health Belief domains via 5-point Likert response scale from “strongly disagree” to “strongly agree”, (3) modified 5-question Wake Forest physician trust scale and Wake Forest medical profession trust scale, and (4) demographics.

Results: 84% (163/193) approached completed the survey. Overall, 55% of caregivers report “always” bringing their child with SCD for prompt evaluation of fevers though 92% agree that it is important to do so. Composite scores of Health Belief domains of perceived susceptibility to fever/infection, perceived benefits to prompt evaluation of fevers, and cues to action were significantly different between those who adhere to recommendation or not. In general, 25% agree their child does not need antibiotics with every fever while 17% agree their child does not need evaluation with fevers after immunizations. 16% agree they have trouble getting to medical attention quickly. 57% agree their employer understands when they miss work due to fever evaluations while 25% agree they are concerned regarding cost of evaluation. Trust in their child’s hematologist and the medical profession was overall high (composite scores 23.4/25 and 21/25, respectively).

Conclusion: Despite a high degree of agreement in importance of fever evaluation and high level of trust in their child’s physician and medical profession, many parents do not consistently seek care when their child has a fever. Future studies should address further barriers to seeking emergency care in children with SCD.
Vitamin D Level and Its Correlation with Hemoglobin in Pediatric Sickle Cell Disease Patients
Jennifer Busse, Kranthi Nandan Seelaboyina, Madhuri Jakkam Setty, Grace Malonga, Thomas Moulton. Bronx Lebanon Hospital, Bronx, New York, United States of America

**Background:** It has been well characterized that people with sickle cell disease (SCD) are likely to be vitamin D deficient. New literature suggests there is an association between vitamin D deficiency and increased anemia in patients with chronic anemia.

**Objectives:** Our hypothesis is that supplementation of vitamin D will improve anemia of vitamin D deficient sickle cell patients.

**Design/Method:** Our sample included a population of 50 SCD patients aged 0 to 21. Using a linear mixed model with an autoregressive relationship and a lag of 1 to account for variance within the subject, we examined the association between serum 25-hydroxyvitamin D (25-OHD) level and hemoglobin, as well as between 25-OHD and reticulocyte count over time. We began at the time of first supplementation of 25-OHD to the recent blood levels in each patient.

**Results:** After adjusting for mean corpuscular volume (MCV), hemoglobin, sickle cell type and hydroxyurea, there was a linear increase in reticulocyte count over time associated with increasing 25-OHD levels ($\beta = 0.000060$, SE = 0.000030, $p = 0.050$). However, after controlling for MCV, reticulocyte count, sickle cell type, and hydroxyurea, we found a trend of a negative association between 25-OHD and hemoglobin levels, which was not statistically significant ($\beta = -0.000008$, SE = 0.000007, $p = 0.267$).

**Conclusion:** Our results did not support our original hypothesis, which stated that supplementation of vitamin D in vitamin D deficient SCD patients would lead to an improvement in anemia. However, a trend was noted, although not significant, of a decrease in hemoglobin with increasing 25-OHD. In turn, there was a statistically significant increase in reticulocyte count with increasing 25-OHD. This suggests that there is increased hemolysis with increased erythropoiesis caused by increasing 25-OHD. This is seen even when controlling for patients taking hydroxyurea. It is difficult to explain this finding with our current data set, therefore further study is required to elucidate this possible correlation. It will be important to examine this relationship further, as supplementing vitamin D in vitamin D deficient SCD patients is becoming standard of care for improvement in bone density.
REFERRAL PATTERNS AND TREATMENT-RELATED MORBIDITIES FOR AYA PATIENTS WITH SARCOMAS
Anthony Audino, Nicholas Yeager, Terah Koch, Mollie Sturm, Sarah O'Brien. Nationwide Children's Hospital, Columbus, Ohio, United States of America

Background: Nearly 70,000 adolescent and young adults (AYAs) are diagnosed with cancer annually, and clinical trial participation in this age group is low. Sarcoma comprises approximately 11% of AYA malignancy, and referral patterns and location of treatment for these patients has been poorly studied.

Objectives: To describe referral patterns and treatment related morbidities for AYA patients with sarcomas.

Design/Method: Data were extracted from the OptumInsight Life Sciences Database, a repository containing medical and pharmacy claims as well as demographic information for ~47 million individuals enrolled in medical and prescription drug coverage. This analysis included individuals 15-39 years with a bone or soft tissue sarcoma diagnosis and chemotherapy administration between 2008-2010.

Results: 464 unique AYA patients with sarcoma were identified. Overall, bone sarcomas were significantly more likely to be treated at pediatric facilities and soft tissue sarcomas at adult hospitals (p=0.0008). Increasing age was significantly associated with hospital type, with only a small minority (~3%) of patients >24 years of age cared for in pediatric hospitals. Even in the youngest AYA patients, only 39% received care in a pediatric institution. Common treatment-related complications, such as mucositis, thrombosis and bacterial infections, were similar between groups.

Conclusion: The majority of AYA sarcoma patients receive treatment in adult cancer facilities, even in the youngest age group (15-19 years). As clinical trials are necessary to improve outcomes in these challenging diseases, efforts to increase participation in AYA patients with sarcoma must target adult and pediatric oncologists.
AEROSOL INTERLEUKIN-2 FOR THE TREATMENT OF PATIENTS ≥12 YEARS OLD WITH OSTEOSARCOMA LUNG METASTASES: A PHASE I TRIAL
Nancy Gordon, Najat Daw, Peter Anderson, Sergei Guma, Hsuan-Chu Chien, Lacey McQuinn, Joshua Hein, Ralph Zinner, Eugenie Kleinerman, Aung Naing. UT MD Anderson Cancer Center, Houston, Texas, United States of America

**Background:** Osteosarcoma (OS) survival has remained at 65-70% for the last 20 years. Our pre-clinical data using a human OS mouse model demonstrated the therapeutic efficacy of aerosol Interleukin-2 (IL-2) in OS lung metastases, and its ability to increase local immune cell proliferation in the presence of low serum levels. Most recently, IL-2 was shown to induce autophagy, an evolutionary, conserved, intracellular self-defense mechanism, in CD4+ T cells and NK cells and contribute to growth factor withdrawal cell death. Inhibition of autophagy augments immune cell function allowing a better anti-tumor effect.

**Objectives:** The primary objective is to test feasibility and safety of aerosol IL-2 in patients > 12 yrs. with lung metastases and determine its maximum tolerated dose (MTD). The secondary objective is to determine IL-2 pharmacokinetics and correlate with local and systemic effects on immune cell proliferation.

**Design/Method:** Patients received aerosolized IL-2 once daily for 3 consecutive weeks (21 day cycle) for 2 cycles with 1-week rest between cycles provided no dose limiting toxicities (DLTs) occur. The first treatment is delivered in the hospital, and subsequent treatments are given at home after patients had been educated and trained. Pre-treatment remote spirometry and pulse oximetry are recorded. From dose levels 1-4 only 1-patient/dose level was enrolled. From dose level 5 on, 3 patients will be enrolled. Once the MTD is reached an additional 14 patients will be treated. Clinical response will be assessed by chest CT and determined using modified Response Evaluation Criteria in Solid Tumor (RECIST) after the 2nd cycle.

**Results:** 5 patients have been enrolled, ages 18, 35, 66, 20 and 15; all male, 3 with Ewing Sarcoma and 2 with osteosarcoma. No side effects had been detected and serum levels of IL-2 were only detected in the fourth patient but were very low.

**Conclusion:** Aerosol IL-2 seems so far feasible and safe. Completion of the Phase I will offer information on the MTD and will provide the basis for future combination therapy trials.
TREATMENT OUTCOME OF CHILDHOOD LOCALIZED BLADDER/PROSTATE RHABDOMYOSARCOMA

Hanafy Hafez, Rania Labib, Enas El nadi, Soha Ahmed, Mohamed Zaghloul, Alaa Younes, Alaa Elhaddad. Children Cancer Hospital Egypt (CCHE 57357), Cairo, Egypt

**Background:** Although multidisciplinary treatment approach is used in treatment of childhood rhabdomyosarcoma (RMS), yet it is still unclear, which treatment strategy is optimal for local control in patients with bladder RMS to achieve better survival and function preservation.

**Objectives:** To assess the treatment efficiency, outcome and factors affecting the local control of localized bladder/prostate RMS

**Design/Method:** Retrospective analysis of 28 patients with localized bladder/prostate RMS treated at children Cancer Hospital, Egypt (CCHE 57357) between August 2007 and August 2013, treated according to IRS V and subsequent COG guidelines.

**Results:** the mean age at diagnosis was 3 years (range 0.4-13.6) and 43% out of them were below 2 years. The Tumor was located in the bladder base in 22 patients (78.5%). Twenty five patients (89%) were diagnosed with clinical group III disease while 2 (7%) with group II and only 1 patient with group I. Complete surgical excision, primary or delayed (with or without microscopic residual) was performed in 5 patients (17.8%). Local control started at ≤week 12 in 17 patients (61%) and after week 12 in 11 patients (39%). Radiotherapy as a sole local control tool in 17 patients (60.7%), combined with surgery in 7 patients (25%) and two patients (below one year) did not receive local control treatment. The mean follow up period was 30.4 months (range 2.6-65.87). The 3 years-Overall and FFS were 78.5 ± 9.8% and 55.7 ± 10.8% respectively. A better 3-year FFS was experienced by those who started local control ≤12 weeks (86 ± 9.1%, p= .028). Children who underwent complete surgical excision with or without postoperative radiotherapy (according to the clinical group), experienced a higher, though insignificant, 3-year FFS (80±17%, p=0.27).

**Conclusion:** Earlier local control at or before week 12 is associated with better outcome in children with bladder RMS. Complete surgical excision with or without postoperative radiotherapy as local control measure lead to better survival, though not ranked to significant level. Lower operability rate is still a major problem in local control in our patients.
TARGETING HISTONE DEACETYLASES (HDACS) AND WEE1 FOR TREATING HIGH-RISK NEUROBLASTOMA

Santosh Hanmod, Guan Wang, Steven Buck, Zhihong Wang, Yubin Ge. Children’s Hospital of Michigan, Detroit, Michigan, United States of America

Background: Despite the recent advances in the treatment regimens, patients with high risk (HR) neuroblastoma have long-term survival rates of <40%. Resistance to the current anti-neoplastic agents continues to be one of the main reasons for treatment failure and progressive disease among this group of patients. Therefore, new agents are needed to improve treatment outcome of patients with HR neuroblastoma.

Objectives: To establish synergistic antitumor interactions between panobinostat (LBH589)( pan-HDAC inhibitor) and MK-1775 (Wee1 inhibitor) in HR neuroblastoma cells and to determine the underlying molecular mechanisms.

Design/Method: In vitro cytotoxicities of panobinostat and MK-1775 at different clinically achievable concentrations either alone or in combination were evaluated in 3 neuroblastoma cell lines, SK-N-AS (AS), SK-N-DZ (DZ) and SK-N-BE(2) (BE)- all derived from HR neuroblastoma patients. Viable cells were measured using MTT reagent, while apoptosis was determined by propidium iodide (PI) staining and flow cytometry analysis. Western blotting was used to assess the expression of total or phosphorylated proteins such as CHK1, p-CDC25C(S216) and p-CDK1(Y15).

Results: Treatment of neuroblastoma cells with panobinostat resulted in dose dependent growth arrest and induced apoptosis in all the 3 cell lines. Treatment with MK-1775 at maximum clinically achievable concentration (500 nM) caused significant growth arrest and apoptosis in only DZ and AS cell lines while had minimum effect on the BE cell line. Further, combination of panobinostat and MK-1775 resulted in synergistic antitumor interactions in all the 3 cell lines. Combination index (CI) ranged from 0.46-0.63 for the BE cell line with up to 4-fold decrease in the IC50 of panobinostat when combined with MK-1775. Maximum antitumor interactions were noted in simultaneous as opposed to sequential administration. Panobinostat treatment resulted in decreased levels of total CHK1 and p-CHK1(S345), leading to further decreased phosphorylation of CDK1(Y15) and CDK2(Y15) induced by MK-1775 when the two agents were administered simultaneously. This was accompanied by increased DNA damage indicated by the increased levels of γH2AX detected by western blots.

Conclusion: Combination of panobinostat and MK-1775 has synergistic antitumor activity against neuroblastoma cell lines and holds promise as a potential effective treatment strategy for management of high risk neuroblastoma patients.
THE EFFECT OF MEBENDAZOLE AND VINCRISTINE ALONE AND IN COMBINATION ON Glioblastoma Multiforme

Derek Hanson, Mark Atlas, Daniel Markowitz, Marc Symons. Hofstra North Shore-LIJ School of Medicine, New Hyde Park, New York, United States of America

Background: Mebendazole is a benzimidazole drug developed for the treatment of human helminthic infections. Recently, mebendazole has been shown to diminish the viability of glioblastoma cells in vitro and to extend the mean survival of glioblastoma-bearing mice by 63%.1 Relatively little is known about mebendazole’s anti-tumor mechanisms, although the drug has been shown to depolymerize microtubules.

Objectives: To improve our understanding of the therapeutic effects of mebendazole by comparing its effect on glioblastoma cells with that of vincristine, a well-established microtubule inhibitor. To establish mebendazole as a viable therapeutic option in vincristine-containing chemotherapy regimens.

Design/Method: GL261 glioma cells were maintained in culture. Half-maximal inhibitory concentrations (IC50) were determined by incubating cells at a range of concentrations of mebendazole and vincristine both alone and in combination for 96 hours. Tubulin polymerization assays were performed by lysing GL261 cells exposed to various concentrations of mebendazole or vincristine. The supernatant containing the depolymerized tubulin and the pellet containing the polymerized tubulin were analyzed by Western blotting.

Results: Mebendazole and vincristine were found to inhibit the survival of GL261 glioma cells with IC50s of approximately 160 nM and 2 nM, respectively. When used in combination, mebendazole and vincristine displayed mild synergism at lower concentrations and behaved additively at higher concentrations. Mebendazole and vincristine caused microtubule depolymerization at doses that were proportional to their IC50s for cell survival.

Conclusion: Mebendazole and vincristine appear to act via a similar cytotoxic mechanism. The mild synergism found at low dose combinations and the otherwise additive behavior of the two drugs suggests that mebendazole may show therapeutic benefit when added to vincristine-containing chemotherapy regimens. Importantly, given the excellent safety profile of mebendazole, this repurposed drug may prove to be a viable replacement for vincristine once clinical efficacy is demonstrated.

REDUCED MHC CLASS I EXPRESSION IN PEDIATRIC MALIGNANCIES MAY LIMIT USE OF MHC-DEPENDENT IMMUNOTHERAPIES
Kellie Haworth, Michael Arnold, Jennifer Leddon, Chun-Yu Chen, Timothy Cripe. Nationwide Children's Hospital, Columbus, Ohio, United States of America

**Background:** Immune-based therapies are gaining traction with increasing reports of antitumor efficacy. Some strategies are MHC-independent, such as T-cells engineered to express chimeric receptors (CARs) and bi-specific antibodies (BiTEs), but others, such as cancer vaccines, are dependent upon recognition of antigenic peptides presented by major histocompatibility complexes (MHC). There is growing recognition that oncolytic viruses also exert their therapeutic effects in part by inducing an adaptive T-cell response against tumor-associated antigens. For these latter types of immunotherapies, it is important to know the MHC Class I expression on tumor cells, and, in the case of virotherapy, the effects of infection on MHC Class I expression. In adult cancers, MHC Class I expression has been extensively studied, with down-regulation seen in 40-90% of cases and associated with a poor prognosis. Few studies have examined MHC Class I expression in pediatric cancers, however. Neuroblastoma has particularly low MHC Class I expression, thought to be down-regulated through reversible mechanisms associated with NF-kB pathway activation. Ewing sarcoma has also been reported to have low MHC Class I expression, correlating with disease progression. For most other pediatric malignancies, however, MHC Class I expression is unknown.

**Objectives:** To characterize MHC Class I expression in pediatric malignancies.

**Design/Method:** We queried mRNA expression microarray databases including clinical and preclinical datasets for MHC Class I expression and are conducting immunohistochemical studies and flow cytometry on primary tumor specimens.

**Results:** Our preliminary data suggest that sarcomas, including Ewing sarcoma, osteosarcoma, and both embryonal and alveolar rhabdomyosarcomas, Wilm’s Tumors, and some brain tumors, such as AT/RT and ependymomas, also exhibit decreased MHC Class I mRNA levels relative to other cancer types. In some rhabdomyosarcomas, MHC Class I can be up-regulated in vitro, indicating a reversible epigenetic mechanism for down-regulation.

**Conclusion:** Establishment of MHC Class I assays will likely serve as important biomarkers for patient inclusion in therapeutic trials of MHC-dependent immunotherapies.
Background: Clinical outcome of papillary thyroid carcinoma (PTC) in children differs significantly from that of adults. There is no clear explanation of this difference although previous studies have demonstrated a lower prevalence of the BRAFV600E mutation in PTC of children. However, data are limited due to the rarity of this diagnosis. BRAFV600E mutation prevalence and its relationship with outcome in pediatric PTC remain unclear.

Objectives: This retrospective analysis of pediatric papillary thyroid carcinoma aims to determine the prevalence of the BRAF mutation and review the clinicopathologic outcomes of pediatric patients treated at our institution. Specifically, age, gender, race, tumor characteristics, and BRAF mutational status were analyzed for possible correlations with outcome.

Design/Method: BRAFV600E mutational status was determined in 27 PTC patients less than 22 years of age using restriction fragment length polymorphism (RFLP) analysis. The relationship between BRAFV600E mutation status, patient and tumor characteristics as well as progression free survival (PFS) were analyzed.

Results: BRAFV600E was present in 63% of patients and occurred more often in male patients versus females (p=0.033). Presence of the mutation did not correlate with any difference in extent of disease at diagnosis, tumor size, capsular invasion, vascular invasion, soft tissue invasion, or margin status. At 10 years, PFS for BRAFV600E positive versus negative patients was 55.5% versus 70.0%, respectively (p=0.48). Overall survival was 100% and median follow-up was 13.9 years.

Conclusion: This is the first study of its kind to indicate that the BRAFV600E mutation occurs in children with PTC at a rate comparable to adults. We also found a correlation of BRAFV600E with the male gender, an observation that has been previously noted in literature pertaining to adult PTC. Finally, although the BRAF mutation occurred frequently in our population, we found no evidence that the mutation correlates with more extensive or aggressive disease. Therefore, our analysis does not support the hypothesis that differences in the biological behavior of adult and pediatric thyroid carcinomas are strongly dependent upon the presence of the BRAF mutation.
PRECLINICAL COMBINATION OF HIPPO PATHWAY ACTIVATION PLUS STANDARD CHEMOTHERAPY IN THE TREATMENT OF ALVEOLAR RHABDOMYOSARCOMA
Ashley Hinson, Lisa Crose, Corinne Linardic. Duke University Medical Center, Durham, North Carolina, United States of America

**Background:** Rhabdomyosarcoma (RMS) is a malignancy with features of skeletal muscle and the most common soft tissue sarcoma of childhood. Alveolar variant RMS tumors (ARMS) bear a chromosomal translocation t(2;13) encoding the fusion protein PAX3-FOXO1, which portends high risk and worse prognosis. We have recently found that PAX3-FOXO1 exerts a malignant phenotype in part by promoting expression of RASSF4, a protein that restrains a relatively newly described tumor suppressor pathway known as Hippo, leading to uncontrolled cell proliferation and tumorigenesis. We hypothesize that inhibiting RASSF4 (thereby activating the Hippo pathway) in combination with standard chemotherapy may be a useful treatment strategy in ARMS.

**Objectives:** To examine the impact of combining RASSF4 genetic suppression with commonly used chemotherapy agents on RMS cell growth in vitro and tumorigenesis in vivo. To then examine the effect of activating the Hippo pathway directly through pharmacologic means, in vitro and in vivo.

**Design/Method:** In vitro, we examined the effect of doxycycline (dox)-inducible RASSF4 shRNAs in combination with the RMS chemotherapies vincristine and dactinomycin on human ARMS (Rh28) cell growth, using manual cell counting and MTT assays. In vivo, we examined the effect of dox-inducible RASSF4 shRNAs and vincristine on the growth of ARMS xenografts in mice. At pre-defined stopping points, tumors were harvested for RNA and IHC analysis. In vitro we then treated RMS cells with PPIX, an inhibitor of the YAP transactivator (YAP is ordinarily silenced by Hippo). In vivo xenograft experiments using another YAP-inhibiting drug known as verteporfin (FDA-approved for macular degeneration) have been initiated.

**Results:** In vitro, ARMS cells exposed to RASSF4 knockdown and vincristine or dactinomycin show decreased cell growth and increased apoptosis. In vivo, mice treated with a combination of RASSF4 knockdown and vincristine showed improved survival (p 0.005) and complete tumor regression. Treatment of RMS cells with PPIX in vitro caused a time-dependent increase in cell death.

**Conclusion:** Combining RASSF4 genetic suppression with standard chemotherapy agents enhances RMS cell death in vitro and abrogates RMS tumorigenesis in vivo. Ongoing efforts are examining the pre-clinical efficacy of pharmacologic Hippo pathway activation in RMS using PPIX and verteporfin.
PRELIMINARY EXPERIENCE WITH DIFFUSION TENSOR IMAGING BEFORE AND AFTER RE-IRRADIATION TREATMENT IN CHILDREN WITH PROGRESSIVE DIFFUSE PONTINE GLIOMA

Soumen Khatua, Ping Hou, Wafik Zaky, Anita Mahajan, Leena Ketonen. UT MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Nearly 300 cases of diffuse intrinsic pontine glioma (DIPG) are diagnosed annually in the USA. The prognosis of these tumors has remained dismal for the last 20 years with a median survival of 1 year and less than 20% of children are alive at 2 years.

Objectives: The purpose of this study is to evaluate quantitative changes in diffusion tensor imaging (DTI) tractography and fractional anisotropy (FA) of the pons along with clinical correlation, in patients who receive re-irradiation for DIPG

Design/Method: A retrospective case review of children with progressive DIPG who received re-irradiation at our institution from 2007 to 2011 after approval from the Institutional Review Board was performed. Tractography analysis, and FA were analyzed pre and post re-irradiation and correlation with clinical features and MR imaging was performed

Results: DTI analysis showed reduced values of FA on tumor progression. Increase in the FA values was noted after re-irradiation in these patients. This correlated with clinical improvement. These changes were concordant with the 3D tractography analysis which showed better visualization of the corticospinal tracts as they course through brainstem and posterior transverse pontine fibers following re-irradiation

Conclusion: Serial changes in the FA values using DTI could provide clinically more correlative information in patients with progressive DIPG, who receive re-irradiation. Though the use and results of this modality has been reported in newly diagnosed DIPG before, evaluation of DTI in children who receive re-irradiation for progressive DIPG has not been reported earlier. Though limited by the small sample size and treatment variability, this study for the first time shows the preliminary experience, potential and likely efficacy of complementing DTI analysis to routine neuroimaging also in patients re-irradiated for progressive DIPG to better assess treatment response
UNIVERSAL MARKER FOR CIRCULATING TUMOR CELL DETECTION FROM PEDIATRIC-TYPE OF TUMORS
Arun Satelli, Xueqing Xia, Zachary Brown Lee, Joseph Ludwig, Keila Torres, Neeta Somaiah, Nancy Gordon, Najat Daw Bitar, Patrick Zweidler-Mckay, Mary Tomaras, Jessica Foglesong, Eugenie Kleinerman, Shulin Li. UT MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Circulating tumor cells (CTCs) are the rare cells present in the blood of patients that have the propensity to metastasize. To date, these CTCs have been detected from the blood of patients with epithelial cancers only. Absence of a specific marker on the surface of sarcoma cancer cells makes it difficult to measure CTCs from blood of patients with sarcoma tumors. Here we report for the first time, cell surface vimentin as a universal marker for the detection of CTCs from blood of patients bearing pediatric-type of tumors.

Objectives: To detect and isolate CTCs from pediatric-type of tumors using a novel monoclonal antibody 84-1 against the cell surface vimentin.

Design/Method: Different pediatric types of cancer cell lines including osteosarcoma, rhabdomyosarcoma and neuroblastoma were evaluated for the expression of cell surface vimentin expression using flow cytometry and immunocytochemistry. Blood from adult patients was collected in CPT tubes that included 12 healthy, 8 osteosarcoma and 3 Ewing sarcoma cancer patients. CD45 positive cells were isolated using EasySep method and CTCs were isolated using 84-1 mAb using magnetic beads. Isolated CTCs were further evaluated for cell surface vimentin expression and tumor specific markers.

Results: Cell surface vimentin was detectable on the surface of cancer cells only, while normal cells were undetectable. Vimentin expression on the surface of cancer cells was confirmed using a membrane marker, wheat germ agglutinin. In a pilot analysis we detected CTCs in osteosarcoma, Ewing sarcoma cancer patients with localized and recurrent disease, while CTCs were undetectable in blood samples from healthy donors. Clinical analysis revealed an increasing number of CTCs in patients with metastasis when compared to that of patients with localized disease. From this preliminary analysis, we were able to predict a threshold for metastatic prediction in Patients with CTCs $\geq$ 3/ mL.

Conclusion: This unique method for analysis of CTCs using cell-surface vimentin will facilitate the application of noninvasive tumor sampling to direct targeted therapies in pediatric cancer patients and will provide a basis for the initiation of long-term clinical studies to test the clinical significance of CTCs in pediatric type of tumors.
MULTIPLE SEGMENTAL CHROMOSOMAL ABERRATIONS IN LOW-RISK NEUROBLASTOMA ARE ASSOCIATED WITH METASTATIC RELAPSE

Jodi Mayfield, Gordana Raca, Madina Sukhanova, Rochelle Bagatell, Meredith Irwin, Anthony Little, Jawhar Rawwas, Susan Cohn. University of Chicago, Chicago, Illinois, United States of America

**Background:** Although outcomes for children with low-risk neuroblastoma are excellent, 10-15% of patients will develop recurrent disease.

**Objectives:** To identify biomarkers associated with relapse, we evaluated the pattern of chromosomal aberrations in tumors from patients with low-risk neuroblastoma.

**Design/Method:** Patients with low-risk (stage 1, 2, MYCN-nonamplified) disease who remained disease-free for > 3 years and patients who developed relapsed disease in local or metastatic sites were identified at University of Chicago, Children’s Hospital of Philadelphia, Hospital for Sick Children (Toronto) and Children’s Hospitals and Clinics of Minnesota. Formalin fixed, paraffin embedded (FFPE) tumors from the time of initial diagnosis were used for whole-genome SNP and copy number analysis using OncoScan™ FFPE Express 2.0 (Affymetrix, Santa Clara, CA). The numbers and chromosomal locations of numerical and segmental aberrations were determined and associations between the genomic aberrations and outcome were evaluated. Segmental aberrations were defined as 100 contiguous oligonucleotide probes that exhibited a different genomic status from the rest of the chromosome.

**Results:** The analytic cohort consisted of 22 low-risk patients; 9 relapsed locally, 7 relapsed at metastatic sites, and 6 remain in remission. No chromosomal aberrations were identified in 4 tumors, including 1 patient with a known family history of neuroblastoma. Numerical chromosomal aberrations (NCA) (range 1-19) were identified in 17 patients; 8 with local relapse, 5 with metastatic relapse, and 4 with no relapse. Segmental chromosomal aberrations (SCA) (range 1-12) were detected in 9 patients; 3 with local relapse, 4 with metastatic relapse, and 2 with no relapse. Based on the distribution of SCA across samples, it was found that greater than 4 SCA were only detected in tumors from patients who developed metastatic relapse (p=0.0048).

**Conclusion:** It is feasible to obtain chromosomal copy number data from FFPE neuroblastoma tissue. NCA and SCA are common in low-risk neuroblastomas. The presence of > 4 SCA may be predictive of metastatic relapse. Prospective studies to determine the prognostic value of SCA in low-risk neuroblastoma are warranted.
SUCCESSFUL MANAGEMENT OF CENTRAL HYPERTERMIA USING PROPRANOLOL IN PEDIATRIC PATIENTS WITH BRAIN TUMORS – A CASE SERIES
Brandon McNew, Ayman El-Sheikh. University of Iowa Children’s Hospital, Iowa City, Iowa, United States of America

Background: Fever of unknown origin is a common presenting symptom for primary and metastatic brain tumor patients. Central hyperthermia, always concluded as a diagnosis of exclusion, can incite repeated exhaustive infectious workups and unnecessary empiric therapies for these patients. The use of propranolol has been described to resolve central hyperthermia in adult patients, resolving fevers within 3 days of initiation. However, no pediatric cases have been described.

Objectives: Report the first case series of the successful management of central hyperthermia using propranolol in three pediatric patients with brain tumors.

Design/Method: Case Series

Results: Patient #1: 18 y.o. male with progressive metastatic Ewing sarcoma, status post autologous stem cell transplant and radiation therapy with skull lesion extending into cavernous sinus. Admitted with fever in the presence of central venous access, patient was non-responsive to empiric broad spectrum IV antibiotics x 11 days. Blood cultures grew no organisms. Extensive viral testing, fungal antigen testing, and CT imaging were unremarkable for infectious source. Patient defervesced within 3 days of initiating propranolol 20mg/m2 every 12 hours. Patient #2: 4 y.o. female with pilocytic astrocytoma WHO grade I, concurrent NF1, status post craniotomy debulking procedure, VP shunt placement. Postoperative day 3 from debulking surgery, recurrent intermittent fevers began, persisting for 4 weeks on empiric broad spectrum IV antibiotics. Daily blood cultures, CSF cultures, and CT imaging were unremarkable for infectious source. Patient defervesced within 3 days of initiating propranolol 20mg/m2 every 6 hours. Patient #3: 14 y.o. female with myxopapillary ependymoma of brain and spine, post radiation, on chemotherapy, admitted for neutropenic fever in the presence of central venous access. Fevers persisted for 26 days despite empiric IV antibiotics in addition to vancomycin, added for Streptococcus viridans grown from admission blood culture, and acyclovir, added day 5 for HSV1 PCR positive oral lesion. All other daily blood cultures were negative for growth. Extensive other viral testing, fungal antigen testing, and CT imaging were unremarkable for infectious source. Patient temperature markedly improved 3 days after initiating propranolol 25mg/m2 every 12 hours.

Conclusion: Propranolol 20-30mg/m2 every 6-12 hours is a worthy trial in pediatric patients with brain tumors with persistent fever of unknown origin.
LOCAL DIRECTED THERAPY FOR INTRAOCULAR RETINOBLASTOMA, A REVIEW OF TOXICITY AND EFFICACY OF INTRA-ARTERIAL CHEMOTHERAPY: CCHMC EARLY EXPERIENCE

Samantha Michaels, Todd Abruzzo, James Augsburger, Zelia Correa, Adam Lane, James Geller.
Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

Background: Low-dose selective intra-ophthalmic artery chemotherapy infusion (SIOAC) has been increasingly used to attempt eye salvage and minimize toxicity from therapy for intraocular retinoblastoma.

Objectives: To review the toxicity and efficacy of intra-arterial chemotherapy delivered to children with intraocular retinoblastoma at our institution.

Design/Method: Following Institutional Review Board approval, case files of all patients with intraocular retinoblastoma treated with SIOAC at Cincinnati Children’s Hospital Medical Center were retrospectively reviewed.

Results: Seventeen patients (ages 5 months to 16 years) with Group C (3), D (14) or E (2) intraocular retinoblastoma (19 eyes) received 87 SIOAC treatments between 2008 and 2013. Prior treatments included intravenous chemotherapy (10), external beam radiation (4), cryo (7) or laser (3) therapy and none (7). Fifty-seven SIOAC cycles included mono chemotherapy (melphalan (41) or topotecan (16)) and 30 included triple SIOAC (melphalan, topotecan, carboplatin). Adverse effects attributed to the 87 procedures included bronchospasm (4), minor bleeding at the groin insertion site (3), anaphylaxis (1), transient lower extremity arterial thrombosis (1) and reversible cerebral vasoconstriction (1). Local reactions in the 17 patients included transient peri-ocular swelling (12), localized hair loss (7) and skin hyperpigmentation (5). Systemic adverse effects attributed to SIOAC occurring in the 17 patients included neutropenia (10), nausea and vomiting (9) and fever (5). Grade 3 and 4 neutropenia were more common with triple therapy cycles (53.3%) than with single therapy (19.6%). Six of 87 cycles required delay and 1 patient had fever and neutropenia. Platelet and red cell transfusions were not required. Enucleation was spared in 8 of 12 pre-treated and 3 of 7 chemotherapy naive eyes (11 of 19; 57.9% overall). Six of 13 eyes and 5 of 6 eyes treated with mono and triple therapy at first SIOAC respectively did not require enucleation. Two of the 3 eyes transitioned from monotherapy to triple therapy were salvaged.

Conclusion: SIOAC can be effective for some patients with intraocular retinoblastoma and may reduce the need for systemic chemotherapy, EBRT and/or enucleation. Triple therapy seems more effective but also more myelosuppressive than single agent therapy. Larger scale clinical trials are necessary to better define the role of SIOAC for intraocular retinoblastoma.
CONGENITAL PINEAL ATYPICAL TERATOID/RHABDOID TUMOR – A RARE TUMOR, ATYPICAL LOCATION AND UNUSUAL AGE AT PRESENTATION
Jeffrey Murray, John Honeycutt, Linda Margraf, Ajit Alles, Hayden Head. Cook Children's Medical Center, Fort Worth, Texas, United States of America

Background: Atypical teratoid/rhabdoid tumor (AT/RT) is a rare embryonal CNS tumor first described in 1987. It typically occurs in very young children (typically less than 3 years), most commonly arises in the posterior fossa, tends to disseminate throughout the CNS and recurs despite intensive multimodal therapy. The prognosis is dismal. Mutations in the INI-1/SMARCB1 tumor suppressor gene are pathogenetic and some patients carry the mutation as a tumor-predisposing germline mutation. Congenital CNS tumors are uncommon and are typically benign teratomas. Pineal-region tumors in children of all ages are most typically of germ cell origin. AT/RT epicentered in the pineal region is unreported.

Objectives: To report congenital AT/RT arising in the pineal region in two young infants.

Design/Method: Two infants with congenital pineal region-epicentered AT/RT are described.

Results: Case 1: A mother’s 3rd trimester sonogram revealed macrocephaly and hydrocephalus; an abdominal prenatal MRI revealed an intracranial mass in the female fetus. Post-natal MRI revealed signs of prenatal brain injury, with only a thin rim of cerebral cortex, massive hydrocephalus and a non-enhancing, mixed solid/cystic tumor causing aqueductal obstruction. Patchy diffusion restriction was apparent. No neuraxis metastases were visualized. A subtotal resection was achieved. Histopathology revealed a malignant small round blue cell tumor with GFAP, synaptophysin, EMA and vimentin staining suggesting a non-PNET lesion. Absent INI-1 staining supported the diagnosis of AT/RT. The child is receiving chemotherapy on a clinical trial. Case 2: A 2-month-old male presented with irritability and a seizure-like episode. MRIs revealed a hemorrhagic non-enhancing mass epicentered in the pineal region with marked diffusion restriction, obstructive hydrocephalus and spinal canal metastases. Biopsy revealed a highly proliferative malignant primitive neoplasm lacking INI-1 staining, confirming the suspicion of AT/RT. A germ-line mutation in the INI-1 gene was identified. The parents chose to pursue no therapy and the infant died 2 weeks later.

Conclusion: These two unusual cases are reflective of a rare tumor occurring at an unusually young age, in an atypical CNS location. As more information is gathered regarding this rare tumor via clinical trials and from case reports, a better understanding of the true incidence, epidemiology and tumor location of AT/RT will be gained.
THE PATHOLOGY OF PEDIATRIC MEDULLOBLASTOMA IN CANADA: RESULTS OF A 20 YEAR EPIDEMIOLOGY STUDY
Serina Patel, Daniel Keene, Maria Kostova, Douglas Strother, Lucie Lafay-Cousin, Chris Fryer, Katrin Scheinemann, Anne-Sophie Carret, Adam Fleming, Vanessa Percy, Samina Afzal, Beverly Wilson, Lynette Bowes, Shayna Zelcer, Chris Mpofu, Mariana Silva, Valerie Larouche, Josee Brossard, Eric Bouffet, Donna Johnston. Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

Background: Pediatric brain tumors are the most common solid tumors in children. Of these, medulloblastoma is the most common malignant brain tumor. There are many pathological subtypes of medulloblastoma and this may influence therapy and outcome.

Objectives: To examine the epidemiology of pediatric medulloblastoma in Canada, specifically the incidence of the pathological subtypes and their survival.

Design/Method: An epidemiological survey was conducted across Canadian institutions, treating pediatric malignancies. All patients diagnosed with medulloblastoma in Canada, under the age of 18, from 1990-2010 were included. Data collected included the date of diagnosis, age at diagnosis, gender, stage, pathology, treatment, recurrence and current status. In this study, the pathological subtypes of medulloblastoma, not otherwise specified (NOS), anaplastic large cell and nodular were examined.

Results: The incidence and survival are shown in Table 1. The incidence of NOS subtype declined over the study time period, while the incidence of anaplastic subtype increased. There is a relationship between survival and pathology subtype, with anaplastic subtype having the lowest 5 year survival

Conclusion: The change in pathology over time may be explained by more precise diagnostic capabilities rather than a true change in epidemiologic patterns. This study highlights areas for future research, recognizing there is a need to correlate subtypes with new molecular markers that can aid in the management of these tumors.

Table 1: Incidence per 100,000 children under 15 years

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5.56 (3.90-8.58)</td>
<td>4.91</td>
<td>6.17</td>
<td>6.27</td>
<td>5.02</td>
<td>69.6%±1.9%</td>
</tr>
<tr>
<td>NOS</td>
<td>3.42 (1.65-6.30)</td>
<td>3.46</td>
<td>3.97</td>
<td>3.46</td>
<td>2.89</td>
<td>71.4%±2.4%</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>0.52 (0.00-1.56)</td>
<td>0.10</td>
<td>0.24</td>
<td>0.60</td>
<td>1.05</td>
<td>61.5%±7.7%</td>
</tr>
<tr>
<td>Nodular</td>
<td>0.66 (1.69-1.35)</td>
<td>0.44</td>
<td>0.81</td>
<td>0.88</td>
<td>0.54</td>
<td>70.7%±9.0%</td>
</tr>
</tbody>
</table>

195% confidence interval
HYPERMETHYLATION OF CANDIDATE TUMOR SUPPRESSOR GENES IN OSTEOSARCOMA

Daniel Pettee, Steven Kuerbitz, Christine Mella. Akron Children's Hospital, Akron, Ohio, United States of America

**Background:** Epigenetic dysregulation of gene expression associated with abnormal methylation may play a role in such tumor phenotypes as chemosensitivity, metastasis, and disease progression.  

**Objectives:** We sought to characterize methylation changes in osteosarcoma and to identify gene targets of epigenetic dysregulation.  

**Design/Method:** Genome-wide methylation profiling of individual CpG dinucleotides was performed for 16 osteosarcoma samples and 8 normal tissue and non-neoplastic control samples using the Illumina HumanMethylation450 BeadChip following bisulfite modification of genomic DNA to identify sites of consistent hypermethylation in tumor samples compared to controls. Site-specific methylation data were analyzed by comparing osteosarcoma samples to non-neoplastic controls using GenomeStudio v1.9.0 software. Each methylation site was sorted based on an average differential score. Candidate tumor suppressor gene targets were then selected for further analysis based on correlation with multiple, highly hypermethylated CpG sites indicative of aberrant CpG island methylation in tumor samples.  

**Results:** We identified candidate tumor suppressor genes PHLDA3, ZIC1, ALX4, RUNX3, CAMPTA1, DLEU7, IRX1, MSX1, and NFY-a in this analysis. Aberrant CpG methylation was confirmed in the tumor samples by the combined bisulfite restriction analysis (COBRA) assay. Expression of these genes in osteosarcoma cell lines HOS, U2OS, MNNGHOS, G292, MG63, and in cultured human mesenchymal stem cells was then analyzed by TaqMan qRT-PCR. We also determined gene expression in cell lines following treatment with the demethylating agent 5-Aza-2’-deoxycytidine compared to untreated cells. Analysis of RUNX3, CAMPTA1, DLEU7, IRX1, MSX1, and NFY-a showed expression in the OS cell lines. PHLDA3 was expressed in hMSC cells and markedly less in MNNGHOS compared to other OS cell lines. ZIC1 was expressed highly in MG63 and G292 compared to other cell lines. ALX4 was expressed highly in HOS and MNNGHOS compared to the other cell lines. Comparing 5-aza-2-deoxycytidine treated and untreated OS cell lines, we found that expression of ZIC1 was significantly higher in the treated group in U2OS and HOS. For ALX4, there was higher expression in the U2OS treated groups.  

**Conclusion:** These initial data indicate that further investigation of ZIC1 and ALX4 is warranted to identify potential roles in osteosarcoma.
PERIPHERAL BLOOD PROGENITOR CELL POPULATIONS ARE INCREASED IN PATIENTS WITH SARCOMA REGARDLESS OF TUMOR CHARACTERISTICS

Kamnesh Pradhan, Julie Mund, Heather Claussen, Yasmin Gosiengfiao, Vlad Radulescu, Jennifer Ballard, Ziyue Liu, Jamie Case, Jamie Renbarger, Terry Vik. Indiana University School of Medicine, Indianapolis, Indiana, United States of America

Background: Our group previously demonstrated that multiparametric flow cytometry (MPFC) can be utilized to identify two phenotypically and functionally distinct circulating hematopoietic stem and progenitor cell (CHSPC) populations (pro-angiogenic and non-angiogenic), as well as endothelial colony forming cells (ECFCs) from the peripheral blood of pediatric patients with malignant solid tumors. In pre-clinical studies we have shown that these circulating cells are vital for tumor induced angiogenesis and growth. The CHSPCs and the ratio of pro-angiogenic and non-angiogenic CHSPCs (CHSPC ratio), along with the ECFCs, are significantly elevated in these patients compared to healthy controls (HC) and may serve as predictive or prognostic biomarkers.

Objectives: To study the association between sarcoma characteristics, namely type, size, stage and CHSPCs, CHSPC ratio, and ECFCs among pediatric patients and the impact of cancer-directed therapies on the above cellular profile in a prospective setting.

Design/Method: An observational, multi-institutional, longitudinal study of children (age range: 1-21 years) with the diagnosis of Osteosarcoma (OS), Ewing’s sarcoma (ES) or Rhadomyosarcoma (RMS) was conducted. The MPFC protocol was used to analyze blood at baseline, after a cycle of chemotherapy, before and after local control, and at end of treatment. Baseline and subsequent time-point measures were compared with each other and HC using Wilcoxon rank sum tests. Descriptive statistics were used to characterize the data.

Results: A total of 29 subjects enrolled at baseline (ES=11, OS=12, and RMS=6) and 21 subjects were tested at all 5 time-points. All patients had elevated levels of CHSPCs, CHSPC ratio, and ECFCs compared to HC (all p values <0.05). No significant differences were present between baseline and subsequent time-points. At baseline there was no difference in the cellular profile between tumor-type (ES and OS only), tumor size, and tumor stage (metastatic v/s non-metastatic).

Conclusion: This is the first study showing CHSPC and ECFC numbers do not differ based on tumor characteristics, and although elevated compared to HC, cancer-directed therapies do not impact their levels. A study with larger sample-size and longer follow-up is needed to assess if these circulating cell populations are predictive of treatment response or prognostic for overall survival. References: 1. Pradhan K, Cytometry B, 2011. 2. Mund J, Angiogenesis, 2013
ZOLEDRONIC ACID AS MAINTENANCE IN HIGH RISK OSTEOSARCOMA
Amina Rafique, Paul Kent, Patrick McIntire, Jason Romancik. Rush University Medical Center, Chicago, Illinois, United States of America

Background: OS patients with metastatic, early relapsed or unresectable OS have < 20 year survival. ZA is a standard treatment for osteopenia and has been shown to have direct antitumor effects in OS. A 2010 study adding a bisphosphonate to standard “MAP” chemotherapy showed improved 5-year overall survival. We offered ZA to osteopenic patients after completion of chemotherapy for high risk OS in a maintenance setting

Objectives: To evaluate overall survival of High risk Osteosarcoma (OS) patients treated with zoleadronic acid (ZA) maintenance

Design/Method: 15 pediatric “high risk” OS patients were treated with ZA in “maintenance” after completion of chemotherapy at our institution over the last 5 years. All had documented osteopenia, and all were treated with a dose of 2.3 mg/m² (max dose 4 mg). We defined “high risk” as poor histologic response, relapse < 24 months since diagnosis, multiple relapses, metastatic disease or unresectable disease. These patients were further subdivided into 3 groups (See Figure). Time = 0 is the date of diagnosis that made the patient eligible for consideration of ZA maintenance.

Results: 159 doses of ZA were given, with a mean of 10.6 doses (3 – 26). 5 of 15 were female, average age at start of ZA maintenance was 17 (7-29). ZA was well tolerated. 10 of 15 patients are alive at median follow up of 42 months.

Conclusion: Our retrospective study suggests that maintenance chemotherapy with ZA may offer a survival benefit to high risk OS patients.

**Graph:**

- **Group A:** Primary OS with poor histologic response → ZA every 3 months.
- **Group B:** Early relapse resected OS → ZA monthly.
- **Group C:** Primary metastatic or unresectable primary/recurrent OS → ZA and Avastin monthly.
NANOPARTICLE DELIVERY FOR THE TREATMENT OF PONTINE GLIOMAS
Harini Rao, Mark Saltzman, Farzana Pashankar. Yale University, New Haven, Connecticut, United States of America

**Background:** Malignant brain tumors in children younger than age 15 years account for ~ 20% of brain tumors. Brain tumor therapy is currently limited in terms of the number of drugs and drug delivery systems to which can be applied. Development of delivery systems is disadvantaged by the availability of suitable models for studying such systems in vitro. A major limitation to pediatric brain tumors is the blood brain barrier. Development in the neuro-oncology field has shown some advancement in treating brain tumors using local delivery mechanisms. Unresectable brain tumors, such as pontine gliomas, do not have known effective long-term therapy. By applying convection delivery mechanisms, these unresectable brain tumors may show some response to targeted delivery.

**Objectives:** To devise a delivery system to directly target pontine gliomas with nanoparticles via convection enhanced delivery.

**Design/Method:** Nanoparticles are developed using a standard method to encapsulate chemotherapeutic agents. A mouse model glioma cell line, NP53 and a glioblastoma (GBM) cell line, U-87 are used to determine drug alone versus nanoparticle encapsulated drug. Carboplatin is currently the drug being tested using cell titer assays in order to obtain cell viability when treated with the drug-nanoparticle combination.

**Results:** Dose responses are observed when testing the cell lines with drug alone and drug encapsulated nanoparticles. Cell viability decreases as drug concentration increases.

**Conclusion:** Encapsulated chemotherapeutic agents, such as Carboplatin can be used to directly target pontine gliomas. Glioma cell lines and GBM cell lines have shown cell death with administration of Carboplatin encapsulated nanoparticles.
ACUTE NEUROTOXICITY RELATED TO HIGH DOSE SYSTEMIC METHOTREXATE CHEMOTHERAPY
Harini Rao, Brian Harshman, Amit Mahajan, Farzana Pashankar. Yale University, New Haven, Connecticut, United States of America

**Background:** Neurotoxicity with MRI changes following intrathecal Methotrexate administration is well documented in the literature, though the mechanism is not completely understood. Acute neurotoxicity following high dose systemic Methotrexate has not been well described before.

**Objectives:** To describe changes of acute neurotoxicity following systemic methotrexate on diffusion-weighted MRI imaging (DWI).

**Design/Method:** Retrospective chart evaluation was performed of patients who developed acute neurologic toxicity after receiving high dose systemic Methotrexate at our institution from April 2009 to March 2012. Imaging findings were reviewed and correlated with duration of treatment and temporal correlation with Methotrexate administration was evaluated. 8 patients were identified. All patients had an MRI at presentation of acute symptoms, including DWI, and 3 of 8 (38%) underwent at least one follow-up MRI.

**Results:** Acute DWI changes were found in all 8 patients, primarily in the centrum semiovale, imaged at 1 to 9 weeks following systemic chemotherapy. Complete clinical recovery was demonstrated in 5 patients and the remaining 3 patients had significant improvement with no major deficits. The DWI changes improved on the 3 follow-up exams with eventual fluid-attenuated inversion recovery (FLAIR) changes on 1 exam.

**Conclusion:** High dose systemic Methotrexate produces similar acute neurotoxicity as does IT administration. Most experience transient stroke-like symptoms with restricted diffusion in the periventricular and/or subcortical white matter on DWI sequences. The majority made a full clinical recovery with the MRI changes representing areas of demyelination or focal subcortical ischemia. Sparing of the gray matter explains the relatively mild and transient nature of neurological deficits.
METAISTIC EPITHELIOID HEMANGIOENDOTHELIOMA TREATED WITH LIVER TRANSPLANT
Andrew Walter, Tracy Hills, Stephen Dunn. A. I. duPont Hospital for Children, Wilmington, Delaware, United States of America

**Background:** Hepatic epithelioid hemangioendothelioma (HEHE) is a rare, vascular, endothelial malignancy found predominantly in adults. There is no standard, curative therapy for HEHE due to the rarity and unpredictable nature of the disease. Largely unresponsive to chemotherapy, liver transplantation is considered a treatment option when complete tumor resection is otherwise impossible.

**Objectives:** Review successful treatment of a teenager with metastatic HEHE.

**Design/Method:** Case review and report.

**Results:** A 12-year-old female with a history of chronic abdominal pain presented with worsening abdominal pain, weight loss, fatigue and intermittent left shoulder pain. A CT abdomen revealed numerous lesions throughout the liver, as well as several tiny lung nodules. An open liver biopsy was done. Immunohistochemistry was positive for CD31, CD34, and Factor VIII antigen, a diagnosis of HEHE was made. She was treated, sequentially, with bevacizumab, interferon alpha-2b and finally carboplatin/etoposide/vincristine. Due to severe thrombocytopenia from chemotherapy and lack of response to therapy, she was referred for liver transplant. She underwent a whole organ, orthotopic liver transplant approximately eight months after her initial diagnosis. Her post transplant course was uneventful and she remains free of progression four years following transplant.

**Conclusion:** Primary malignant hepatic tumors comprise less than 2% of all childhood cancers. HEHE represents only a tiny fraction of this 2%. Distinctive pathological findings include positive staining for factor VIII related antigen and endothelial markers CD31 and CD34. The tumor mass is often large at presentation and unresectable by partial hepatectomy alone. While various chemotherapeutic agents have been tried there is a lack of consensus regarding effective treatment. Surprisingly, the presence of metastatic disease in patients with HEHE does not appear to be associated with decreased overall survival, as in this case. Our patient has continued to do well post transplant with stable pulmonary nodules. She remains on sirolimus, which, by virtue of its anti-angiogenic properties, could be contributing to the lack of progression of the pulmonary nodules in this vascular tumor. It is not clear if her pulmonary nodules represent tumor so we cannot claim that she is free of disease. However, she is doing well four years post transplant and planning to attend college.
OUTCOMES WITH ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CONGENITAL AND ACQUIRED BONE MARROW FAILURE SYNDROMES: AN INSTITUTIONAL EXPERIENCE

Amulya Nageswara Rao, Gourde Julia, Vilmarie Rodriguez, Shakila Khan. Mayo Clinic, Rochester, Minnesota, United States of America

Background: Allogeneic hematopoietic stem cell transplantations (HSCTs) are being increasingly used in the treatment of bone marrow failures syndromes (BMFS) and outcomes have improved dramatically over the past couple of decades.

Objectives: To review the clinical outcomes of patients aged 0-21 years treated with allogeneic HSCTs for congenital or acquired BMFS.

Design/Method: Ten year retrospective case series.

Results: This study included 15 transplants (9 female; 6 male). Primary transplant indications included acquired severe aplastic anemia (SAA) (n=11), Fanconi anemia (n=1), congenital amegakaryocytic thrombocytopenia (n=2), Diamond Blackfan anemia (n=1). One patient with SAA later developed features of dyskeratosis congenita. Bone marrow was the stem cell source for all transplants. Conditioning regimens included cyclophosphamide/Campath-1H (alemtuzumab)/total body irradiation (TBI) (n=5), cyclophosphamide/antithymocyte globulin (ATG) (n=4), busulfan/cyclophosphamide (n=2), fludarabine/Campath-1H/TBI (n=1), busulfan/cyclophosphamide/Campath-1H (n=2), cyclophosphamide/TBI/ATG (n=1), and cyclophosphamide/TBI (n=1). Graft versus host disease (GVHD) prophylaxis was with tacrolimus/methotrexate (n=10), tacrolimus (n=4), and cyclosporine/methotrexate (n=1). Median age at transplant was 8.3 years (range; 0.9-19.8 years). Median time between diagnosis of primary condition and transplant was 0.7 years (range; 0.1 to 8.6 years). Seven transplants were unrelated donor transplants, 7 had sibling donors and 1 had a parent for donor. Median time to engraft was 23 days (range; 18-30 days). One patient had a graft failure 10 months posttransplant. He had a successful second transplant. Only 1 patient (7%) developed grade IV acute and significant chronic GVHD. Median follow up time was 1375 days (range 236 - 3756 days). Event free survival was 100% at 100 days and 92% at 3 years. There were no patient deaths. Significant infectious complications included varicella zoster (n=3), active CMV disease (n=1), PCP pneumonia and retinal toxoplasmosis (n=1), and pulmonary aspergillosis (n=1). One patient developed PTLD and was successfully treated with rituximab.

Conclusion: Our cohort demonstrates that both matched unrelated and related allogeneic HSCTs are safe and effective in patients with congenital and acquired BMFS. Use of bone marrow as the stem cell source, appropriate choice of conditioning regimens and GVHD prophylaxis, strict prophylaxis and infection surveillance have greatly reduced the burden of severe GVHD, graft failure, and transplant related morbidity and mortality.
T CELL-DEPLETED HAPLOIDENTICAL ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN AND ADOLESCENTS
Ho Joon Im, Kyung Nam Koh, Jong Jin Seo, Jin Kyung Suh, Seong Wook Lee, Eun Seok Choi. Asan Medical Center, Seoul, Republic of Korea

Background: Haploidentical haematopoietic stem cell transplantation (HHCT) has become a possible alternative treatment for patients with malignant or non-malignant diseases who lack an HLA-matched related or unrelated donor. However, a high rate of graft rejection and refractory graft versus host disease (GVHD) have been major drawbacks to the universal use of HHCT for patients who need transplantation for cure but lack a suitable donor. In addition, delayed immune recovery and a high prevalence of infection are major ongoing problems.

Objectives: We evaluated the feasibility of CD3-depleted haploidentical stem cell transplantation (HHCT) in children and adolescents with malignant and non-malignant diseases.

Design/Method: Between July 2008 and January 2013, 28 patients underwent a total of 35 HHCTs with in vitro CD3-depleted peripheral blood stem cells, of which nine patients had hematologic malignancy (one ALL, six AML, and two MDS-RCMD), 18 had non-malignant hematologic disease (one Fanconi anemia, 16 acquired SAA, and one congenital dyserythropoietic anemia), and one had refractory neuroblastoma.

Results: Of the 28 patients, 26 achieved neutrophil engraftment at a median of 11 days (range, 9–15 days) post-transplant. Two patients failed to achieve primary engraftment, and five patients experienced graft rejection after primary engraftment. All 7 patients underwent second HHCT and achieved stable engraftment. Thus, the final engraftment rate was 100%. The cumulative incidence (CI) of ≥ grade II and ≥ grade III acute GVHD were 33.3% and 14.3%, respectively and the 1-year CI of extensive chronic GVHD was 11.1%. Three patients died of non-relapse-related causes (two of CMV disease, and one of encephalopathy) and one patient died of leukemia relapse. The non-relapse mortality at 1 year was 10.7%. At a median follow-up of 27.3 months (range, 11.4–66.9 months), the overall survival at 2 years was 83.6%. The event-free survival for the 25 patients with non-malignant diseases or malignant diseases in remission at the time of transplantation was 96.0%.

Conclusion: HHCT is a realistic alternative for pediatric patients with malignant or non-malignant diseases who lack a suitable donor.
IMPACT OF HIGH-RESOLUTION TYPING FOR HLA-A, -B, -C AND -DRB1 ON OUTCOME OF UNRELATED SINGLE-UNIT CORD BLOOD TRANSPLANTATION IN PEDIATRIC PATIENTS

Background: Current practice in choosing potential donors for umbilical cord blood transplantation (UCBT) involves matching at the antigen level for HLA-A and HLA-B by low-resolution (LR) typing and at the allele level for HLA-DRB1 by high-resolution (HR) typing.

Objectives: To determine the significance of HR HLA matching on UCBT outcome in our study population of 64 pediatric patients ≤21years-old, providing 68 total transplants for malignant and non-malignant diseases.

Design/Method: We identified 64 UCBT recipients (≥2.0X10^7TNC/kg) and compared original HLA typing (LR HLA-A-B; HR HLA-DRB1) to HR HLA typing (HR HLA-A-B-C-DRB1). IRB approved retrospective chart review was conducted to determine incidence of engraftment, relapse, acute and chronic graft-versus-host disease (GVHD), early transplant-related infections and death. The following subgroups were identified: <4/8 versus ≥4/8, <5/8 versus ≥5/8 and <6/8 versus ≥6/8 allelic matches, and analyzed for each variable using Fisher exact test.

Results: 15% of units were matched at all loci; 7% were mismatched at 1, 16% at 2, 28% at 3, 27% at 4, 4% at 5, and 2% at both 6 and 7 alleles. Ten of 13 (77%) transplants originally matched at LR HLA-A-B and HR HLA-DRB1 remained matched at the allelic level (HR HLA-A-B-C-DRB1). Comparison of the 3 subgroups as outlined above showed significant reduction in death in transplants matched at ≥6/8 alleles (p = 0.017) versus <6/8 alleles. Although decreased in incidence, there was no significant association of graft failure, GVHD or infections.

Conclusion: HR typing should be evaluated for UCB selection as ≥6/8 allele match predicts decreased mortality in our small cohort.

Incidence and probability of engraftment, acute and chronic GVHD, infection and death in UCBT recipients based on HR HLA typing

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Engraftment</th>
<th>p</th>
<th>aGVHD</th>
<th>p</th>
<th>cGVHD</th>
<th>p</th>
<th>Infection</th>
<th>p</th>
<th>Death</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4/8 (5)</td>
<td>n = 3 (3/5)</td>
<td>0.627</td>
<td>n = 2 (2/5)</td>
<td>0.656</td>
<td>n = 0 (0/5)</td>
<td>1.000</td>
<td>n = 1 (1/5)</td>
<td>1.000</td>
<td>n = 2 (2/5)</td>
<td>1.000</td>
</tr>
<tr>
<td>≥ 4/8 (63)</td>
<td>n = 45 (45/63)</td>
<td></td>
<td>n = 20 (20/63)</td>
<td></td>
<td>n = 6 (6/63)</td>
<td></td>
<td>n = 14 (14/63)</td>
<td></td>
<td>n = 21 (21/63)</td>
<td></td>
</tr>
<tr>
<td>&lt; 5/8 (23)</td>
<td>n = 16 (16/23)</td>
<td>1.000</td>
<td>n = 8 (8/23)</td>
<td>0.789</td>
<td>n = 0 (0/23)</td>
<td>0.089</td>
<td>n = 5 (5/23)</td>
<td>1.000</td>
<td>n = 11 (11/23)</td>
<td>0.106</td>
</tr>
<tr>
<td>≥ 5/8 (45)</td>
<td>n = 32 (32/45)</td>
<td></td>
<td>n = 14 (14/45)</td>
<td></td>
<td>n = 6 (6/45)</td>
<td></td>
<td>n = 10 (10/45)</td>
<td></td>
<td>n = 12 (12/45)</td>
<td></td>
</tr>
<tr>
<td>&lt; 6/8 (42)</td>
<td>n = 27 (27/42)</td>
<td>0.179</td>
<td>n = 15 (15/42)</td>
<td>0.595</td>
<td>n = 3 (3/42)</td>
<td>0.668</td>
<td>n = 9 (9/42)</td>
<td>1.000</td>
<td>n = 19 (19/42)</td>
<td>0.017</td>
</tr>
<tr>
<td>≥ 6/8 (26)</td>
<td>n = 21 (21/26)</td>
<td></td>
<td>n = 7 (7/26)</td>
<td></td>
<td>n = 3 (3/26)</td>
<td></td>
<td>n = 6 (6/26)</td>
<td></td>
<td>n = 4 (4/26)</td>
<td></td>
</tr>
</tbody>
</table>
DIVERSE PRESENTATIONS OF HLH AND HLH PREDISPOSING SYNDROMES
Laura McCarthy, Eric Bugaieski, Manuel Doria, Karen Fernandez, Penelope Sandiford, Reuben Antony. Children's Hospital of Illinois, Peoria, Illinois, United States of America

Background: In Hemophagocytic Lymphohistiocytosis (HLH) activation of CD8+ lymphocytes, macrophages and high levels of IFN-G, IL-1, IL-6, IL-10 cause a hyperinflammatory state with different organ systems variably involved, often resulting in confounding clinical/laboratory presentations. HLH can be caused by inherited mutations that impair lymphocyte cytotoxic function or sporadically triggered by malignancy, rheumatologic disorders and infection.

Objectives: Using clinico-pathological data/images and radiology images we outline our experience managing 6 children with HLH/HLH predisposing syndromes.

Design/Method: Case Series

Results: Patients: (1) 16 year old male presented with EBV infection, hematuria and diarrhea. He met HLH-2004 clinical/laboratory diagnostic criteria without bone marrow (BM) hemophagocytosis. Familial HLH (FHLH) studies revealed XIAP deficiency. He was treated with Dexamethasone, Rituximab and IVIG and has been referred for a matched unrelated donor (MUD) stem cell transplant (SCT). (2) 13 year old sibling of patient 1 was diagnosed with XIAP deficiency shortly after patient 1. He has not had HLH but has had recurrent purulent abscesses (non-spore forming gram (+) bacilli) on his face/neck. He is being evaluated for SCT. (3) 14 year old female presented with fever, histoplasma pneumonia and pleural effusions. BM showed hemophagocytosis; FHLH studies were negative. She was treated with anti-fungals and HLH-2004 therapy (without Etoposide) with no recurrence. (4) 5 year old male with pancytopenia, diarrhea, anuria, confusion, seizures. BM showed erythrophagocytosis and LP showed pleocytosis/increased protein. FHLH studies showed a heterozygous 272C:T(A91V) variant in the PRF1 gene. Treated with intrathecal Hydrocortisone, Dexamethasone, renal-dose Etoposide, and Alemtuzumab. Despite ECMO support, patient died. (5) 5 year old female with fever, rash, respiratory distress, and tarry stools. She received ventilator support, inotropes and ECMO but died within 48 hours. Post-mortem studies revealed hemophagocytosis in the spleen/lymph nodes/BM/liver/respiratory tract/pancreas. FHLH studies were negative but rickettsial antigens-genome identified in all tissues examined. (6) 4 month old male with fever, diarrhea, hepatomegaly, pancytopenia. Stool studies (+) for rotavirus. FHLH studies demonstrated 2 STXBP2 mutations (1621 G>A/703 C>G). After HLH-2004 therapy, he underwent an MUD cord blood transplant but succumbed to complications.

Conclusion: We present these patients to highlight the diverse presentations of HLH so that this potentially devastating syndrome can be diagnosed quickly and promptly treated.
CASE SERIES OF VENOUS THROMBOEMBOLISM FROM A PEDIATRIC SICKLE CELL DISEASE CENTER AND FIRST CASE REPORT OF MAY-THURNER SYNDROM IN SICKLE CELL DISEASE

Jessie Barnum, Stephen Nelson. Children's Hospitals and Clinics of Minnesota, Minneapolis, Minnesota, United States of America

**Background:** The association of hypercoagulability with sickle cell disease (SCD) has been established. Prevalence of deep vein thrombosis (DVT) in the adult SCD population has been reported; a multicenter retrospective review of over 97 million African-American adults discharged from 1991 through 2003 revealed DVT in 0.7% of adults with SCD.1 A multicenter retrospective review of over 2.9 million children discharged from over 34 US Children’s Hospitals from 2001 through 2007 revealed a DVT rate of 0.46%.2 DVT prevalence in the pediatric SCD population has not yet been published. May-Thurner syndrome (MTS) is an anatomic cause for DVT which is also known as iliac vein compression syndrome. It classically involves compression of the left common iliac vein by the overlying right common iliac artery.

**Objectives:** Investigate the prevalence of DVT in our pediatric SCD population, and describe the first reported case of MTS in a patient with sickle cell disease.

**Design/Method:** Consecutive retrospective case series of admissions to Children’s Hospitals and Clinics of Minnesota from January 2003 through October 2013 involving ICD-9CM codes of “sickle cell” and “thrombosis.” Chart review of MTS patient.

**Results:** Five of 180 patients (2.8%) with SCD had a DVT. Four patients were female and one was male. Mean age was 11.2 years (2-19 years). Three patients had central venous catheters. Two patients were admitted for acute chest syndrome. One patient was found to have May-Thurner syndrome and multiple pulmonary emboli. She underwent angioplasty with directed tPA and stent placement as well as anticoagulation.

**Conclusion:** Our case series reveals seven times the rate of DVT in hospitalized pediatric SCD patients when compared to a recent report in pediatric patients.2 Multicenter pediatric studies are warranted to further elucidate the prevalence and risk factors. While MTS is rare, we advocate that it be considered in children with a left lower extremity DVT. Diagnosis of MTS is critical, as management is complex and typically requires treatment in concert with an interventional radiologist or surgeon.1 Stein PD et al, Am J Med, 20062 Raffini L et al, Pediatrics, 2009
THROMBOSIS ASSOCIATED WITH IVIG: CASE REPORT AND PROVINCIAL ANALYSIS BASED UPON QUEBEC HEMOVIGILANCE SYSTEM

Joy Benadiba, Nancy Robitaille, Yves Pastore. Universitary hospital of Sainte Justine, Montreal, Quebec, Canada

Background: Background: Intravenous Immunogloblin (IVIG) is frequently used in the treatment of immune-mediated disorders such as immune thrombocytopenia (ITP), inflammatory diseases and immune deficiencies. It is prepared from plasma pooled from healthy donors and used since 1952. Over the last decade, IVIG use has dramatically increased across the world. IVIG is generally considered safe and secure with acceptable adverse events including headaches or fever. However, rare serious adverse events (SAE) can occur.

Objectives: Objective: Following a case report of a pediatric patient with IVIG-associated thrombotic complication, we reviewed the incidence of SAE through reports of Quebec Hemovigilance System (QHS).

Design/Method: Method: Retrospective review of QHS database of thrombotic complications possibly associated with IVIG, including detailed report on pediatric patient.

Results: Results: Through QHS, we found 4 reports of thrombotic events possibly related to IVIG, all but one having occurred in adults. The single paediatric case occurred in a 16-year-old female receiving IVIG for history of severe ITP and menorrhagia. Ten days after a third IVIG course, she developed cerebral thrombosis. Based upon QHS reports, thrombotic complications occurred for 0.6-1.6% of all reported IVIG-related SAE. Over a five-year period (2005-2010), there have been 112 CNS-related events such as severe headaches or aseptic meningitis. The incidence ranged between 1:6683 and 1:9580 events per gram of IVIG given.

Conclusion: Conclusion: Since the first report of IVIG-associated thrombosis in 1986, more than one hundred cases have been reported, with only six pediatric cases. Patient’s predispositions were found to be associated with higher risk of thrombosis, as well as rapid infusion, high dosage and concentration. The thrombotic effects of IVIG may be due to contamination with activated factor XI, arterial vasospasm or increased blood viscosity. ITP has itself been paradoxically recognized as a possible pro-thrombotic condition. Clinicians should have a high suspicion for intracranial complications, including thrombosis, in patients receiving IVIG and history of recurrent headache. IVIG related complications should be thoroughly investigated and properly reported, in order to improve hemovigilance system and study of such rare SAE.
A RARE CASE OF SIBLINGS WITH METASTATIC EWING'S SARCOMA
Behzad Bidadi, Vilmarie Rodriguez, Peter Rose, Carola Arndt, Amulya NageswaraRao. Mayo Clinic, Rochester, Minnesota, United States of America

Background: Ewing’s sarcoma is a rare small round blue cell tumor that usually presents by the second decade of life. Most cases are characterized by a translocation between the EWSR1 gene and an ETS family gene. Ewing's sarcoma is more commonly seen in Caucasians than other racial groups. There are no known associated familial cancer syndromes. Familial Ewing’s sarcoma is exceedingly rare and there are only three reports of female siblings with Ewing’s sarcoma.

Objectives: To describe a case of siblings with Ewing’s Sarcoma and to review the rare potential for genetic predisposition.

Design/Method: Case report of two siblings with Ewing’s sarcoma and literature review.

Results: The first affected sibling was eighteen when he was diagnosed with Ewing's sarcoma of his right humerus metastatic to lungs. He initiated chemotherapy per protocol AEWS0031 with a compressed cycle regimen of vincristine, doxorubicin and cyclophosphamide alternating with ifosfamide and etoposide. His treatment included surgical resection of the primary lesion and lung radiation. Two months after treatment, he was found to have biopsy proven local recurrence and pulmonary metastases. He progressed during salvage chemotherapy and died four months following recurrence. Two months later, his 17 year old sister presented with respiratory distress and SVC syndrome related to a large mediastinal mass confirmed to be Ewing’s sarcoma. PET scan demonstrated widely disseminated disease including metastases to the manubrium, skull, left scapula, vertebrae and right tibia. Treatment included the aforementioned chemotherapy regimen and radiation to all sites of disease. She is alive ten months after diagnosis. Recent PET scan showed improved response with no progression. She underwent P53 gene testing that was unremarkable. There is no history of consanguinity and there is otherwise no significant family history of cancer. The patients have an unaffected brother. Genomic analysis of the patient and immediate family is underway.

Conclusion: To our knowledge, this is the first reported case of siblings with Ewing’s sarcoma who were of different genders. Similar to prior reports in siblings, our patients also had aggressive metastatic disease. Genomic analysis could reveal insight into an underlying genetic predisposition to Ewing’s sarcoma.
RASBURICASE-INDUCED METHEMOGLOBINEMIA AND HEMOLYSIS IN A FEMALE PATIENT
James Bistolarides, Elitsa Nicolaou, Chi Braunreiter. Helen DeVos Children's Hospital, Grand Rapids, Michigan, United States of America

Background: Hyperuricemia and tumor lysis syndrome associated with malignancies can be successfully managed with rasburicase. Rasburicase reduces serum uric acid (UA), but produces hydrogen peroxide, which increases oxidative stress. In patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, this stress can result in methemoglobinemia, hemolysis, or both. As G6PD deficiency is an X-linked recessive disease, reported cases are male patients.

Objectives: To describe a female patient with no clinical history of G6PD deficiency, who developed methemoglobinemia, hemolysis, and respiratory distress after rasburicase.

Design/Method: The patient is a 15-year-old adopted African American female admitted with multiple progressive neurologic deficits secondary to large chloromas, peripheral blasts consistent with leukemia, and serum UA of 9.9 mg/dL. She was adopted at a young age with no reports of medication allergies, anemia, or jaundice with antibiotics. A test dose of rasburicase (0.06mg/kg) was administered without complications. Eight hours later, she received an additional 0.14mg/kg (total 0.2mg/kg) dose. Shortly after, she developed respiratory distress, with methemoglobin level peaking at 16% (normal 0-2.5%) and hemolysis, with hemoglobin decreasing from 9.3 to 4.7g/dL. G6PD activity was later found to be 7.8 U/g Hb (normal 8.8-13.4 U/g Hb).

Results: To the best of our knowledge, this is the first case of a female patient developing methemoglobinemia and hemolysis with rasburicase. Females can express X-linked recessive disorders by being a carrier, via lyonization whereby random X inactivation leads to gene expression of the persisting X chromosome, or by inheriting one mutant X chromosome from each parent. Testing for G6PD activity in high-risk populations is recommended, but may not be readily available. Despite efforts to discern her disease status by obtaining a detailed history and administering a small test dose of rasburicase, these were insufficient to elucidate her enzyme activity level.

Conclusion: Females of high-risk populations can be G6PD deficient. Smaller doses of rasburicase may yield insufficient oxidative stress for mild disease and should only be considered in an emergency situation; a larger study is required to demonstrate safety and efficacy. Absent complications should not be a substitute for G6PD screening, as this may provide a false indication of safety.
TREATMENT OF AGGRESSIVE ABDOMINAL CARCINOMA OF UNKNOWN PRIMARY IN PEDIATRIC PATIENT
JoAnn Bolude, Tiffany Molina, Aaron Sugalski. University of Texas Health Sciences Center, San Antonio, Texas, United States of America

**Background:** In pediatrics, carcinoma of unknown primary (CUP) is a very rare diagnosis that usually holds a dismal prognosis. Frequently, at diagnosis the tumor is unresectable and metastatic.

**Objectives:** We present a 9 yr old patient who presented with severe weight loss, early satiety, and a large palpable abdominal mass. She had a good response to an alternative chemotherapy regimen and ultimately had a gross total resection of her disease.

**Design/Method:** Diagnosis of our patient’s tumor was difficult due to poor differentiation of the tissue and the primary site being unclear. Tumor markers were normal except for the CA-125 elevated at 1581 U/mL. After extensive investigation and many immunostains, multiple pathologists were able to rule out typical pediatric abdominal tumors including neuroblastoma, Wilms Tumor, rhabdoid tumor, renal cell carcinoma and the diagnosis was made, with presumed left renal primary. Adult data on CUP and renal carcinoma shows an increased sensitivity to cisplatin-based therapy for such tumors. The decision was made to treat with a total of 6 cycles with gemcitabine (100mg/m2), paclitaxel (1000mg/m2) and carboplatin (AUC 6/dose). Cycles were given every three weeks. All three drugs were given on day 1, and gemcitabine and paclitaxel was given on day 8, with no chemo on day 15.

**Results:** Periodic evaluation with CT scans and monitoring of CA-125 levels were performed after every 2 cycles. Significant decrease (greater than 50% shrinkage of bulky disease) was seen and we observed a steady decline in the CA-125 tumor marker to a level of 3.2 U/mL after six cycles with weight gain of 7.5 kilograms. She then had surgical exploration with resection of residual L kidney tissue, tail of pancreas, spleen, posterior L diaphragm, 2 lesions on aorta and 3 lesions from liver. The tissue from surgery showed 75-80% tumor necrosis and we plan to consolidate her therapy with two more cycles of chemotherapy.

**Conclusion:** This pediatric case demonstrates the efficacy of a platinum-based regimen as a cornerstone for treatment of CUP malignancies. It supports the success of future use for this regimen not only in the adult, but also in the pediatric world.
HEREDITARY SPHEROCYTOSIS DUE TO BIALLELIC OR MONOALLELIC ANKYRIN MUTATIONS
Satheesh Chonat, Neha Dagaonkar, Tamara Maghathe, Jesicca Connor, Eric Mullins, Kejian Zhang, Theodosia Kalfa, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

Background: Hereditary Spherocytosis (HS) is the most frequent cause of congenital anemia in northern European descendants. It is a genetically heterogeneous disease caused by defects in ankyrin, α- and β-spectrin, band 3, and protein 4.2, affecting the vertical association of the cytoskeleton and RBC lipid bilayer. Ankyrin gene (ANK1) mutations, causing spherocytosis type 1 (OMIM #182900), are the most common cause of dominant HS.

Objectives: To establish genetic diagnosis in children with non-immune hemolytic anemia using Next-Generation sequencing (performed within an IRB-approved research study).

Design/Method: Case series describing a child with transfusion-dependent HS due to biallelic ANK1 mutations and two siblings with dominant HS due to monoallelic ANK1 mutation.

Results: Case 1: Four-year-old biracial male presented soon after birth with non-immune hemolytic anemia and a negative family history for anemia, jaundice, cholelithiasis, or splenectomy. He has been on chronic transfusions since birth. Next-Generation sequencing revealed two Ankyrin mutations: c.2205G>C (p.Y735*), a novel mutation causing premature termination, and c.3224G>A (p.T1075I), known as ankyrin-Tubarao. Sanger sequencing of parental DNA for the involved ANK1 exons, revealed that the African-American father carried p.T1075I, while p.Y735* was a de novo mutation, absent in both parents. The patient is currently treated with RBC transfusions every 1-2 months and oral iron chelation for transfusional hemosiderosis. With the establishment of his diagnosis as HS and no mutations identified in the stomatocytosis-associated genes, he will proceed to splenectomy after 5 years of age.

Cases 2&3: Three-year-old biracial female presented at second day of life with anemia and jaundice. The African-American father had history of chronic hemolytic anemia with jaundice and cholelithiasis. Diagnosis of HS was made based on the presence of spherocytes on the blood smear, high MCHC and the recent genetic analysis revealing a novel ANK1 mutation: c.3464delG, causing frame-shift. Her younger sister has the same mutation causing dominantly inherited HS.

Conclusion: Hereditary Spherocytosis is a fascinating diagnosis with wide phenotypic variability. Use of Next-Generation sequencing in these disorders can allow for a rapid diagnosis even in patients requiring regular transfusions and can assist physicians in the management of these patients.
CHILDHOOD OPTIC NERVE SHEATH MENINGIOMAS
Satheesh Chonat, Ralph Salloum, John Breneman, Michael Gray, Bernadette Koch, Maryam Fouladi.
Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, United States of America

**Background:** Optic nerve sheath meningiomas (ONSM) represent approximately 2% of all orbital tumors in childhood and are most commonly seen in middle-aged females. We present a case of this very rare tumor in a child and review the literature.

**Objectives:** To describe the presentation of ONSM in children and highlight challenges in diagnosis and management.

**Design/Method:** Case report and systematic review of the literature.

**Results:** A 13-year-old female presented with progressive visual decline in her left eye over 3 months, diplopia for 6 weeks and left-sided retro-orbital headache. Examination revealed mild Left eye proptosis, full, painless extraocular movements, mild afferent pupillary defect and visual acuity of 20/200. Examination of the right eye was normal. Magnetic resonance imaging (MRI) of the orbits and brain showed a homogenous 2.3×2.2×2.1 cm mass with an epicenter in the medial rectus muscle. The mass was hypointense on T2-signal with abnormal enhancement and extension along the optic nerve sheath. No other intracranial abnormalities were noted. The radiographic differential diagnoses were lymphoma, rhabdomyosarcoma or meningioma. A positron emission tomography scan demonstrated increased fluorodeoxyglucose uptake. Biopsy revealed a grade 1 meningotheelial meningioma. Cytogenetic studies revealed loss of one copy of chromosome 22, common in meningiomas. She received fractionated stereotactic radiotherapy (FSRT) (54Gy in 30-fractions) to the retro-orbital tumor. Her visual acuity has improved to 20/40 in the left eye on her most recent exam. She continues to have mild diplopia and exotropia, the latter improved with transposition surgery. Patient remains progression-free 18 months after diagnosis. Testing for neurofibromatosis type 2 was negative.

**Conclusion:** Four to 7 percent of ONSM occur in females < 20 years. Primary ONSM arises from the area between the arachnoid and dural sheaths of the optic nerve and generally presents with painless, progressive loss of vision, proptosis, limited eye movement, orbital pain and headaches. MRI is diagnostic with the characteristic feature of “tram-tracking” (non-enhancing radiolucent optic nerve surrounded by thickened enhancing optic nerve sheath). FSRT is the treatment of choice, with no mortality reported. Visual control rates range between 91% to 95%. Complete or partial resection may be warranted in patients with irreversible vision loss.
INFECTIONS MIMICKING MALIGNANCY REPORT OF TWO CASES OF ABDOMINAL TUBERCULOSIS AND ACUTE EBV INFECTION SIMULATING NEOPLASM

Hatel Rana Moonat, Ossama Maher, Cesar Nunez, Soumen Khatua, Shimin Hu, Wafik Zaky. UT MD Anderson Cancer Center, Houston, Texas, United States of America

Background: A suspected malignant process has to be confirmed in a timely manner so appropriate therapy is initiated. Pediatric cancers can present with typical clinical, laboratory, and radiographic findings. It is imperative, however that non-malignant conditions with atypical or advanced presentations should be considered in the differential diagnosis.

Objectives: We report two pediatric cases referred to our hospital with a presumptive diagnosis of a malignancy. After extensive work up, Mycobacterium tuberculosis and an Epstein-Barr virus (EBV) infection were found to be the cause of these neoplasm like presentations.

Design/Method: A MEDLINE search was conducted for queries including “Children,” “EBV infection,” “tuberculosis,” and “malignant neoplasm”. Relevant papers were selected for literature review.

Results: Case 1: A previously healthy 15-year-old female presented with a 2-week history of left sided abdominal pain, night sweats, and a 10lb unintentional weight loss. Initial laboratory values were within normal limits except for elevated LDH. An abdominal CT scan showed significant omental thickening with multiple intra-peritoneal and mesenteric lymph nodes enlargement, and suspicious adnexal masses simulating lymphoma. However, exploratory laparoscopy and biopsy of the omentum showed caseating granulomas. Acid-fast bacilli were isolated from the culture, confirming peritoneal tuberculosis. Case 2: A six year old male was transferred to the Intensive Care Unit with respiratory distress after a newly diagnosed nasopharyngeal mass. He had a three day history of fevers, bilateral extensive cervical and facial swelling. His laboratory data showed elevated liver enzymes and a markedly elevated LDH. MRI of the face and neck showed a large, bulky nasopharyngeal mass and associated extensive bilateral cervical lymphadenopathy strongly suggesting a malignant process. The mass was biopsied and steroid was started. Two days later, his EBV panel and pathology showed an acute EBV infection.

Conclusion: Pediatric cancers can have atypical initial presentations as noted above. These findings can overlap with an infectious etiology, however which is more common in pediatrics. Physicians must be aware of uncommon presentations of non-malignant conditions. This allows correct management (antimicrobials or supportive care versus chemotherapy) and reduces unnecessary hospital referrals and extensive work-up.
METASTATIC ANGIOMATOID FIBROUS HISTIOCYTOMA WITH CREB1 GENE REARRANGEMENT

Ossama Maher, Cynthia Herzog. UT MD Anderson Cancer Center, Houston, Texas, United States of America

**Background:** Angiomatoid fibrous histiocytoma (AFH) is an indolent tumor with metastasis occurring in less than 1% of cases, which are generally non-fatal and localized to regional lymph nodes. There are no known clinical, morphologic, or genetic factors that correlate with metastasis or recurrence. Adjuvant radiotherapy or chemotherapy is sometimes indicated for metastatic or unresectable tumors.

**Objectives:** We report a successful surgical treatment of a case of metastatic AFH in the pelvis after complete resection of the primary tumor in the right thigh.

**Design/Method:** A MEDLINE search was conducted in the English language for queries including "Children", "AFH", "CREB1 rearrangement" and "metastasis". Relevant papers were selected for literature review.

**Results:** An 11-year-old Hispanic female presented with 3-month history of a painless mass in the right thigh and unintentional weight loss. Magnetic resonance imaging (MRI) showed a 4.8 x 2.1 x 3 cm mass along the medial aspect of the distal femur. She underwent an initial resection with positive margins, followed 6 weeks later by a wide local excision. Pathology showed fascicles of spindle cells that were positive for desmin expression with fibrohistiocytic differentiation. These findings supported the diagnosis of AFH. She was subsequently managed by close surveillance. Eighteen months later, she presented with a painless palpable mass in the right pelvic area. She had documented weight loss, fever and night sweats. MRI of the pelvis showed a 2.2 cm x 2.4 cm mass within the right lower quadrant adjacent to the iliopsoas muscle. There was associated adenopathy within the right internal and common iliac region. Repeated biopsies were non-diagnostic. Due to high concern of malignancy, complete excision of the mass was pursued. The pathology was positive for metastatic AFH. Fluorescence in situ hybridization demonstrated CREB1 gene (2q33) re-arrangement. Postoperatively, the patient was monitored periodically with physical exam and repeated imaging. She remained free of disease 3 years after the last surgery without any further treatment.

**Conclusion:** Complete surgical resection of AFH even after distant metastasis is an effective treatment modality without the need of adjuvant chemotherapy and/or radiotherapy. The association between of CREB1 gene rearrangement and metastatic potential of these low-grade tumors need to be explored in future studies.
CONGENITAL SPINAL CANAL TUMORS: A REPORT OF TWO INFANTS WITH UNUSUAL NEUROIMAGING AND HISTOPATHOLOGY
Jeffrey Murray, John Honeycutt, David Donahue, Hayden Head, Ajit Alles. Cook Children's Medical Center, Fort Worth, Texas, United States of America

Background: Congenital spine abnormalities are usually non-neoplastic and related to aberrant embryogenesis. True tumors of the spine are extraordinarily rare in newborns and often difficult to characterize precisely on diagnostic imaging and histopathology. Reports of such tumors are sparse in the medical literature.

Objectives: To report two cases of congenital spinal canal tumors, emphasizing diagnostic imaging and histologic characteristics.

Design/Method: Following IRB approval, records from 2 infants with congenital spinal canal tumors were reviewed.

Results: Case 1: A 35 week gestation female developed respiratory distress at birth and was found to have hemidiaphragmatic paralysis and unilateral upper extremity paresis. Brain MRI was normal. Spine MRI revealed a C3-C4 enhancing spinal canal mass, compressing the spinal cord and appearing intradural but extramedullary. Via C2-C5 laminectomies, an intradural, intra-/extra-medullary, tumor was resected. Histopathology revealed a tumor descriptively classified as ‘myofibroblastic proliferation’, densely adherent to the cord, with immunoreactivity to alpha-actin and negative for desmin. The tumor karyotype was normal (46,XX). Adjuvant therapy was not given. The infant required postoperative rehabilitation and has had no evidence of recurrent tumor. Case 2: A 3 month-old female presented with vague abdominal symptoms and decreased lower extremity movement. Brain MRI was normal. Spine MRI revealed an expansile, enhancing, C7-T11 tumor appearing to be intramedullary, with bipolar edema, hypervascularity or infiltration of the cord. Via C6-T11 laminectomies, a 7.6 cm tumor was removed, en bloc, ‘peeling’ away from the compressed cord, yet with some foci of adherence/invasion of the cord. Histopathology revealed a cellular, heterogeneous tumor, descriptively classified as a ‘malignant tumor with glial, neuronal and mesenchymal differentiation’ with focal peripheral GFAP positivity, scattered synaptophysin positive ganglion cell nodules, and islands of cartilage and osteoid. MIB1 was focally increased. A clonal tumor karyotype was identified: 47,XX,+mar?der(20)t(1;20)(p32;q13)[19]/48,idem,der(11)t(7;11)(q11.2;q23),+mar[1]. The child recovered well from surgery, remains paraparetic and is receiving adjuvant therapy.

Conclusion: Congenital spinal canal tumors are rare and often atypical in their neuroimaging and histologic characterization. Extramedullary location might be predominant. Aggressive resection is often feasible. Further reporting of these rare congenital tumors will permit further understanding of histology, molecular biology and neurodiagnostics.
TREATMENT OF OSTEOSARCOMA WITHOUT METHOTREXATE IN A PEDIATRIC PATIENT WITH DOWN SYNDROME
Audrey Nath, Aaron Sugalski. University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States of America

Background: Osteosarcoma is the most common primary bone tumor, with peak incidence from ages 12-16. While osteosarcoma has been associated with inherited disorders such as hereditary retinoblastoma, Li-Fraumeni and Rothman-Thomson syndrome, it has no known association with Down syndrome; there has been only one report of a case of osteosarcoma in a child with Down syndrome (Wilimas 1977). Although chemotherapy regimens with high-dose methotrexate have been the mainstay of medical therapy for osteosarcoma in pediatric patients, literature of acute lymphoblastic leukemia in Down syndrome patients has shown that these individuals have heightened sensitivity to the toxicities of methotrexate, notably myelosuppression. The patient described in the 1977 case with Down syndrome and osteosarcoma received standard therapy with high-dose methotrexate and died from sepsis 18 days later. There have been no published treatment plans for osteosarcoma specific to patients with Down syndrome.

Objectives: The goal of this study was to create a novel chemotherapy regimen without the use of methotrexate for a 13-year-old male with Down syndrome who developed a localized, high-grade osteosarcoma of the left proximal tibia.

Design/Method: A combination of cisplatin/carboplatin, ifosfamide and doxorubicin was chosen based on promising results from the St. Jude Children’s Research Hospital OS99 trial. A chemotherapy regimen was created using a total of one dose of carboplatin (with dose targeted to an AUC of 8mg/ml/min over one hour), 480mg/m2 of cisplatin, 450 mg/m2 of doxorubicin and 62 g/m2 of ifosfamide. These medications were divided over 11 cycles, each approximately 3 weeks in length.

Results: Following one year of treatment with the described novel chemotherapy regimen and above-the-knee amputation of left lower extremity, there were no bony tumors or metastases found on x-rays, bone scan or chest CT.

Conclusion: This case describes the first known successful treatment of osteosarcoma in a child with Down syndrome. Given the regression of the patient’s high-grade osteosarcoma with the combination of cisplatin/carboplatin, ifosfamide and doxorubicin, this regimen may be of benefit to other pediatric patients with Down syndrome who require treatment of osteosarcoma and are unable to tolerate the toxicities of high-dose methotrexate. (Wilimas, Clin Pediatr, 1977)
CONCOMITANT PRESENTATION OF KAWASAKI DISEASE AND HODGKIN LYMPHOMA: AN UNUSUAL ASSOCIATION.
Donna Bell, Ken Young, P Syamasundar Rao, Cesar Nunez. UT MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Kawasaki disease (KD) was originally described by Tomisaku Kawasaki in 1967. KD is a systemic vasculitis of unknown etiology with the potential for cardiovascular complications. KD is more common in children under 5 years. Diagnostic criteria for KD include 5 out 6 clinical features. The association between Kawasaki disease and malignancy is rare.

Objectives: We will describe a patient with an unusual presentation of Kawasaki disease and Hodgkin lymphoma.

Design/Method: Case Report.

Results: 11 y.o African American boy presented to an outside hospital with fever, conjunctivitis, swelling of hands and feet, rash over extremities and peeling of hands and feet. Diagnosed with Kawasaki Disease and received 2 doses of IVIG, high dose aspirin and solumedrol. EBV titers were elevated at the time of diagnosis. Echocardiogram demonstrated bilateral proximal coronary artery ectasia. He was discharged home on aspirin and prednisone and readmitted for fever recurrence within 24 hours. Physical exam revealed inguinal, axillary and cervical lymphadenopathy. Repeat echocardiogram showed worsening coronary dilation. Because of persistence of fever, other causes of fever were investigated. EBV PCR of 36,000 copies and Mycoplasma IgM were also present. Fine needle aspiration of the left axillary node demonstrated large atypical lymphocytes. Right inguinal node, excisional biopsy demonstrated T-cell rich large B-cell lymphoma. Upon arrival to our institution the lymph nodes were reducing in size. Mother denied unintentional weight loss and reported improvement in the peeling skin. Physical examination revealed palpable bilateral cervical, axillary, and inguinal lymphadenopathies. No hepatosplenomegaly. Multiple small hyper-pigmented macular lesions. A review of the pathology was compatible with nodular lymphocyte predominance Hodgkin Lymphoma. The patient completed staging and was classified as a stage III B. He started treatment with Rituximab with no clinical response and went on to receive chemotherapy based on COPP/ABV as per COG 5942. He received Lovenox instead of aspirin during treatment. His EBV PCR titer remained significantly elevated and reduced with chemotherapy. Patient completed 6 courses of chemotherapy and remains in clinical remission.

Conclusion: The association of KD with lymphatic malignancy is rare. Persistence fever and other signs of inflammation should prompt further investigations to exclude malignancy.
A NEW CASE AND REVIEW OF ALL REPORTED CASES OF CONGENITAL DYSERYTHROPOEITIC ANEMIA CAUSED BY A MUTATION IN ERYTHROID TRANSCRIPTION FACTOR KLF1

Rebecca Ortolano. Madigan Army Medical Center, Tacoma, Washington, United States of America

**Background:** Congenital dyserythropoietic anemias (CDAs) represent a heterogeneous group of inherited red blood cell disorders resulting in ineffective erythropoiesis. There are three major types of CDAs, however, several CDA variants have been identified. KLF1 is a transcription factor required for cell division in erythroid differentiation and maturation. Additionally, it functions in the switch from fetal hemoglobin to adult hemoglobin. A recently described mutation in KLF1 results in a dominant negative effect on the transcriptional activity of KLF1.

**Objectives:** Four other patients have been reported with an E325K mutation in KLF1. All patients had severe hemolytic anemia and elevated fetal hemoglobin and nucleated red cells in peripheral blood. We report a case of this dominant mutation in the KLF1 gene resulting in congenital dyserythropoietic anemia, hemolysis, and a persistence of fetal hemoglobin.

**Design/Method:** A retrospective chart review and review of the literature was performed.

**Results:** Our patient is a term female whose newborn course was complicated by pulmonary hypertension, hepatosplenomegaly, and anemia. She required a red blood cell transfusion on day of life one. There was inadequate Hemoglobin in sample obtained prior to her first transfusion for Hemoglobin analysis on newborn screen. She recovered from her initial complications but continued to require red cell transfusions every 2 to 4 weeks for the first year of life. Hemoglobin electrophoresis at 6 months revealed 40% hemoglobin F, 58% hemoglobin A, and a small fast band of unknown significance. Her initial peripheral blood and multiple repeats revealed many nucleated red cells and elevated reticulocyte counts. Her smears were otherwise normocytic and normochromic. Her bone marrow biopsy revealed hypercellularity with marked erythroid hyperplasia without classic feature of types 1-3 of CDA. Myeloid maturation and megakaryocytes were unremarkable and the aspirate was without increased blasts. Now, at 2 years of life, she has not required a transfusion in over 8 months and has demonstrated no evidence of hemosiderosis.

**Conclusion:** We both report a new case and review the four previously reported cases of CDA due to KLF1 mutation to highlight the common features of this atypical CDA.
Background: Sickle cell disease (SCD) without hydroxyurea therapy is neither associated with, nor is protective of, hematological malignancies. The management and clinical course of a leukemia or lymphoma in a patient with SCD may be determined by multiple factors.

Objectives: We describe specific aspects of treating ALL in a child with SCD.

Design/Method: A retrospective review of medical records was conducted for this case report.

Results: A 6½-year-old African-American girl with SCD (SC type) was incidentally found to have 20% peripheral blasts during a routine clinical visit. She had a mild-to-moderate clinical phenotype with baseline hemoglobin (Hg) S-47.5%, C-44.5%, A2-4.2%, and F-3.5%. Marrow exam demonstrated B-lymphoblastic leukemia (41% blasts) without detectable blasts in the CSF. After a well-tolerated three-drug induction, the patient was stratified to a very high-risk group due to the presence of an MLL rearrangement t(11;14)(q21;q23) in 3/20 metaphases. By day 29 of treatment, the bone marrow had no blasts with undetectable MLL rearrangement and chemotherapy was tolerated well. During consolidation she had a few re-admissions for fever/neutropenia, but was not critically ill. She received 9 PRBC transfusions over the first 10 months. Serial Hg isoelectric focusing analyses showed decreased HgS and HgC and increased HgA, as expected with transfusions. However, HgF also increased above baseline and spiked to 13% following self-recovery with reticulocytosis prior to maintenance. She had behavioral issues, which intermittently worsened with steroids and discontinuation of Abilify during neutropenic periods. She did not have an increased frequency of vaso-occlusive crises (VOC). Chemotherapy side effects were within the expected range with mostly grade 2-3 hematological toxicity, fevers, and nausea/vomiting. She has remained in remission and is getting a second cycle of maintenance therapy.

Conclusion: It appears that clinically moderate SCD did not interfere with pediatric ALL chemotherapy, which was well tolerated. This tolerability and absence of VOC worsening can be explained by periodic transfusions decreasing Hg S and C. In addition, observed increase of HgF was possibly stimulated by post-chemotherapy erythropoiesis.
UNUSUAL PRESENTATION OF CHRONIC GRANULOMATOUS DISEASE: RENAL TUMOR-LIKE GRANULOMA

Kristina Prus, Benjamin Rhee, Reuben Antony, Roberto Gordillo, Eric Bugaieski, George Johnson, Karen Fernández. OSF St. Francis Medical Center, Peoria, Illinois, United States of America

Background: Chronic Granulomatous Disease (CGD) is characterized by recurrent infections usually occurring in men in early childhood. While many systems may be affected in CGD, the most common locations for infections are in the lungs, skin, liver, and bones. Genitourinary involvement is less common, and presentations with renal abscesses/tumors are rare.

Objectives: To describe a patient with CGD who presented with a renal tumor-like granuloma.

Design/Method: Case report

Results: A 15-month-old previously healthy male initially presented with anemia and a right kidney mass. At 9 months of age he was found to be anemic on a routine screen (Hb 8 mg/dl, MCV of 60 Fl) with no improvement after oral iron therapy. An extensive work-up failed to identify the etiology of the anemia. Results included a normal ferritin, normal hemoglobin electrophoresis, normal vitamin B12 and folate levels, normal serum iron and normal iron saturation. Bone marrow aspiration was negative for malignancy and showed thrombocytosis, erythroid hypoplasia, and no iron stores. Elevated ESR and CRP was seen on multiple occasions. The patient did not experience previous infectious illness but did have occasional fevers around age 15 months. On examination the patient was short (<3rd percentile) and pale with a prominent abdomen and a systolic murmur. No obvious dysmorphology or signs of overgrowth syndrome were noted. Abdominal ultrasound showed a right-sided mass arising from the kidney. CT scan confirmed a right renal mass in the lower pole and several retroperitoneal lymph nodes concerning for malignancy. After right nephrectomy, pathology revealed necrotizing granulomas but no malignancy. Additional workup included a negative tuberculosis PCR, negative fungal and mycobacterial stains and negative ANCA testing. Tissue culture was not done. CGD testing with DHR fluorescence demonstrated an oxidative burst in only 1% of neutrophils, highly suggestive of X-linked CGD. Genetic testing revealed a nonsense mutation in CYBB c.1326 C>G; p.Tyr442X, confirming the diagnosis. Subsequently, PCP and fungal prophylaxis was commenced, and the patient was referred for consideration of bone marrow transplant.

Conclusion: While genitourinary presentations are known in CGD, renal granulomas presenting as tumor-like lesions are exceptionally rare. To our knowledge this is the first patient reported with this unusual presentation.
ROTATIONAL THROMBOELASTOMETRY FOR ASSESSMENT OF HEMOSTASIS IN PLATELET DELTA STORAGE POOL DEFICIENCY
Michael Reyes, Ibrahim Ahmed, Sara Koenig, Shirley Abraham. The University Of New Mexico, Albuquerque, New Mexico, United States of America

**Background:** Platelet delta storage pool deficiency is a heterogeneous group of disorders resulting in mild to moderate mucocutaneous bleeding. These disorders result from a decrease in the number and/or content of platelet dense granules. Modalities to assess for the presence or affect of these disorders on hemostasis are often of variable clinical utility due to limited sensitivity or prolonged turn-around-time. Electron microscopy is highly sensitive and is the gold standard for detection of delta storage pool deficiency. Its use, however, is impractical in most clinical settings and does not provide a functional assessment of platelet function or of hemostasis.

**Objectives:** To describe a rapid and relatively inexpensive method for the assessment of hemostasis in a patient with delta storage pool deficiency.

**Design/Method:** A 3 year old male presented with high risk Pre-B acute lymphoblastic leukemia and with prolonged episodes of epistaxis despite adequate platelet counts. He was subsequently diagnosed with a delta storage pool deficiency by electron microscopy. In accordance with the high risk Pre-B ALL protocol he was scheduled to receive multiple lumbar punctures and intrathecal methotrexate administrations, however adequate hemostasis became a concern with each procedure.

**Results:** In anticipation of repeat lumbar punctures a baseline pre-transfusion sample was sent for hemostatic assessment by rotational thromboelastometry (ROTEM). The pre-transfusion ROTEM showed a normal FIBTEM tracing with abnormalities of multiple parameters of the EXTEM (clot formation time (CFT, 144s), alpha angle (62°), and maximum clot formation (MCF, 52mm)) indicating platelet dysfunction. Given the findings, 1 unit of apheresis platelets and tranexamic acid were administered prior to lumbar puncture. A post-transfusion sample was then sent for ROTEM, which showed that all hemostatic parameters had corrected into the normal range (CFT 75s, alpha angle 75°, MCF 62mm) and lumbar puncture was performed without bleeding complications.

**Conclusion:** The case presented indicates that ROTEM may provide a rapid and accurate assessment of hemostasis in patients with dense granule deficiency. The rapid turn-around-time of ROTEM facilitates assessment of hemostasis prior to invasive procedures and surgeries.
EMBRYONAL Rhabdomyosarcoma (ERMS) in a Child Associated with SOS1 Gene Duplication and Noonan-Spectrum-Like Features

Baheyeldin Salem, Christopher Rossi, Leslie Doros, Patroula Smpokou. Children's National Medical Center, Washington DC, District of Columbia, United States of America

**Background:** Childhood rhabdomyosarcoma (RMS), a soft tissue malignant tumor of mesenchymal origin, accounts for approximately 3.5% of cancer cases among children aged 0 to 14 years. The incidence is 4.5 per million children. Most cases occur sporadically with no recognized predisposing factors. Genetic conditions associated with RMS include Li-Fraumeni syndrome, pleuropulmonary blastoma, neurofibromatosis type I, Costello syndrome, Beckwith-Wiedemann syndrome and Noonan syndrome (NS). NS is a dominant disorder characterized by short stature, distinct facial features, developmental delay, congenital heart defects and an increased risk of malignancy. It is caused by a germline mutation in components of RAS/MAPK signal transduction cascade (PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, SHOC2, MEK1, CBL)

**Objectives:** Novel report of a gene mutation associated with cancer development

**Design/Method:** Case Report

**Results:** We are reporting a case of a 4-year-old female with a history of hypotonia, global developmental delay, as well as distinctive facial features compatible with a Noonan-spectrum disorder who was diagnosed with chest wall Embryonal RMS (ERMS) after presenting with respiratory distress. A chromosomal microarray analysis revealed a pathogenic mosaic duplication of chromosome 2p35.3p21 encompassing 267 genes including the SOS1 gene. Cytogenetic analysis of bone marrow aspirate revealed an abnormal diploid clone characterized by additional unknown material on 17q (which likely represents the chromosome 2 duplication). Noonan gene panel from peripheral blood was normal by sequencing; however, duplications or deletions were not assessed. Chromosome analysis on peripheral blood revealed a mosaic, unbalanced translocation between chromosomes 2 and 17 in 40 of 51 cells. Parental chromosome analyses were normal. SOS1 mutational sequencing and duplication/deletion testing on the tumor tissue is underway

**Conclusion:** We hypothesize that the development of ERMS in this patient with clinical features of NS is due to the mosaic somatic duplication of the SOS1 gene as a result of an unbalanced chromosomal rearrangement between chromosomes 2 and 17, which likely occurred post-zygotically. ERMS has been reported in a few clinical case reports of patients with NS caused by SOS1 missense mutations. To our knowledge, this is the first clinical report of a SOS1 gene duplication causing a NS phenotype and childhood cancer.
Using an intensive monitoring, bedside algorithm for individually dose adjusting high dose methotrexate in acute lymphoblastic leukemia patients with a significant risk for toxicities: A single institution retrospective review

Jennifer Foster, Patrick Thompson, Eric Schafer. Baylor College of Medicine, Houston, Texas, United States of America

**Background:** High dose methotrexate (HDMTX) is a critically important component to the successful treatment of pediatric acute lymphoblastic leukemia (ALL). However, many patients receiving HDMTX experience severe and prolonged toxicities. There is no standard way to administer HDMTX to patients at risk of toxicity. Most protocols recommend either a flat 25% dose reduction or omission of HDMTX.

**Objectives:** To determine the safety and efficacy of administering HDMTX based on an individualized intensive monitoring algorithm to patients at high risk of MTX toxicity.

**Design/Method:** We developed a bedside algorithm for individually adjusting the total MTX dose given for ALL patients receiving HDMTX. Based on 2 (peak) and 6 (steady state) hour MTX concentrations, adjustments in the rate of MTX administration were made towards a goal end 24 hour steady state MTX level (Cpss) of 65 micromolar. Since 2009, 12 ALL patients who had previously experienced or who were at high risk to experience MTX toxicities, have received HDMTX on versions of our protocol. These patients received HDMTX either at full dose (FD) of 5 g/m² or at an initial dose reduction (DR) of 20-25%. Data was available and reviewed on 10 patients receiving 21 cycles.

**Results:** Five patients (10 cycles) received a DR and 5 patients (11 cycles) received FD MTX. More dose adjustments were made in patients receiving FD (0.6 vs. 1). There was no significant difference between the mean dose of MTX given (3.2+/-0.5 g/m² per cycle vs. 3.7+/-0.8 g/m² per cycle) or the mean Cpss (63.8+/-24.2 micromolar vs. 63+/-15.1). MTX cleared by 48 hours in 6/10 of the DR group and 4/11 of the FD group. For those with delayed clearance the mean clearance was similar (83.3+/-8.6 hours vs. 84.9+/-8.8 hours). Toxicities were comparable in grade and scope between groups. Grade 3/4 toxicities were not observed in renal, neurologic or the category for which the patient was given MTX under intensive monitoring.

**Conclusion:** Our algorithm allowed the safe administration of HDMTX to ALL patients at high risk of MTX toxicities and obviated the need for any pre-treatment MTX dose reduction. A formalized prospective study is currently on-going.
MYELOID SARCOMA PRESENTING AS ACUTE APPENDICITIS IN A PEDIATRIC PATIENT UNDERGOING CHEMOTHERAPY FOR ACUTE MYELOGENOUS LEUKEMIA: A CASE REPORT WITH IMMUNOHISTOCHEMICAL STUDIES AND REVIEW OF THE LITERATURE

Stefanie Thomas, Jessica Barry, Aron Flagg, Raymond Tubbs, Rabi Hanna. Cleveland Clinic Children's, Cleveland, Ohio, United States of America

**Background:** Myeloid sarcoma (MS) is a solid neoplasm composed of immature myeloblasts involving the tissue of an extramedullary anatomic site, often associated with acute myelogenous leukemia (AML). Extramedullary involvement may occur in any organ or tissue, with the most common being the skin (leukemia cutis). Symptoms of MS are related to the anatomic location and may be asymptomatic or an incidental finding in the evaluation of a patient with AML.

**Objectives:** We describe a 3 year old male patient with AML-M5 with FLT3-ITD undergoing chemotherapy that was found to have a myeloid sarcoma of the appendix during intensification of his therapy. The child received induction therapy with cytarabine, daunorubicin, and etoposide. He developed transient cardiomyopathy, and then received fludarabine, cytarabine, and granulocyte colony stimulating factor followed by high-dose cytarabine and etoposide. On day 20 of the latter cycle, he presented with acute abdominal pain and right lower quadrant tenderness with rebound and guarding, suspicious for acute appendicitis. Abdominal CT scan was consistent with appendicitis, and he underwent laparoscopic appendectomy. Subsequent diagnosis of appendiceal MS was made based on immunohistochemical studies.

**Design/Method:** Clinical history and pertinent studies were obtained from the medical record. Immunohistochemical staining of the appendix tissue with CD3, CD20, CD33, CD34, CD43, CD68, CD117 and muramidase was reviewed. Review of literature with a focus on pediatric cases of myeloid sarcoma was performed.

**Results:** Histology of the appendix tissue showed an atypical mononuclear cellular infiltrate consistent with MS supported by positive immunophenotypic staining for myeloid markers CD33, CD43 and subset positive for muramidase. Concurrent bone marrow aspiration showed no morphologic evidence of AML.

**Conclusion:** Myeloid sarcoma involving the appendix can present with symptoms of acute appendicitis, and can mimic typhlitis in the neutropenic patient. The broad differential in a child with abdominal pain creates a challenge for pediatric oncology practitioners. Immunohistochemical staining and use of flow cytometry can facilitate an accurate diagnosis. The prognostic significance of MS in patients with AML is felt to be poor. To our knowledge, there have been no cases of myeloid sarcoma involving the appendix in a patient currently receiving therapy for AML.
NEXT-GENERATION SEQUENCING OF AN UNDIFFERENTIATED SARCOMA TUMOR SAMPLE LEADS TO IDENTIFICATION OF GERMLINE BRCA2 AND MLH1 MUTATIONS.

Elizabeth Varga, Nicholas Yeager. Nationwide Children’s Hospital, Columbus, Ohio, United States of America

Background: Next-generation tumor DNA sequencing is increasingly being utilized to help identify therapeutic targets for patients with malignancy. This technology has the capability to reveal the presence of germline mutations, which may significantly impact cancer risk for patients and their family members.

Objectives: To describe a case where tumor DNA sequencing impacted the care of a patient by identifying two hereditary cancer predisposition syndromes. To contribute to the understanding of the phenotype associated with double heterozygosity for Hereditary Breast and Ovarian Syndrome (HBOCS) and Lynch syndrome.

Design/Method: A 23 year old Caucasian patient with undifferentiated sarcoma developed a pleural based lesion following two prior treatment regimens. A biopsy was performed and tissue sent for genomic analysis in an attempt to identify potential therapeutic targets. The assay simultaneously analyzed the entire coding sequence of 236 cancer-related genes (3,769 exons) plus 47 introns from 19 genes often rearranged or altered in cancer.

Results: Pathogenic alterations identified in tumor included BRCA2 R645fs*15 (also known as c.1929delG and 2157delG) and MLH1 E694* (also known as c.2080G>T and p.E694X). Because germline BRCA2 and MLH1 alterations are associated with HBOCS and Lynch syndrome respectively, analysis of blood DNA was performed and confirmed these to be constitutional alterations.

Conclusion: Sarcoma has only rarely been associated with HBOCS or Lynch syndrome, and to date, has not been reported in cases of double heterozygosity for these syndromes. Individuals with both HBOCS and Lynch syndromes have a high risk of secondary malignancy based on available case reports. Our patient will require heightened surveillance for other malignancies, and genetic testing of multiple family members is underway to better assess their cancer risks. This case illustrates important considerations for practitioners who offer next-generation sequencing assays of tumor DNA about the appropriate follow-up of potential germline alterations.
PRENATAL DIAGNOSE OF CHRONIC CEREBRAL SINOVENOUS THROMBOSIS: IS ANTICOAGULATION THERAPY WARRANTED?
Gabriela Villanueva, Saba Ahmad, Edward Michals, Mary Schmidt. University of Illinois Hospital and Health Sciences System, Chicago, Illinois, United States of America

Background: Pediatric Cerebral Sinus Venous Thrombosis (CSVT) is increasingly recognized as a cause of pediatric stroke. More than 40% of CSVT occurs in the neonatal period and is associated with poor outcome in more than 50% of the patients. Anti-coagulation therapy (ACT) is safe and effective in adults however the use of ACT has only gradually increased in neonates due to the common association with hemorrhages. Newer recommendations and guidelines from various European, Canadian and now US organizations support the use of ACT given the poor outcome in this population.

Objectives: To report on a neonate with a prenatally diagnosed chronic CSVT and review the appropriate literature regarding management.

Design/Method: Review of medical imaging, electronic record and recent medical literature.

Results: At 20 weeks gestation, a routine prenatal ultrasound identified a cerebral cyst of unclear etiology in a fetus during an otherwise uncomplicated pregnancy. At 30 weeks gestation, a fetal MRI demonstrated CSVT. Maternal thrombotic work-up was negative, and the completion of the pregnancy and delivery were uneventful with Apgars of 9/9. MRI/MRV of the brain on DOL 1 revealed a thrombus in the confluence of sinuses, and bifurcation in the superior sagittal sinus suggesting re-canalization or collateral flow. Risks and benefits of ACT were discussed with the family and due to the chronicity of the thrombus and the asymptomatic neonate, no ACT was started. MRI/MRV of the brain on DOL 8 showed no significant changes. In outpatient short term follow-up, no problems were noted. In a review of the literature, all the pediatric studies focused on acute CSVT in either symptomatic patients or patients with pre-disposing medical conditions prompting cerebral imaging. Current guidelines (Monagle, CHEST, 2012) recommend ACT for neonates with CSVT with or without intracranial hemorrhage except with massive bleeds. No reports exist on management of chronic CSVT in neonates.

Conclusion: The use of prenatal ultrasound and fetal MRI may identify cases of preterm and therefore chronic CSVT and allow for prenatal counseling and early recognition of the condition. However, the benefit of ACT in patients with preterm chronic CSVT may be quite limited and not comparable to acute CSVT.
A CASE OF PLUMMER-VINSON SYNDROME IN AN ADOLESCENT WITH HELICOBACTER PYLORI INFECTION
Aubri Waters, David Robinson, Robert Cornfeld, David Harper. Madigan Army Medical Center, Tacoma, Washington, United States of America

**Background:** Among the variants of chronic dysphagia, one of the rarest in children is that of Plummer-Vinson syndrome, or dysphagia associated with iron deficiency and an upper esophageal or “post-cricoid” web. Factors including environment, nutrition, immunology, and infection may play a role in its development.

**Objectives:** To report an unusual case of Plummer-Vinson syndrome, which has been noted just 12 times previously in children under age 18, and never associated with Helicobacter pylori (H. pylori) in this age group.

**Design/Method:** A retrospective chart review and review of the literature was performed.

**Results:** We report a 16 year old female Cambodian patient with severe iron deficiency anemia, dysphagia, and esophageal webs diagnosed with Plummer-Vinson syndrome. The patient described choking on her food and was eating nearly a full liquid diet. Although she had a 2 year history of anemia, the patient could not tolerate oral iron replacement secondary to nausea and later dysphagia. She endorsed symptoms of iron deficiency anemia including fatigue and decreased school performance. The patient had a 1.5kg weight loss over the preceding 2 years. Labs showed a severely microcytic iron deficiency anemia and upper GI series showed a linear filling defect at the mid-cervical esophagus. Upper endoscopy confirmed two proximal esophageal anterior webs and diffuse inflammation in the gastric body and biopsies were strongly positive for H. pylori. The patient was treated with intravenous iron sucrose, underwent serial endoscopy dilations, and began eradication of H. pylori with antibiotics with subsequent symptomatic and clinical improvement.

**Conclusion:** This is the first reported child to have developed H. pylori-associated Plummer-Vinson syndrome. Plummer-Vinson syndrome with concomitant H. pylori has previously been reported in one adult patient in the literature. H. pylori infection may be underreported as a factor in the cause of iron deficiency anemia leading to the syndrome as in our patient. This is also the first reported patient with Plummer-Vinson syndrome to undergo iron repletion with intravenous iron. Intravenous iron may be a useful medication in patients with iron deficiency anemia who are unable to swallow oral medications or who need rapid iron replacement (Jessner, Am J Gastroenterol 2003).
SIMULTANEOUS PRESENTATION OF WILM'S TUMOR AND IMMATURE OVARIAN TERATOMA IN BECKWITH-WIEDEMANN SYNDROME

Jason White, Akash Nahar, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania, United States of America

**Background:** The Beckwith-Wiedemann syndrome (BWS) is a cancer predisposition syndrome characterized by a predilection to embryonal tumor growth, especially Wilm’s tumors, adrenocortical carcinomas and hepatoblastomas. Genetic analysis of patients has revealed a link to the imprinted domain of the 11p15.5 chromosome and methylation status of the H19 locus and Igf-2. These genes have also been studied in other cancers, especially ovarian teratomas. Our case is a patient with a simultaneous presentation of a Wilm’s tumor and immature ovarian teratoma and subsequently diagnosed with BWS, which has not been previously described.

**Objectives:** To further understand molecular and genetic basis of tumorigenesis.

**Design/Method:** Case Review

**Results:** A three-year-old Hispanic female presented with abdominal pain for one week. Her exam showed hemihypertropy of her right side, distended abdomen and a mass in the periumbilical region. CT of her abdomen/pelvis showed a density on the superior pole of her right kidney and a separate cystic mass in the pelvis. Alpha fetal protein (AFP) was elevated at 96.7 and CA-125 was elevated at 36.9. She underwent exploratory laparotomy with right nephrectomy and right salpingo-oophorectomy. Pathology of the kidney mass showed blastemal elements with no atypia, consistent with Wilm’s tumor of favorable histology. The ovarian mass was consistent with an immature ovarian teratoma. There was no metastasis. Chromosomal microarray analysis (CMA) revealed that approximately 25% of peripheral blood cells carried uniparental disomy of chromosome 11p15.5 to 11p15.2, which encompasses the Beckwith-Wiedemann syndrome crucial region. Methylation studies were performed on the H19 and IGF-2 genes, confirming the diagnosis of BWS. She was treated as per COG Wilm’s tumor protocol with vincristine, dactinomycin and doxorubicin and flank radiation and went into remission and is doing well.

**Conclusion:** Advances in molecular and genetic analysis have been able to link diseases that were thought to be unrelated. H19 methylation has been noted for its apparent role in increased tumorigenesis in mice, but no association has thus far been found in humans. Our patient exhibits the proposed link of H19 methylation and tumorigenesis in humans. Future reporting of similar cases may enhance new therapies that lead to improved outcomes.
IMPROVED OUTCOME OF EXTRADURAL, CERVICAL MALIGNANT RHABDOID TUMOR WHEN MARROW-ABLATIVE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL RESCUE IS ADDED TO PRIMARY MULTIMODAL THERAPY

Adam Wolfe, Christian Capitini, Shahriar Salamat, Kenneth Desantes, Kristin Bradley, Bermans Iskandar, Taryn Bragg, Tabassum Kennedy, Neha Patel. University of Wisconsin Hospital and Clinics, Madison, Wisconsin, United States of America

Background: Malignant rhabdoid tumor (MRT) is an aggressive neoplasm of childhood, with a poor prognosis due to its tendency to progress during or shortly after therapy. MRT in a paraspinal, epidural location is rare, based on few cases reported in the literature. These lesions are often unamenable to complete surgical resection. For all extracranial MRT, primary multimodal therapy including surgical resection, local irradiation and intensive chemotherapy has resulted in estimated survival of 20-30%. In the largest published case series to date, 2/2 patients with stage III-IV became long-term survivors following high-dose chemotherapy followed by autologous stem cell rescue.

Objectives: We report here two cases of non-metastatic extradural, paraspinal MRT of the neck, in which we have achieved sustained radiographic remission for ≥2 years since diagnosis.

Design/Method: Case 1 is a 13-year-old boy who presented after several months of progressively worsening neck pain. MRI spine revealed an enhancing epidural mass at C2-C4, with extension through the left C2-C3 neural foramen, displacement of the spinal cord, and erosion of the C3 vertebral body. Case 2 is a 19-month-old girl who presented after several months of progressive right-sided neck tilt and pain, poor appetite, weight loss, anxiety and fatigue. MRI neck revealed an enhancing soft tissue mass in the right sub-occipital region extending into the retro-clival epidural space with associated lytic lesions in the clivus, lateral mass of C1 and occipital condyle. Histologically, the tumor specimen in both cases revealed solid sheets of epithelioid cells with eccentric nuclei and eosinophilic cytoplasm. Immunohistochemistry (cytokeratin +, hSNF5/INI1 -) was consistent with MRT. Metastatic evaluation were negative in both patients.

Results: Following sub-total excision in first case and biopsy in the second, both patients received alkylator-based, intense multi-agent chemotherapy and localized radiotherapy. Both patients then proceeded to Consolidation with carboplatin, etoposide and melphalan followed by autologous stem cell rescue.

Conclusion: Both patients currently have no evidence of active disease, 4.5 years (Case 1) and 2 years (Case 2) from diagnosis. These cases illustrate that aggressive, multimodal therapy followed by autologous stem cell rescue should be considered for localized extracranial, extrarenal MRT.
USE OF MOHS’ OINTMENT TO REDUCE THE SIZE OF AN ADVANCED EMBRYONAL RHABDOMYOSARCOMA IN THE RIGHT NASAL VESTIBULE AND THEREBY IMPROVE QUALITY OF LIFE
Tanabe Yujiro, Ueda Takahiro, Hayakawa Jun, Miho Maeda, Ito Yasuhiko. Nippon Medical School, Bunkyo, Tokyo, Japan

Background: Advanced head and neck cancer impairs patients’ quality of life (QOL) and can also lead to death. Mohs’ chemosurgery, originally developed for the treatment of skin cancer, involves the use of Mohs’ ointment, which consists of zinc chloride, to fix tissues and dissect them. This therapy can be applied to different clinical settings. In advanced head and neck cancer, Mohs' chemosurgery relieves the symptoms of inflammation and skin infiltration, such as bleeding, infection, exudation, and severe pain.

Objectives: We present a case of reduction in the size of an embryonal rhabdomyosarcoma in the right nasal vestibule by treatment with Mohs’ ointment, resulting in an improvement in the patient’s QOL.

Design/Method: Case Report

Results: We present the case of a 15-year-old girl who was diagnosed with an embryonal rhabdomyosarcoma in the right nasal vestibule at the age of nine. She underwent surgery and received radiotherapy, proton beam therapy, and several adjuvant chemotherapeutic regimens. However, the cancer recurred on four occasions. Mohs’ ointment was administered along with irinotecan to control tumor increase. This resulted in a remarkably decrease in the size of the surface tumor. Treatment with Mohs’ ointment was useful in improving airway narrowing, preventing infection and bad odor, and reducing bleeding from a part of the tumor; this resulted in an improvement in the QOL of the patient. However, despite a reduction in the surface mass, she died 9 months after treatment with Mohs’ ointment because of disease progression.

Conclusion: There are few reports on the use of Mohs’ ointment in pediatric cancer cases. Mohs’ ointment was safe and effective in reducing the size of the advanced tumor in our case. Hence, we opine that the use of Mohs’ ointment in patients with localized advanced head and neck tumors could prolong patient survival.
SURVEY OF SELF REPORTED BASELINE HOME PAIN MANAGEMENT IN A SICKLE DISEASE ASSOCIATED PAIN CRISIS
Saroj Purohit, Wondwessen Bekele, Girmay Tekle-Yohannes. Newark Beth Israel Medical Center/CHONJ, Newark, New Jersey, United States of America

Background: Sickle cell Disease (SCD) is inherited blood disorder with multisystem involvement and painful vaso occlusive crisis (VOC). Mild VOC is unrecognized and often sub-optimally managed. Prompt initiation of pain medications may prevent severe pain crisis.

Objectives: To determine baseline home pain management practices in children and adolescent with SCD associated VOC, and develop strategies to improve quality of care during VOC in patients with SCD.

Design/Method: We developed questionnaire with 15 easily understandable questions. The questionnaires were completed by parents in children younger than 12yrs, while patients 12yr or older were allowed to self-administer the questionnaire with the help of adult caregiver.

Results: Thirty-five children and adolescent with SCD answered the questionnaire, out of which most of them were had diagnosis of Hb-SS (74%) and male gender (71%). VOC was reported during last 2 months by 29/35 (83%) patients. The preferred home pain medication used was single analgesic NSAID 14/29 (48%). Tylenol-codeine and combinations were used in 14% and 24% respectively. Analgesic dosing frequency used was once/day in 7/29 (24%) and every 4-6hrs in 44% of patients. Missed school of at least 3 days was reported in 62% of cases. Concern for medication side effect was reported in 23% of cases. Multiple emergency department visits and hospitalizations for VOC during 1 year duration were 46% and 77%. Clinic attendance at least 3 times per year was reported by 66% cases. Majority of the cases (94%) reported receiving education regarding home pain management.

Conclusion: Our survey demonstrated that VOC is very common with over 80% cases reporting pain in past 2 months before the survey. Many patients relied on low potency single analgesics; with inadequate dose frequency during acute VOC. VOC can be successfully managed at home with continuing education of family about timely and adequate pain management. Our study is ongoing and survey will be used for the future intervention to improve the quality of care. Patients and their family need to be educated about home pain medication use; including how to use combination of analgesics. We recommend providing patients with written instruction regarding home pain management.
SUPPRESSION OF MYELOID PROGENITOR GROWTH AND RECOVERY WITH GRANULOCYTE COLONY STIMULATING FACTOR IN A PATIENT WITH METHIMAZOLE-INDUCED AGRANULOCYTOSIS

Tania Sarker, Bulent Özgönenel, Manisha Gadgeel, Steve Buck, Amita Adhikari, Y Ravindranath

Children’s Hospital of Michigan, Detroit, Michigan, United States of America

Background: Methimazole (MMI), one of the most widely used antithyroid medication, is well-known to cause agranulocytosis.

Objectives: We discuss the bone marrow culture results of a case of MMI-induced agranulocytosis in an 18-year-old girl with Graves thyrotoxicosis, whose myeloid suppression was successfully treated with Granulocyte Colony Stimulating Factor (G-CSF).

Design/Method: The bone marrow mononuclear cells were cultured in semi-solid methylcellulose growth medium containing recombinant cytokines and erythropoietin with 10% patient serum before and after treatment with G-CSF. The cultures were done in triplicate and Colony Forming Units – Granulocyte, Macrophage (CFU-GM) colonies were scored on day 14.

Results: Bone marrow prior to initiation of G-CSF was mildly hypocellular with complete absence of myeloid precursors, with striking plasmacytosis (28% plasma cells). 16 days after treatment with G-CSF, whereas the bone marrow still showed an absence of myeloid precursors morphologically, flow cytometry detected an increase in myeloid progenitors from 4% to 26%. In serum-treated cultures, CFU-GM increased from 1.7 ± 0.6 colonies (mean ± standard deviation) to 85.0 ± 8.0 colonies (p = 0.003). Figure 1 shows the clinical course of the patient, and the changes in the neutrophil, platelet, and reticulocyte counts.

Conclusion: Prompt withdrawal of the offending drug and treatment with G-CSF till count recovery are important in management of MMI-induced agranulocytosis. Our findings also suggest that flow cytometric evaluation of marrow myeloid precursors can be used as a guide to anticipate neutrophil recovery.

Figure 1. The patient’s clinical course is illustrated, with changes in blood parameters, including the absolute neutrophil count (ANC), the absolute reticulocyte count and the platelet count (both per mm3). The bone marrow aspirations were on days #3 and #19 of hospitalization. G-CSF (Neupogen) was started on day #4 and continued until day #26 of hospitalization. On admission patient was started on Dexamethasone with a gradual weaning from day #24. In the interim she also received one dose of IVIG on day #16 and four rounds of plasmapheresis (on days 19, 21, 24, and 26). Her course was complicated with development of candidemia on day #11 and cerebral sinus venous thrombosis on day #12 of hospitalization. Patient got surgical thyroidectomy on day #34 followed by persistent elevation of the absolute neutrophil count, reticulocyte count, and platelet count.
TRANSCRANIAL DOPPLER ULTRASOUND AND PEAK SYSTOLIC VELOCITY IN SICKLE CELL DISEASE
Musab Al-Yahia, Raid Amin, Jeffrey Schwartz. Nemours Children's Clinic, Pensacola, Florida, United States of America

Background: Ischemic stroke occurs in up to 11% of patients with homozygous sickle cell disease (SCD) by the age of 20 years. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial validated the use of transcranial doppler (TCD) in risk stratifying SCD patients for stroke utilizing the Time Averaged Mean of the Maximum (TAMM) velocities in the major cerebral blood vessels. A subsequent evaluation of the data found that the peak systolic velocity (PSV) correlated with the respective TAMMs as well as the risk of stroke.

Objectives: The primary aim of the present study was to confirm that PSV correlates with TAMM. The secondary aim was to evaluate correlations between PSV and cerebral complications.

Design/Method: A retrospective analysis was performed on a TCDs obtained between 2008-2012 on patients with SCD at the Nemours Children’s Clinic in Pensacola, Florida. Demographic information included gender and diagnosis. Data from the TCDs included TAMM and PSV. A PSV of 200 cm/s or greater was considered elevated based on prior studies. Outcome measures included complications (stroke and vasculopathy on MRI and MRA, respectively) and the initiation of a chronic transfusion regimen.

Results: A total of 256 TCDs were performed on 97 patients. Homozygous SS accounted for 75% of patients. A strong positive correlation between TAMM and PSV in all major cerebral arterial vessels was confirmed (Pearson Correlation Coefficient ranged 0.778 – 0.915). Of 12 patients started on chronic transfusions, 4 had an overt stroke and 10 had evidence of vasculopathy. While no patient with a complication had an elevated TAMM and normal PSV, 3 patients had elevated PSV and normal TAMM (1 with stroke, 2 with vasculopathy).

Conclusion: The present study confirmed a statistically significant correlation between PSV and TAMM. There were several patients with complications who had abnormal PSV but normal TAMM although the small numbers precluded statistical evaluation. This data suggests that PSV could be utilized as an additional tool in determining risk of stroke in SCD. A prospective study in a larger population is necessary to confirm whether PSV is predictive of clinical outcomes including vasculopathy.
INCREASED ENDOPLASMIC RETICULUM STRESS RESPONSE IN MYELOID CELLS IN PEDIATRIC ACQUIRED APLASTIC ANEMIA: A SINGLE INSTITUTION EXPERIENCE
Alpa Sidhu, Michael Callaghan, Manisha Gadgeel, Steven Buck, Andrew Fribley, Sureyya Savasan.
Childrens Hospital of Michigan, Detroit, Michigan, United States of America

**Background:** Autoimmune response targeted at the altered hematopoietic stem cells highlights the current understanding of acquired aplastic anemia (AAA) pathogenesis. High incidence of clonal disorders following successful immunosuppressive therapy (IST) points to a persistent defect in the stem cell population. The upregulation of the unfolded protein response UPR is the cell’s rejoinder to a variety of stresses, which either result in restoring homeostasis or cell death via upregulation of the transcription factor CHOP. Immune response directed against stress-related proteins has been proposed in various autoimmune disorders.

**Objectives:** We hypothesized that there is an inherent increased sensitivity to various cellular stressors, including the ones that target ER in myeloid cells in AAA leading to decreased proliferation and potentially contributing to the development of autoimmunity.

**Design/Method:** Archived bone marrow aspirate samples from patients with AAA that were treated on IST (11 patients, 18 samples) and patients without AAA or cancer as controls (8 patients, 8 samples) were used in this study. The samples were cultured in methocult CFU-GM selective media to obtain myeloid cells. Then quantitative real time PCR analysis for UPR-related transcripts, luminescent proliferation and flow cytometry analyses were performed.

**Results:** In comparison with controls, the AAA cells show increased CHOP induction (12.33 vs. 3.71 fold, p=0.0011) and sensitivity as measured with decreased proliferation (35% vs 62.6%, p < 0.0001) to treatment with tunicamycin, an ER stress inducer. This difference was independent of the clinical state of the patient - diagnosis/relapse vs. response. The presence of PNH was associated with lower induction of CHOP (6.7 versus 13.9 fold, p = 0.07). Untreated AAA cells show a decreased cell surface expression intensity of BiP/GRP78 (5.56 vs. 2.70, p=0.0005).

**Conclusion:** Our results support an increased response to induced ER stress as an inherent characteristic of AAA myeloid cells. This may be reflective of a generalized cellular stress control defect irrespective of response to IST and may also be a potential contributing trigger for the development of autoimmune reaction. Further prospective studies with greater number of patients may help elucidate the mechanism of inherent sensitivity to cellular stress in this rare disease.
Background: Patients (pts) with sickle cell disease (SCD) experience variable disease severity and clinical manifestations.

Objectives: We describe treatment patterns and clinical outcomes from a prospective registry of patients with SCD.

Design/Method: 57 US hematology centers enrolled patient’s ≥2 years of age with HbSS, HbSC, or HbS/β-thalassemia and conducted assessments every 6 months for 3 years (ClinicalTrials.gov NCT01220115).

Results: A total of 498 patients (317 pediatrics/181 adults) completed the baseline visit. At baseline, frequencies of asthma, dactylitis, and splenic sequestration were higher among pediatrics, while avascular necrosis, gall bladder disease, chronic/pulmonary hypertension, and leg ulcers were higher in adults (Table 1). Pain was the most common crisis, accounting for a greater proportion of crises in adults. Prior to study, more pediatrics were hospitalized for acute chest syndrome (ACS)/pneumonia and fever vs. adults (P<.0001), while more adults were hospitalized for pain crises (P=.0147). At 24 months, hospitalizations due to ACS/pneumonia and fever remained higher in pediatrics, while pain crises and infections remained higher in adults. Rates of transfusion and/or chelation prior to study were higher in adults vs. pediatrics, while the proportion was similar during study. Overall, the rate of absenteeism trended lower in the 24 months on study in both groups compared with the 12 months prior to the study.

Conclusion: SCD is associated with significant complications contributing to high hospitalization and absenteeism rates. Further follow-up in this registry will provide additional information about disease patterns and patient management. Acknowledgment: This study was funded by Novartis Pharmaceuticals Corporation.
<table>
<thead>
<tr>
<th>Table 1. Clinical Complications and Treatment Patterns</th>
<th>&lt;18 years (n=317)</th>
<th>≥18 years (n=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical history, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aplastic episode</td>
<td>31 (9.8)</td>
<td>15 (8.3)</td>
</tr>
<tr>
<td>Asthma/Reactive airway disease</td>
<td>97 (30.6)</td>
<td>29 (16.0)</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>8 (2.5)</td>
<td>61 (33.7)</td>
</tr>
<tr>
<td>CNS, abnormal TCD</td>
<td>23 (8.8)</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td>CNS, seizure</td>
<td>14 (4.4)</td>
<td>13 (7.2)</td>
</tr>
<tr>
<td>CNS, silent infarct</td>
<td>24 (7.6)</td>
<td>11 (6.1)</td>
</tr>
<tr>
<td>CNS, stroke (lifetime)</td>
<td>32 (10.1)</td>
<td>27 (14.9)</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>74 (23.3)</td>
<td>12 (6.8)</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>47 (14.8)</td>
<td>80 (44.2)</td>
</tr>
<tr>
<td>Leg ulcer</td>
<td>0 (0.0)</td>
<td>18 (9.9)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>3 (0.9)</td>
<td>19 (10.5)</td>
</tr>
<tr>
<td>Splenic sequestration</td>
<td>72 (22.7)</td>
<td>15 (8.3)</td>
</tr>
<tr>
<td><strong>Clinical Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with SCD crises in 5 years prior to study, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>229 (72.2)</td>
<td>156 (88.2)</td>
</tr>
<tr>
<td>Infections (≥1)</td>
<td>139 (43.8)</td>
<td>62 (34.3)</td>
</tr>
<tr>
<td>ACS/Pneumonia</td>
<td>136 (42.9)</td>
<td>40 (22.1)</td>
</tr>
<tr>
<td>Stroke (lifetime)</td>
<td>32 (10.1)</td>
<td>27 (14.9)</td>
</tr>
<tr>
<td>Priapism (males)</td>
<td>15 (8.4)</td>
<td>14 (16.5)</td>
</tr>
<tr>
<td>Pts with SCD crises in 24 mos on study, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>202 (63.7)</td>
<td>110 (80.3)</td>
</tr>
<tr>
<td>Infections (≥1)</td>
<td>99 (31.2)</td>
<td>50 (27.6)</td>
</tr>
<tr>
<td>ACS/Pneumonia</td>
<td>50 (15.8)</td>
<td>16 (8.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9 (2.8)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Priapism (males)</td>
<td>9 (5.0)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td><strong>Pts hospitalized in 24 mos on study, n (%)</strong></td>
<td>185 (58.4)</td>
<td>96 (53.0)</td>
</tr>
<tr>
<td>Causes*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>113 (35.6)</td>
<td>81 (44.8)</td>
</tr>
<tr>
<td>Fever*</td>
<td>48 (15.1)</td>
<td>13 (7.2)</td>
</tr>
<tr>
<td>ACS/Pneumonia</td>
<td>59 (17.4)</td>
<td>24 (13.3)</td>
</tr>
<tr>
<td>Infections</td>
<td>5 (1.6)</td>
<td>6 (3.3)</td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts transfused, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During 12 mos prior to study</td>
<td>139 (43.8)</td>
<td>96 (53.0)</td>
</tr>
<tr>
<td>During 24 mos on study</td>
<td>145 (45.7)</td>
<td>84 (46.4)</td>
</tr>
<tr>
<td>Chelation therapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts ever chelated prior to study</td>
<td>62 (19.6)</td>
<td>59 (32.6)</td>
</tr>
<tr>
<td>During 24 mos on study</td>
<td>38 (11.4)</td>
<td>14 (7.7)</td>
</tr>
<tr>
<td>Pts used hydroxyurea, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to study</td>
<td>140 (44.2)</td>
<td>88 (48.6)</td>
</tr>
<tr>
<td>During 24 mos on study</td>
<td>147 (46.4)</td>
<td>79 (43.6)</td>
</tr>
<tr>
<td>Absenteeism, 12 mos prior to study, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missed school</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 10 days</td>
<td>101 (51.0)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>11 to 20 days</td>
<td>49 (23.2)</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td>&gt;20 days</td>
<td>30 (15.2)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Missed work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 10 days</td>
<td>NA</td>
<td>24 (44.4)</td>
</tr>
<tr>
<td>11 to 20 days</td>
<td>NA</td>
<td>10 (18.6)</td>
</tr>
<tr>
<td>&gt;20 days</td>
<td>NA</td>
<td>12 (22.2)</td>
</tr>
</tbody>
</table>

*P<0.01 comparison between age groups.

**Pts may have had multiple types of crises and causes for hospitalization.

ACS, acute chest syndrome; SCD, sickle cell disease.
A PILOT STUDY TO EXAMINE THE EFFECT OF EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) ON PLASMA FACTOR XIII LEVELS

Dimarys Sanchez, Shelley Crary, Richard Fiser, Michael Schmitz, Parthak Prodhan, Xinyu Tang, Todd Nick, Kimo Stine. Arkansas Children's Hospital, Little Rock, Arkansas, United States of America

Background: Severe cardiopulmonary compromise may require ECMO support. A balance between anticoagulation and risk of hemorrhage is critical to the management of these patients. Reduced serum concentrations of Factor XIII (FXIII) in adults undergoing cardiopulmonary bypass have been associated with increased risk of hemorrhage. The effect of ECMO on FXIII levels has not been previously investigated.

Objectives: To determine if (1) ECMO support is associated with changes in FXIII levels in children and (2) if such changes are associated with clinically important outcomes.

Design/Method: Single center prospective study of children (ages 0-21) supported with ECMO. Samples for FXIII, D-Dimers, Fibrinogen and Thrombin Time were collected prior to or during ECMO initiation, 2 hours, 24 hours, 3-5 days and 14-21 days after ECMO support and 1-3 days after ECMO discontinuation.

Results: We have enrolled 21 patients (13 female, 8 male; median age 0.2 years). Patients required ECMO support for cardiac failure (4), pediatric respiratory failure (3), neonatal respiratory failure (9), septic shock (4) and refractory cardiac arrest (1). Figure 1a and 1b show the mean and standard deviation (SD) of FXIII and Fibrinogen, respectively.

Conclusion: This is the first study evaluating FXIII levels in children undergoing ECMO. Interim analysis does not demonstrate any significant change in FXIII activity. Further analysis of the association between FXIII levels and blood transfusion requirements, as well as of FXIII changes in different clinical subgroups is planned. Our results will provide important information towards determining if children undergoing ECMO would benefit from FXIII replacement. Investigator initiated study sponsored by CSL Behring.

FIGURE 1:

a) FXIII Mean and SD

b) Fibrinogen Mean and SD

(FXIII Range: 60-150)  (Fibrinogen Range: 150-400)
THE EFFECT OF AGE AND PATIENT HISTORY ON THE PREVALENCE OF TRUE BLEEDING DISORDERS IN PEDIATRIC PATIENTS REFERRED FOR ABNORMAL COAGULATION TESTS

Kayllie Wang, Li Wang, Peter Shaw. Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, United States of America

**Background:** Abnormal coagulation tests (ACT) are a common source of referral to pediatric hematologists. ACT are found through preoperative screening or in patients with a bruising or bleeding history. There are few studies that have proven the utility of screening tests such as the prothrombin time (PT), partial thromboplastin time (PTT) and closure times (CT).

**Objectives:** Our goal was to evaluate the prevalence of true bleeding disorders in children referred for ACT. We hypothesized that patients with bleeding or bruising history with ACT would be more likely to have a true bleeding disorder.

**Design/Method:** We performed a retrospective chart review of patients referred to the Coagulation Clinic at Children’s Hospital of Pittsburgh from March 2004 to May 2013. Inclusion criteria were age younger than 22, no thrombocytopenia, no previously diagnosed coagulopathy and no anticoagulant or nonsteroidal anti-inflammatory drug use. Patients received a standard diagnostic workup. The two groups analyzed were patients referred for ACT and patients referred for ACT with bleeding or bruising history. The primary outcome was the diagnosis of a true bleeding disorder, possible bleeding disorder or no bleeding disorder. We analyzed the data using a Chi-squared test for univariate analysis and logistic regression for multivariate analysis.

**Results:** Out of 534 patients, 276 (51.7%) were male and 258 (48.3%) were female. The mean age was 8.3 years±4.7. 130 (24.3%) had a true bleeding disorder, 61(11.4%) had a possible bleeding disorder, and 343 (64.2%) had no bleeding disorder. Patients with bleeding or bruising were more likely to have a true bleeding disorder (p=.039). When we divided patient age into 5-year intervals, older age was associated with having a true bleeding disorder (p<.001). Older patients were also more likely to have definite von Willebrand’s disease (vWD) (p=.001) or platelet function disorders (p<.001). From the logistic regression, bleeding or bruising (p=0.015) and age groups (p<.001) were both significantly associated with true bleeding disorders.

**Conclusion:** Pediatric patients referred for ACT and bruising or bleeding symptoms were more likely to have a true bleeding disorder compared to patients solely referred for ACT. Older patients were also more likely to have true bleeding disorders.
CONGENITAL THROMBOTIC THROMBOCYTOPENIC PURPURA (CTTP) IN THE UNITED STATES - A PILOT DATA REGISTRY OF 49 PATIENTS
Tammuella Singleton, Louis Aledort, Cindy Leissinger, Garrett Bergman. Tulane University School of Medicine, New Orleans, Louisiana, United States of America

**Background:** Congenital thrombotic thrombocytopenic purpura (CTTP), also known as Upshaw-Schulman Syndrome (USS), is rare, and life-threatening disease. It is characterized by the symptoms also seen in acquired or idiopathic TTP. With the absence of ADAMTS13, unusually large VWF multimers are released from vascular endothelial cells. The inappropriately cleaved VWF multimers result in thrombocytopenia, microangiopathic hemolytic anemia, and subsequent microvascular thrombosis. Unlike acquired TTP, CTTP/USS is defined by a deficiency in ADAMTS13 with the absence of an ADAMTS13 inhibitor. CTTP typically presents with a Coombs negative severe neonatal anemia and jaundice usually requiring red cell exchange. In childhood, patients experience repeated episodes of thrombocytopenia and microangiopathic hemolytic anemia. The standard treatment for repeated episodes includes infusions of fresh frozen plasma (FFP).

**Objectives:** To determine how many Congenital TTP patients are being treated by hematologists in the United States.

**Design/Method:** 48 adult and pediatric hematologists, in the United States, were contacted by phone and email. 15 additional pediatric hematologists participated in an individual interview.

**Results:** With the initial telephone encounter, 35 CTTP patients were identified. 6 additional patients were confirmed with follow up contact of the 48 adult and pediatric hematologists by email. Individual visits with 15 additional pediatric hematologists revealed 8 additional CTTP patients. 49 patients with congenital TTP were identified.

**Conclusion:** It was previously estimated that there were only 100 cases of CTTP worldwide, with an incidence rate of no more than 1/1,000,000 person/year. CTTP comprises only 10% of all TTP patients with known ADAMTS13 deficiency. Additionally, CTTP has been previously reported to have an age of onset ranging from early childhood to 79 years. Although CTTP reported in all continents, and the international Hereditary TTP Registry (www.ttpregistry.net; NCT 01257269) was established in 2009. The international registry previously reported 83 patients from 74 families in 18 countries. Although the number of CTTP cases in the United States has not been well defined, we identified 49 patients with CTTP. This pilot registry revealed more patients than expected, and will provide a platform to further investigate the natural history of this disease in the United States.
PEGASPARAGINASE TREATMENT IN PEDIATRIC ACUTE LYMPHOBLASTIC MALIGNANCY ALTERS THROMBIN GENERATION THROUGH MODULATION OF THE PROTEIN C AND S SYSTEM

Jack Staddon, Kristi Smock, Joshua Schiffman, Michael Engel, Mark Fluchel, Andrew Weyrich. University of Utah School of Medicine, Salt Lake City, Utah, United States of America

Background: Pediatric patients with acute lymphoblastic leukemia/lymphoma (ALL) treated with pegasparaginase are at increased risk of thrombosis. The mechanisms behind this increased risk are unknown. Global measures of thrombin generation have previously been used to indicate an individual’s risk of bleeding or thrombosis. Limited studies have focused on global thrombin generation models in pediatric ALL patients on pegasparaginase.

Objectives: To determine if pegasparaginase treatment in pediatric ALL alters global thrombin generation.

Design/Method: Pediatric ALL patients at the University of Utah were approached before pegasparaginase treatment to obtain informed consent. Whole blood was drawn before and after treatment to obtain paired plasma samples. Global thrombin generation was measured using a fluorogenic substrate specific for thrombin in the presence or absence of thrombomodulin. Clinical coagulation parameters on plasma samples were measured at ARUP Laboratories.

Results: Twelve pediatric ALL patients (median age 8 years old, 75% male) were recruited with a median post-pegasparaginase blood draw of 6.5 days. In the absence of thrombomodulin, no significant differences were found in any thrombin generation parameters except for the area under the curve (AUC) was increased after pegasparaginase treatment (5422 ±272 vs. 3915 ±418 nmoles*min; p = 0.002). Addition of thrombomodulin, which activates the protein C and S system, significantly prolonged and lowered multiple parameters of thrombin generation in both pre-and post-pegasparaginase samples. However, the anticoagulant effects of the protein C and S system were significantly less (compared to no thrombomodulin) in plasma samples collected post-pegasparaginase treatment compared to pre-pegasparaginase treatment (peak thrombin concentration: 48% vs. 65% decrease, p=0.027; rate of thrombin generation: 53% vs. 70% decrease, p=0.045, AUC: 51% vs. 67% decrease, p=0.016). Total protein C antigen and free protein S antigen were significantly reduced following pegasparaginase (46% of normal vs. 83%, p<0.001; 46% vs. 89%, p<0.001).

Conclusion: Our results suggest the decrease in protein C and S levels after pegasparaginase alter global thrombin generation and subsequently increase the risk of thrombosis in pediatric ALL patients treated with pegasparaginase.
HAEMOPHILIA PRESENTING WITH SUBGALEAL HAEMORRHAGE IN THE NEONATAL PERIOD: A CASE SERIES
Aditi Vedi, Susan Russell, Grainne Dunne. Sydney Children's Hospital, Sydney, NSW, Australia

Background: A third of newly diagnosed children with haemophilia lack a family history precluding optimal perinatal management. The majority are diagnosed following a bleeding episode. Subgaleal haemorrhage (SGH) can occur following vacuum deliveries and the diagnosis of underlying haemophilia may not be immediately considered in affected children.

Objectives: To identify factors contributing towards a delay in diagnosis of haemophilia as the underlying diagnosis in neonates with SGH.

Design/Method: A retrospective review of the medical records of neonates, who presented with SGH and were subsequently diagnosed with haemophilia, was undertaken. Details regarding the delivery, severity of SGH, treatment, presence or absence of intracranial haemorrhage, time to diagnosis of haemophilia, and neurological outcomes were recorded.

Results: Four children (3 males, 1 female) with mild (1), and severe (3) haemophilia A (3) and B (1), referred to our haemophilia treatment centre over the past 10 years, presented with a significant SGH. All were first children with no family history of haemophilia and were delivered at term by vacuum extraction. One also had forceps applied and had a skull fracture. Three had associated intracranial haemorrhage, two with significant immediate neurological compromise. All four required blood products, including two with shock and disseminated intravascular coagulation (DIC). The diagnosis of haemophilia was made between 4 days and 16 months following the SGH, and the time from prolonged APTT result to factor assay ranged from 2 hours to 16 months. All children survived; one child has significant learning difficulties. One developed a high titre Factor VIII inhibitor.

Conclusion: Factors that may have contributed to a delay in diagnosis of haemophilia were attributing the SGH to the Ventouse delivery, lack of family history, female gender, temporary correction of the abnormal coagulation profile by blood products and lack of awareness. SGH in a neonate should not be attributed to instrumental delivery alone, particularly in the context of cardiovascular or neurological compromise and DIC. Co-existing haemophilia must be considered in infants of both genders with SGH to enable prompt diagnosis and treatment with the appropriate recombinant factor.
RISK OF PERINATAL INTRACRANIAL HEMORRHAGE AND THE ROLE OF PRENATAL GENETIC TESTING IN INDIVIDUALS WITH TYPE 3 VON WILLEBRAND DISEASE
Deepti Warad, Aubrey Manahan, Dawn Olive, Amy Eckerman, Michelle Kluge, Vilmarie Rodriguez, Rajiv Pruthi. Mayo Clinic, Rochester, Minnesota, United States of America

Background: Type 3 von Willebrand disease (vWD) is an autosomal recessive disorder with an incidence of 1 in 0.5-1 million/year in USA and is characterized by virtual absence of von Willebrand factor (vWF) in the plasma. Diagnosis is typically made during infancy during evaluation of spontaneous, post-surgical or traumatic bleeding symptoms similar to severe hemophilia. Major neonatal bleeding is uncommon, however, may be serious e.g. intracranial hemorrhage (ICH). In severe hemophilia, up to 4% of neonates may experience ICH, however such data for type 3 vWD are lacking. Increasing knowledge about causative mutations has led to recommendations for prenatal genetic testing with a view to aid with labor and delivery to avoid ICH in the newborn.

Objectives: To report our institutional experience with type 3 vWD patients.

Design/Method: Retrospective chart review was performed on 10 patients (7 males, 3 females) with type 3 vWD identified from our Comprehensive Hemophilia Treatment Center, Rochester, MN database.

Results: Nine patients (90%) experienced their first significant bleed during infancy at a median age of 2 days (range 1–365 days). Presenting symptoms included prolonged bleeding with circumcision (n=5, 50%), petechiae and ecchymoses (n=2, 20%), prolonged umbilical cord bleeding, and truncal hematomas in 1 each. One patient presented at 55 years of age with per-rectal bleeding. vWD diagnosis was established in the neonatal period n=4 (40%), infancy n=4 (40%), and adulthood n=2 (at 25 and 57 years). Only 50% patients had family history of vWD. Baseline laboratory data, available in 9 patients, demonstrated FVIII:C of <10%, vWF:RCo of <12% and vWF:Ag of <10%. Plasma vWF multimer analysis of all 10 patients revealed undetectable plasma vWF consistent with type 3 vWD.

Conclusion: In this cohort, perinatal ICH or life-threatening bleeds did not occur in any patient. In the light of these findings, this experience, although limited, questions the need to expose fetuses to the risks of prenatal diagnosis and additional studies with larger series of patients are needed.
TWICE-DAILY DOSING OF PROPRANOLOL FOR TREATMENT OF INFANTILE HEMANGIOMAS IS SAFE AND EFFECTIVE

Amanda Winters, Carol Chute, Adrienne Hammill, Ravi Elluru, Roshni Dasgupta, Belinda Dickie, MarySue Wentzel, Denise Adams. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

Background: Since the initial description of hemangioma involution in response to propranolol in 2008, propranolol has emerged as a first-line therapy for complicated infantile hemangiomas. Numerous meta analyses and case reports have documented high response rates of these vascular tumors to propranolol, with minimal side effects. A recent consensus statement advocated three times daily (TID) dosing of propranolol for treatment of infantile hemangiomas. However, twice daily (BID) dosing of propranolol may be equally efficacious given that similar total daily doses can be achieved, and may promote improved adherence to therapy.

Objectives: To demonstrate safety and efficacy of twice daily (BID) dosing of propranolol for patients aged 1 to 36 months with complicated infantile hemangiomas.

Design/Method: This study was a retrospective chart review of patients evaluated and treated at Cincinnati Children’s Hospital Medical Center from January 2009 through June 2013. IRB approval was obtained for the study. Our current protocol involves starting patients on 0.5 mg/kg/day of propranolol BID and titrating the dose upward to an effective dose between 1 and 3 mg/kg/day. Patients are monitored for adverse effects such as hypoglycemia, hypotension, heart rate changes, and reflux. Propranolol is then weaned both actively (adjusting frequency of dosing) and passively (no adjustment for weight gain).

Results: 203 patient records were reviewed. 4/203 patients (2%) experienced moderate to severe toxicity which necessitated treatment discontinuation: 1 child had recent airway reconstruction, was eating poorly, and experienced hypoglycemia, 2 patients had wheezing on propranolol thought secondary to underlying reactive airway disease, and 1 patient had continued bradycardia during initiation of treatment. Other side effects were minor and self-limiting including diarrhea during the first few days of treatment (5%), sleep disturbance (8%), and esophageal reflux (0.5%). Only 8/203 patients (4%) had rebound growth of hemangiomas. Of these, 2 had completed treatment and 6 were tapering, on daily dosing. Patients were 9 – 14 months of age at the time of rebound and were resumed at their last effective dose prior to rebound growth.

Conclusion: Twice daily dosing of propranolol for treatment of infantile hemangiomas that require therapy is safe, effective, and easy for families to administer.
AN ASSOCIATION OF CD68+ TUMOR INfiltrATING MACROPHAGES AND EBV STATUS WITH OUTCOME IN PEDIATRIC HODGKIN LYMPHOMA
Hanadys Ale, Guillermo DeAngulo, Amilcar Castellano-Sanchez, Robert Poppiti, Carole Brathwaite.
Miami Children's Hospital, Miami, Florida, United States of America
Background: The tumor microenvironment of classical Hodgkin Lymphoma (cHL) is very diverse. Neoplastic Hodgkin and Reed-Sternberg cells (HRS) coexist with a heterogeneous cellular infiltrate of non-neoplastic cells including CD68+ macrophages. The presence of Epstein - Barr virus (EBV) has also been consistently found in the microenvironment of a high proportion of cHL cases. We previously identified CD68 positive histiocytes as a significant predictor for adverse outcome in pediatric Hodgkin lymphoma.
Objectives: The purpose of this study is to examine the tumor microenvironment of pediatric patients with cHL and to correlate the presence of EBV with the expression of CD68+ macrophages and their association with prognosis.
Design/Method: We analyzed the tumor microenvironment of a historical cohort of 25 pediatric cHL cases from the files of Miami Children’s Hospital Department of Pathology. Tumor associated macrophages were assessed via CD68 immunohistochemistry in paraffin-embedded tissue obtained at the time of diagnosis. EBV status of the tumors was determined using EBV encoded RNA (EBER) in situ hybridization. We then associated the expression of CD68 and the EBV status with the prognosis by further correlating these biomarkers with the patient outcomes in a retrospective analysis.
Results: Approximately half of the patients (52.0%) were positive for EBV. An increased number of tumor associated CD 68+ macrophages were correlated with the presence of EBV-positive Hodgkin’s tumor cells (sig. 0.011). EBV positivity by itself also showed correlation with outcome. There was a significant increased risk of relapse (sig=0.030), and a significant increased risk of death from lymphoma (Sig=0.026) for those patients with positive EBV status.
Conclusion: We have evidence that the tumor microenvironment plays a vital role in the pathogenesis of cHL. Our study demonstrates that there is a correlation between CD68+ tumor infiltrating macrophages with EBV positive status and adverse prognosis in pediatric cases. This observation may contribute to our understanding of biomarkers in cHL, which can help us segregate patients according to risk stratification, allowing therapy to be selected based on specific prognostic indicators. Our findings may also provide the basis for individualized patient treatment.
CHEMOTHERAPY-INDUCED PERIPHERAL NEUROTOXICITY ASSOCIATED WITH A NOVEL MUTATION IN GARS
Michael Holloway, Bradley DeNardo, Kevin Nguyen, Colby Davis, Chanika Phornphuktal, Robbert Creton, Rachel Altura. Brown University, Providence, Rhode Island, United States of America

**Background:** Vincristine is a front-line chemotherapy agent for acute lymphoblastic leukemia that contributes to the excellent survival rate of this disease. Unfortunately, 30-50% of children with high-risk leukemia require vincristine dose reductions due to chemotherapy-induced peripheral neurotoxicity (CIPN). Although CIPN symptoms are largely reversible, a subset of patients with undiagnosed demyelinating or axonal forms of hereditary peripheral neuropathy, including Charcot-Marie-Tooth (CMT) can experience irreversible, long-term neurotoxicity and subsequent death following even a single dose. Treatment for severe cases of CIPN involves limiting or discontinuing highly efficacious therapy, but this reduces overall survival rates. Neither the prevalence of genetic susceptibility to CIPN in patients with leukemia/lymphoma is known, nor is the mechanism by which it causes neurotoxicity. Using Next-generation sequencing, we analyzed a panel of hereditary-neuropathy-linked genes in a 12 yo girl with grade 4 CIPN that developed after 12 mg of vincristine. This analysis revealed a heterozygous G > A point mutation in the 3’ donor splice site of exon 8 of the glycyl-tRNA synthetase gene (GARS). The identical mutation was identified in the patient’s father and nerve conduction studies were consistent with clinical type 2D CMT.

**Objectives:** To characterize the phenotype of the novel GARS mutation and CIPN using an in vivo vertebrate zebrafish model.

**Design/Method:** We used RT-PCR and Western blots of the patient’s peripheral blood leukocytes and a patient derived lymphoblast line to characterize the effect of the mutation on GARS protein expression. We then modeled the mutation in zebrafish using gars morpholinos. We quantified the effects of vincristine and mutant gars on motor axons and movement in zebrafish larva using immunostaining with acetylated-tubulin and a behavioral assay, respectively.

**Results:** Treatment of 48 and 72 hpf larva with vincristine resulted in a dose-dependent decrease in axon length and response to a motor stimulus. The GARS morphant phenotype resembled that of vincristine-treated animals, with decreased arborization and movement defects noted in animals treated with both morpholino and chemotherapy.

**Conclusion:** Zebrafish are a valuable model to study the neurotoxic effects of CIPN. A threshold of GARS protein may be required to protect neurons from damage induced by microtubule-targeting agents.
PELVIC MASS PRESENTING SIMULTANEOUSLY IN IDENTICAL TWINS: DIAGNOSIS OF MYELOID SARCOMA PURE ERYTHROID DIFFERENTIATION
Priscila Badia, Athena Pefkarou, Alejandro Levy. Miami Children's Hospital, Miami, Florida, United States of America

**Background:** Myeloid sarcoma is an extramedullary tumor of immature granulocytic cells usually presenting along with acute myeloid leukemia in the bone marrow. Rarely can it present before the classic clinical and laboratory manifestations of the leukemia or other myeloid disorders, it may therefore be named primary or isolated sarcoma. This unusual tumor commonly presents in bone, peritoneum and soft tissue. The clinical presentation will depend on the affected organ due to mass effect or dysfunction. Immature granulocytic cells in tumor biopsies will give the final diagnosis. Due to the rarity of the disease and few trials, specific treatment have not been established; however they are invariably treated according to the acute myelocytic leukemia protocol, this has been the preferred treatment as per previous study results.

**Objectives:** To report a case of identical twins with history of twin-twin transfusion presenting with simultaneous pelvic masses.

**Design/Method:** Describe the clinical presentation, radiological images, pathology results and molecular analysis of myeloid sarcoma in identical twins.

**Results:** A three year old female twin A of identical twins presented with lower abdominal pain and swelling of the right thigh and abdomen. Ultrasound revealed a pelvic mass and right hydronephrosis. After MRI evaluation, she underwent tumor biopsy and ureteral stent placement. Biopsy confirmed myeloid sarcoma. Clinically, she has deteriorated with weight loss, constipation and swelling of the extremity. She will undergo bone marrow biopsy and aspiration for evaluation of hematological disease and further treatment plan to take place. Both impressively and interestingly, twin B, presented three weeks later with limping and left leg pain. A pelvic mass was palpated on physical exam. Abdominal ultrasound showed a pelvic mass and right hydronephrosis. She is having tumor biopsy as well as bone marrow biopsy and aspiration and bilateral stent placement for a final diagnosis and initiation of treatment. Fluorescence in-situ hybridization, molecular analysis and genetic testing will also take place.

**Conclusion:** Isolated Myeloid Sarcoma is a very rare tumor presenting in approximately 2/1,000,000 in adult report literature. The simultaneous presentation and the history of twin-twin transfusion warrants further investigation at both the molecular and genetic level of this fascinating case.
RENIN PROGENITORS IN THE BONE MARROW: A NOVEL ORIGINA FOR B-CELL LEUKEMIA

Brian Belyea, Fang Xu, Ellen Pentz, Silvia Medrano, Minghong Li, Yan Hu, Maria Luisa Sequeira-Lopez, Ariel Gomez. University of Virginia, Charlottesville, Virginia, United States of America

Background: Renin-expressing cells are progenitors for many cell types in the body. In the kidney, they give rise to juxtaglomerular cells, a process regulated by the Notch/RBP-J signaling pathway. Renin precursors, of unknown function, have also been identified in extra-renal tissues. However, the existence, identity, function, and regulation of renin-expressing cells in the bone marrow are unknown.

Objectives: To characterize the identity and function of renin-expressing cells within the hematopoietic system and evaluate their transcriptional regulation by RBP-J.

Design/Method: Renin-expressing and renin-lineage cells within the hematopoietic system were characterized using transgenic reporter mice, lineage tracing, flow cytometry, and colony forming assays. RBP-J was deleted in renin cells by crossing mice that express Cre recombinase under control of the renin locus with RBP-Jfl/fl mice. Progeny mice were characterized using clinical assessment, histologic evaluation, flow cytometry analysis, transplantation assays, and gene expression studies.

Results: Renin-expressing cells within the bone marrow are B-lymphocyte progenitors. Deletion of RBP-J in these renin-expressing progenitors enriches the precursor B cell gene program, constrains lymphocyte differentiation, and alters the regulation of cell cycle progression, ultimately leading to the development of cell-autonomous precursor B-cell leukemia. These renin-expressing cells appear uniquely vulnerable to neoplastic transformation as other conditional models of RBP-J deletion do not result in leukemia.

Conclusion: We deleted RBP-J in renin-expressing cells in mice resulting in the striking development of precursor B-cell leukemia. The cell of origin for this leukemia is a novel renin-expressing progenitor with a B-lymphocyte pedigree. To our knowledge, this is the first report demonstrating RBP-J silencing as an initiating event in B-cell leukemogenesis. The discovery of these unique renin progenitors in the bone marrow and this new model of leukemia may enhance our understanding of normal and neoplastic hematopoiesis.
UNIQUE CASE OF CUTANEOUS LCH PROGRESSING TO DISSEMINATED JXG
Smita Bhaskaran, Rachel Egler, Linda Sandhaus, Xueli Hao. Rainbow Babies and Children’s Hospital, Cleveland, Ohio, United States of America

**Background:** Cutaneous Langerhans Cell Histiocytosis (LCH) may progress to multisystem LCH with an incidence of 40%. Its progression to Juvenile Xanthogranuloma Disease (JXG) is rare with less than 10 reported. Disseminated JXG (d-JXG) occurs in 4-5% of JXG cases, of which a fraction present with bone marrow involvement. Multisystem LCH and d-JXG maybe clinically indistinguishable and often pose a diagnostic dilemma. No standard therapy exists for d-JXG.

**Objectives:** To report the diagnosis and treatment of a patient with cutaneous LCH that progressed to d-JXG.

**Design/Method:** Patient presented at 3 months of age with cutaneous LCH (CD1a and S100 positive). After failure on topical steroids, she was started on oral methotrexate 20mg/m²/week. After a year’s treatment with methotrexate, skin was not completely healed, so mercaptopurine 50mg/m²/day was added. A month later she presented with pancytopenia, heptosplenomegaly, transaminitis, conjugated hyperbilirubinemia. Further evaluation revealed multiple lytic bony lesions, some with soft tissue extension and splenic lesions with hemosiderin deposition. Bone marrow had 95% cellularity with extensive infiltration by cohesive aggregates of large histiocytes displaying prominent hemophagocytosis. The histiocytes were negative for S100, langerin and CD1a, and positive for vimentin, CD68, Factor VIII, thrombomodulin and CD163, consistent with JXG. Genetic testing for congenital hemophagocytic lymphohistiocytosis was negative.

**Results:** Clofarabine 25 mg/m²/dose x 5 days and prednisone 2mg/kg/dose daily were started. Clofarabine was repeated every 28 days for 6 cycles. Prednisone was continued for 5 weeks, then tapered over one month as the patient improved. After 2 cycles, the patient’s transaminitis, hyperbilirubinemia and cytopenias resolved. After six cycles, the hepatosplenomegaly resolved, boney lesions were healing with resolution of soft tissue components, and splenic lesions were stable. Bone marrow showed persistent histiocytic infiltrate, but hemophagocytosis was not apparent.

Complications of therapy included febrile neutropenia, myelosuppression, adrenal insufficiency and iron overload.

**Conclusion:** Progression to d-JXG with bone marrow involvement is a rare complication of cutaneous LCH that requires careful pathologic review. No standard treatment regimen exists. Initial Clofarabine significantly reduced the disease burden, but disease is not fully resolved. A lower dose maintenance course of Clofarabine is planned, with possible alternatives including HSCT if disease recurs.
MORE THAN MEETS THE EYE: INTRAOCULAR MALT LYMPHOMA IN PEDIATRICS: A CASE REPORT

Sucharita Bhaumik, Marijean Miller, Leigh Marcus. Children's National Medical Center, Washington, District of Columbia, United States of America

Background: Mucosa Associated Lymphoid Tissue (MALT) type lymphomas are indolent tumors, extremely rare in childhood as nearly all pediatric patients have aggressive Non-Hodgkin’s Lymphoma. They usually occur in the gastrointestinal tract, and involvement of ocular adnexal tissues has been rarely reported in children. Most commonly they involve conjunctiva, eyelid, lacrimal gland and sac.

Objectives: We describe a young boy with MALT ocular lymphoma who presented with an atypical conjunctivitis and discuss treatment options.

Design/Method: 12 yo Cameroonian male presented to eye clinic with a 10 day history of right lower eyelid swelling, pain, redness and visual blurring which was diagnosed as pseudomembranous conjunctivitis with periorbital cellulitis. Empiric antibiotics were administered but his symptoms progressed. He was then admitted to the hospital for further management. He reported no constitutional symptoms. Slit lamp exam showed right eye follicular conjunctivitis, chemosis with pseudomembrane formation, periorbital edema and tenderness with no proptosis. CT scans showed preseptal enhancement of the right eye and there was no evidence of orbital cellulitis, no extraorbital involvement of the optic nerve, lacrimal gland, extraocular muscles or brain. Initial incisional biopsy showed extranodal marginal zone MALT lymphoma of conjunctiva, with serology and pathology negative for infections.

Results: He initially received IV antibiotics, and then completed a 1-month oral antibiotic course of doxycycline. He then underwent complete surgical resection of the mass and repeat biopsy was negative for any clonality. He continues to be followed up in both oncology and ophthalmology clinic and remains in complete remission 12 months after diagnosis.

Conclusion: Treatment of pediatric ocular adnexal lymphoma is tailored to extent of disease to avoid deleterious effects of chemoradiotherapy in children. MALT most likely emerges from a background of benign chronic inflammatory disorders. Removing the source with surgical resection or treatment with antibiotic therapy (if associated with Chlamydia, HIV or other infection) can induce remission. Localized, unilateral, completely resected extragastric MALT lymphoma in children has an excellent prognosis and does not require systemic therapy. Long-term follow up is important to look for recurrence or systemic lymphoma development.
PREDICTORS OF CANCER DIAGNOSTIC INTERVALS AND ASSOCIATIONS WITH OUTCOME IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA: A POPULATION-BASED COHORT STUDY USING HEALTH SERVICES DATA

Sumit Gupta, Paul Gibson, Jason Pole, Rinku Sutradhar, Lillian Sung, Astrid Guttmann. Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada

Background: While diagnostic interval lengths in cancer are of significant concern to patients, providers and policymakers, little is known about whether lengths systematically vary according to patient and healthcare factors, and about their impact on cancer outcomes.

Objectives: Our primary objectives were to construct and validate a diagnostic interval measure based on health services data in the context of a universal health care system among children with acute lymphoblastic leukemia (ALL), in order to determine predictors of prolonged diagnostic interval and the associations with disease severity at diagnosis and event-free survival (EFS).

Design/Method: All children with ALL diagnosed 1995-2011 in Ontario, Canada were linked to population-based health administrative databases. Healthcare claims within six months prior to diagnosis were used to define healthcare episodes for each patient. Diagnostic interval was defined as the time between the first episode with a diagnostic code a priori classified as consistent with underlying ALL, and date of diagnosis, and validated by correlation with a chart abstraction-based measure. We used logistic regression to model the association of patient and health services factors with interval length and Cox proportional hazards to model interval length to EFS.

Results: 1,541 patients were successfully linked. The healthcare-based diagnostic interval measure met validity criteria (ρ=0.41; p<0.0001). Diagnostic intervals were generally short (median 2 days, IQR 1-3). Predictors of longer intervals included having a general practitioner (GP) as primary care physician vs. a pediatrician [adjusted odds ratio 1.60, 95% CI 1.04-2.47; p=0.03]. High risk disease (high white blood cell count at presentation or T-cell lineage) was associated with shorter intervals. While prolonged diagnostic intervals were associated with superior EFS [hazard ratio 0.71, 95% CI 0.52-0.98; p=0.04], this association was completely explained by confounding by disease biology.

Conclusion: Healthcare administrative data represent a novel and valid method by which to measure the cancer diagnostic interval in pediatric ALL and potentially in other cancers. In childhood ALL, though prolonged intervals were associated with some healthcare factors, intervals were short, more a marker of disease severity, and not an independent predictor of outcome. These findings may be used to counsel caregivers, address parental guilt and inform policy.
THE ROLE OF ATM AND BCL11B IN LYMPHOID MALIGNANCIES

Kerice Pinkney, Wenxia Jiang, Chen Li, Jennifer Crowe, Serine Avagyan, Xiangyu Liu, Brian Lee, Kenta Yamamoto, Shan Zha. Columbia University Medical Center, New York, New York, United States of America

Background: Ataxia-Telangiectasia Mutated (ATM) is a serine/threonine protein kinase and a key regulator for DNA damage responses. Homozygous germ line mutations of ATM cause Ataxia-Telangiectasia (A-T) syndrome, with increased risk for pediatric lymphoid malignancies, especially T-cell acute lymphoblastic leukemia (T-ALL). ATM-deficient mice recapitulate many phenotypes of A-T and routinely develop thymic lymphomas with recurrent translocations that share molecular origins with those in human T-ALL. Specifically, ATM-deficient murine thymic lymphomas carry heterozygous deletion of the telomeric region of chromosome 12, including Bcl11b, a transcription factor important for T-cell development.

Objectives: Based on the frequent heterozygous inactivation of Bcl11b in ATM-deficient murine thymic lymphomas (>80%) and human T-ALL(~9%), we hypothesized that Bcl11b acts as a haploinsufficient tumor suppressor gene and loss of Bcl11b function accelerates T cell tumor development in ATM-deficient mice.

Design/Method: Bcl11b +/- Atm +/- mice were bred with Atm +/- mice to generate Bcl11b +/- Atm -/- (n=10 to date) and control Atm -/- (n=28) and Bcl11b +/- (n=5) mice. Premalignant and tumor bearing mice were analyzed with thymus pathology confirmed by histology, immunohistochemistry and flow cytometry.

Results: Atm -/- control mice succumbed to thymic lymphomas at ~ 97 days. So far two Bcl11b +/- Atm -/- mice died of thymic lymphomas at 113 and 136 days. Two Bcl11b +/- Atm -/- mice died at 61 and 84 days without thymic lymphomas, but instead exhibited severe dermatitis with grossly enlarged submandibular lymph nodes likely due to superimposed skin infection. The remaining six Bcl11b +/- Atm -/- are 42 to 50 days old with no evident pathology. Notably two Bcl11b +/- Atm +/- mice also developed enlarged submandibular lymph nodes (without thymic lymphomas) at 120 and 153 days.

Conclusion: Our current findings suggest that simple loss of Bcl11b function is not sufficient to accelerate ATM-deficient thymic lymphomas. Ongoing analyses will determine whether Bcl11b +/- abrogates the need for chromosome 12 deletion and translocations. Bcl11b is known to suppress skin inflammatory responses by regulating the Th2-type cytokines. While previously reported in only Bcl11b-/- mice, our findings suggest that Bcl11b heterozygosity may predispose to epidermal dysregulation and skin infection in an ATM-deficient background.
ACUTE KIDNEY INJURY IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA
Nina Guo, Chatchawin Assanasen, Daniel Ranch. University of Texas Health Science Center San Antonio, San Antonio, Texas, United States of America

**Background:** Children with acute lymphoblastic leukemia (ALL) are at risk for acute kidney injury (AKI) due to factors such as tumor lysis and nephrotoxic medications, and AKI is associated with increased morbidity and mortality. However, AKI has likely been underreported in the literature due to the lack of a standard definition.

**Objectives:** With the development of the pediatric RIFLE (pRIFLE) criteria, we aim to determine the incidence of AKI in our ALL population and to evaluate for possible AKI risk factors.

**Design/Method:** Retrospective chart review of newly diagnosed pediatric ALL patients from 1/2009 to 5/2013. Baseline creatinine clearance (CrCl) was determined using the Schwartz formula, and AKI was defined by an acute decrease in CrCl according to the pRIFLE criteria.

**Results:** We identified 46 patients diagnosed during the study period. Most were of Hispanic descent, and 63% were males. All patients had normal baseline CrCl. Using the pRIFLE criteria, the incidence of AKI was 63% during the study period. Most patients developed mild AKI (class ‘R’ (26/29 patients), class ‘I’ (2/29), class ‘F’ (1/29)). 15% of patients developed AKI during the first admission, 59% had more than 1 episode of AKI during the study period, and 1 patient required acute dialysis for tumor lysis syndrome. During the first admission, older age (P<0.0001) and higher serum uric acid (P=0.01) were associated with AKI. Leukemia diagnosis (pre B-cell vs T-cell), gender, white blood cell count, and radiographic contrast exposure were not associated with AKI. Mean initial hospital stay in patients with AKI was not significantly longer than those without AKI. In the first 3 months after diagnosis, 23/46 patients received high-dose methotrexate, and 43% of these had had a prior AKI episode. However, the incidence of delayed methotrexate clearance was not increased compared to those without prior AKI.

**Conclusion:** AKI was a common occurrence in our patients. Most patients had mild AKI by pRIFLE criteria, and older age and higher serum uric acid were identified as risk factors. AKI was not associated with longer initial hospital stays or delayed methotrexate clearance. Further study is required to identify the etiologies of AKI, and to determine the long-term complications.
Enhanced Risk of Lymphoma in Autoimmune Lymphoproliferative Syndrome (ALPS) Due to FAS Mutations

V Koneti Rao, Philip Rosenberg, Susan Price, Fred Gill, Stefania Pittaluga, Thomas Fleisher, Michael Lenardo, Elaine Jaffe. National Institutes of Health, Bethesda, Maryland, United States of America

Background: Autoimmune lymphoproliferative syndrome (ALPS) due to defective FAS is characterized by lymphadenopathy, splenomegaly and peripheral accumulation of DNT cells with multilineage cytopenias.

Objectives: This is an update of their lymphoma risk first reported in 2001 in a series of 10 patients from 8 families following a longer follow up of a cohort of 150 patients from 78 families.

Design/Method: To quantify the incidence of lymphoma, we compared the observed numbers of lymphoma among this cohort to the expected number (O/E ratio) after accounting for age, sex, birth cohort, and race, based on the experience of the US Surveillance, Epidemiology, and End Results Program (www.seer.cancer.gov)

Results: Thirteen of the sixteen cases (13 males and 3 females) of lymphoma were diagnosed in individuals younger than 29yrs. Ten cases of Hodgkin’s lymphoma in 150 patients compared to 0.067 expected in general population conferred an observed to expected ratio (O/E) of 149 (95%, confidence interval (CI) = 71 – 274). Six cases of Non-Hodgkin lymphoma were observed compared to 0.099 expected (O/E = 61; 95% CI = 22 – 132). Both O/E ratios are highly significant as standardized incidence ratio (SIR) values for ALPS-FAS patients are 149 and 61 for Hodgkin and Non-Hodgkin lymphoma, respectively, in the current report versus 51 and 14, respectively, in the 2001 report. Rate of Hodgkin’s lymphoma was significantly elevated in age group 0-9, 10-19, and 20-29, and non-Hodgkin’s Lymphoma in age groups 10-19 and 20-29.

Conclusion: Children with ALPS-FAS have a greater relative risk of lymphoma than previously reported. Straus Blood 2001.

<table>
<thead>
<tr>
<th>Age interval</th>
<th>Cancer Group</th>
<th>Observed</th>
<th>Expected</th>
<th>O/E</th>
<th>CI Lower</th>
<th>CI Upper</th>
<th>Persons</th>
<th>Person Years at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>Hodgkin Lymphoma</td>
<td>4.00</td>
<td>0.004+</td>
<td>1091.72</td>
<td>297.46</td>
<td>2795.25</td>
<td>150.00</td>
<td>1397.95</td>
</tr>
<tr>
<td>0-9</td>
<td>Non-Hodgkin Lymphoma</td>
<td>0.00</td>
<td>0.011+</td>
<td>0.00</td>
<td>0.00</td>
<td>325.68</td>
<td>150.00</td>
<td>1397.95</td>
</tr>
<tr>
<td>10-19</td>
<td>Hodgkin Lymphoma</td>
<td>4.00</td>
<td>0.020+</td>
<td>195.14</td>
<td>53.17</td>
<td>499.64</td>
<td>119.00</td>
<td>910.24</td>
</tr>
<tr>
<td>10-19</td>
<td>Non-Hodgkin Lymphoma</td>
<td>2.00</td>
<td>0.014+</td>
<td>146.88</td>
<td>17.79</td>
<td>530.60</td>
<td>119.00</td>
<td>910.24</td>
</tr>
<tr>
<td>20-29</td>
<td>Hodgkin Lymphoma</td>
<td>1.00</td>
<td>0.025+</td>
<td>40.28</td>
<td>1.02</td>
<td>224.43</td>
<td>60.00</td>
<td>453.62</td>
</tr>
<tr>
<td>20-29</td>
<td>Non-Hodgkin Lymphoma</td>
<td>2.00</td>
<td>0.013+</td>
<td>151.50</td>
<td>18.35</td>
<td>547.25</td>
<td>60.00</td>
<td>453.62</td>
</tr>
</tbody>
</table>
ASSESSMENT OF BONE MINERAL DENSITY IN LONG-TERM SURVIVORS OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA/ ACUTE LYMPHOBLASTIC LYMPHOMA
Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Punjab, Pakistan

Background: Various chemotherapy agents such as methotrexate and glucocorticoids can affect the normal bone growth by interfering with the process of bone mineral acquisition. This can in turn affect the skeletal development as most of the patients diagnosed with childhood ALL / acute LL are young and are in phase of rapid growth. The association has been studied in Caucasian patient population, in our study we assessed the these common risk factors in south east Asian patients.

Objectives: To evaluate the bone mineral density in children and young adults who were treated for pediatric acute lymphoblastic leukemia (ALL) and acute lymphoblastic lymphoma (LL)

Design/Method: All patients with ALL/acute LL followed at long term follow up clinic who were at least 5 years post treatment and in remission were included in the study at a single center. Bone mineral density of lumber spine was measured in 34 patients, 10 female and 24 male. Mean Age at diagnosis was 7.6 yrs., 26 had standard risk Pre B ALL, 2 with high risk Pre B ALL, 3 T cell ALL and 3 T cell Lymphoblastic lymphoma. All patients received less than 5 gm/m2 of methotrexate (dose range was 1.2gm/m2 to 3.1 gm/m2). 21 patients received < 9gm/m2 of corticosteroids and 13 patients receive > 9 gm/m2 of corticosteroids. Bone mineral density was measured at mean age of 9 years post treatment.

Results: Z-score values of lumbar spine in 32 patients were normal (> -2.0), and two were abnormal (< -2.0-both were in osteoporotic range). In the patient population studied, prevalence of abnormally decreased BMD was 6 %. In two patients with abnormal BMD both commonly known risk factors (HDMTX and high glucocorticoid) were not present.

Conclusion: In our patient population risk factors for development of osteopenia/osteoporosis may be different from Caucasian patients with ALL and acute LL
t(5;14)(q31;q32) IN A UNIQUE CASE OF B-LYMPHOBLASTIC LEUKEMIA (B-ALL) WITH EOSINOPHILIA DEMONSTRATES A PHILADELPHIA CHROMOSOME-LIKE (Ph-like) PHENOTYPE

Jason Glover, Rachel Chin, Janice Olson, Faith Galderisi, Jason Hyde, Yassmine Akkari, Stephen Hunger, Richard Harvey, Cheryl Willman, Nameeta Richard. Randall Children's Hospital at Legacy Emanuel, Portland, Oregon, United States of America

Background: ALL with eosinophilia (ALLeo) accounts for < 1% of cases of ALL, and is characterized by a peripheral blood eosinophil count of > 1,500 mm3 and may be associated with end-organ damage. A translocation of chromosomes 5 and 14 [t(5;14)] that juxtaposes the IL3 and IGH genes is often present in ALLeo. There are reports that ALLeo portends a poor prognosis, thought to be due hyperleukocytosis and end organ damage. We present the case of a 14 y.o. previously healthy male with symptoms including: 12 days of fever and generalized erythema, swelling of his face and chest, night sweats, headache, dizziness, and weakness. His initial WBC was 107,000/µL with 62% eosinophils. Peripheral blood smear revealed dysplastic eosinophils and by flow cytometry 8% circulating blasts. Bone marrow flow cytometry revealed B-ALL with blasts expressing CD10, CD19, CD20 (subset), CD22, CD79a, HLA-DR, CD34, and TdT. PCR testing showed clonal IGH and T-cell receptor gamma gene rearrangements. Chromosome analysis revealed 46,XY,t(5;14)(q31;q32)[4]/47,idem,+X[2]/46,XY[20].

Objectives: To report a case of pre-B ALL presenting with hypereosinophilia and the novel finding of a Ph-like phenotype.

Design/Method: Case report. A low density array (LDA) 8-gene PCR assay that has been optimized to define Ph-like ALL (Harvey, ASH 2013) was performed. The cutoff to define patients as Ph-like with this assay is 0.50.

Results: The leukemia was determined to have the Ph-like gene expression profile (score 0.80).

Conclusion: ALLeo is a well-recognized rare subset of ALL typically characterized by a very high percentage of circulating and marrow eosinophils, often with only a low percentage of marrow blasts. Only the blasts contain the t(5;14), the eosinophil are reactive, presumably driven by high levels of IL3 produced by the translocation. Ph-like ALL cases have a gene expression profile highly similar to that present in Philadelphia chromosome positive ALL but lack BCR-ABL1 fusion. Ph-like ALL cases contain a variety of genetic rearrangements and gene fusions that activate kinase and cytokine receptor signaling, but the IGH-IL3 translocation has not previously been implicated. Study of additional cases is needed to determine if the Ph-like phenotype is consistently present in this unique ALL subtype.
Comparative Analysis of Heterodimer-Specific TLR2 Ligands Reveals Divergent Downstream Effects of TLR2/1 and TLR2/6 Ligands in Pediatric B Cell Precursor Acute Lymphoblastic Leukemia

Nina Rolf, Amina Kariminia, Sabine Ivison, Gregor Reid, Kirk Schultz. Child & Family Research Institute, Div Ped Hem/Onc/BMT, Vancouver, British Columbia, Canada

Background: Severe bacterial infections have been reported to induce spontaneous acute lymphoblastic leukemia (ALL) remissions, which intriguingly suggest that bacterial components may trigger ALL elimination. The broadest range of bacterial pathogens is recognized by Toll-like receptor (TLR) 2, one of a family of pathogen recognition receptors that induce strong activation of the innate and adaptive immune system. While considerable preclinical and clinical data recently verified potent anticancer effects for purified TLR ligands against established tumors, conflicting findings for the role of TLR2 stimulation in tumor cells have most likely hindered the development of TLR2 agonists as adjuvants in anti-cancer immune-therapy. However, the impact of heterodimerization, a unique characteristic of TLR2 that may explain such conflicting results, has yet to be evaluated.

Objectives: Pam3CSK4 (TLR2/1) and Pam2CSK4 (TLR2/6) are two well-characterized heterodimer-specific TLR2 ligands not known to cause overwhelming sepsis. Recently, their exact binding properties were identified by crystallography, offering a reliable in-vitro model to study functional downstream effects of TLR2/1 (Pam3CSK4) versus TLR2/6 (Pam2CSK4) stimulation. In this study we compare the outcomes of heterodimer-specific signaling in acute lymphoblastic leukemia (ALL).

Design/Method: We investigated whether both TLR2 ligands a) modulate CD40 expression and b) induce death in 4 primary ALL samples and 4 ALL cell-lines. Furthermore, using the best responding cell-line, we investigated which downstream signaling pathways were activated by either ligand.

Results: This study demonstrates that two well-characterized heterodimer-specific TLR2 ligands, Pam3CSK4 (TLR2/1) and Pam2CSK4 (TLR2/6), upregulate CD40 expression in cell lines and primary leukemia samples. However, only Pam3CSK4 (TLR2/1) induces caspase-mediated apoptosis of ALL blasts and sensitizes them to vincristine-mediated cytotoxicity. Both heterodimer-specific ligands activate NFkB and PI3K signaling pathways in ALL blasts, though with strikingly divergent kinetics, which may underlie their distinct downstream effects.

Conclusion: We are the first to report a novel divergence in downstream responses of TLR2/1 versus TLR2/6 ligation, emphasizing the need for comparative studies of heterodimer-specific TLR2 stimulation in tumor cells. Based on our results, TLR2/1 ligand Pam3CSK4 through its direct effects on leukemic blasts possesses potential for generating anti-ALL activity.
EFFECTS OF ETHNICITY ON HEALTH BEHAVIORS OF ADOLESCENT AND YOUNG ADULT CHILDHOOD CANCER SURVIVORS

Maritza Ruiz. CHOC Children's/University of California, Irvine, Orange, California, United States of America

**Background:** Progress in the management of cancer in adolescents and young adults (AYA) has led to increased longevity. However, AYA survivors remain at risk for long-term morbidity and mortality as a result of disease, treatment, and associated chronic health conditions. Engagement of adverse health behaviors are important predictors of poor health outcomes. Despite the necessity to minimize adverse health behaviors in this population, few studies have focused on the effects of ethnicity on health behaviors of AYA survivors.

**Objectives:** The aim of this study was to compare the effects of ethnicity on health behaviors of AYA childhood cancer survivors.

**Design/Method:** A cross-sectional cohort study design was utilized to assess the health behaviors of Hispanic (N=49) and non-Hispanic White (N=55) AYA childhood cancer survivors from a single cancer center. Participants completed the Child Health and Illness Profile, Adolescent Edition (CHIP-AE) to assess specific health behaviors: exercise, diet, alcohol and drug use, smoking, and sexual activity.

**Results:** Participants (12-33 years old) reported similar demographic information, except for household income and medical insurance status. The Hispanic group reported lower household income and were less likely to be insured than their non-Hispanic White counterpart (p=0.01, p=0.02, respectively). Hispanic survivors were less likely to report eating salty foods (8.2% vs. 23.6%, p=0.03), smoking cigarettes (8.2% vs. 25.5%, p=0.02), wearing a bicycle helmet (61.9% vs. 94.2%, p<0.01), and walking more than a mile within the past month (36.7% vs. 60.0%, p=0.02). There were no group differences in sexual activity, age of first sexual encounter, and use of protection. Ethnicity was a significant predictor for cigarette smoking (OR 4.02, 95%CI 1.03-15.73), alcohol use (OR 3.41, 95%CI 1.32-8.77), wearing a bicycle helmet (OR 7.74, 95%CI 2.25-26.61), and walking more than one mile within the past month (OR 3.42, 95%CI 1.39-8.41), after controlling for insurance status and income.

**Conclusion:** Overall, AYA childhood cancer survivors report few adverse health behaviors although ethnic background may influence the development and practice of these behaviors. Hispanic AYA survivors were less likely to report alcohol and nicotine use, however they were also less likely to engage in safety behaviors and exercise, even after controlling for socioeconomic status. Future studies clarifying the mechanisms behind these differences are warranted.
DOES MAINSTREAMING ONCOLOGY PATIENTS INTO GENERAL PEDIATRIC CLINICS INCREASE RATES OF FEBRILE NEUTROPENIA HOSPITALIZATIONS?

Haneen Shalabi, Angela Katsma, Lara Dugas, Marie-Ellen Sarvida, Loyola University Medical Center, Maywood, Illinois, United States of America

**Background:** Fever in an immunocompromised patient is sometimes the only sign that demonstrates a serious infection. Innate immunity is often affected in immunocompromised patients due to tumor location, radiation, anti-neoplastic treatment, and indwelling catheters. Fevers, especially with neutropenia, remain a significant cause of morbidity and mortality in oncology patients. At this institution, the pediatric and adult oncology clinics were combined in a comprehensive cancer center. In 2010, the pediatric oncology clinic was integrated into the general pediatric clinic in an effort to mainstream pediatric oncology patients with their peers.

**Objectives:** The objective of this retrospective study is to determine whether the rate of febrile neutropenia (FN) hospitalizations for active oncology patients increased after combining the oncology and general pediatric clinics.

**Design/Method:** We reviewed the charts of new oncological diagnosis, N=112, over a three year period (2008-2010). Data collected on these newly diagnosed patients included type of malignancy, number of clinic visits at the cancer center (isolated oncology) vs. combined clinic, and number of FN hospitalizations before and after the transition was made. STATA V-12 was used for statistical analysis.

**Results:** Data collected over the three year period showed that after integrating into the pediatric clinic, oncology patients were less likely, OR 0.51 (95% CI: 0.2783-0.9383; P <0.03) to be hospitalized for fever and neutropenia. In general, patients with hematological malignancies were at an increased risk, OR 3.77 (95% CI: 2.03-7.00; P < 0.001) of being hospitalized than patients with other malignancies. There was no relation to frequency of clinic visits and FN hospitalizations before and after the clinic combined.

**Conclusion:** Oncology patients receiving treatment such as chemotherapy and radiation therapy are at increased risk of serious bacterial infection. Because of this, providers and parents are cautious regarding when patients should be in contact with their immunocompetent peers. This is the first study in the literature to our knowledge that shows that immunocompromised patients in active therapy can be alongside well and sick children without increasing their risk of febrile neutropenia hospitalizations. This study has major implications in the ability of oncology patients to be mainstreamed, even while they are receiving immunocompromising therapies.
TO COMPARE THE ROLE OF HYDROXYUREA AND HYPERHYDRATION VERSUS HYPERHYDRATION ALONE TO DECREASE TOTAL LEUKOCYTE COUNT IN CHILDREN OF ACUTE LEUKEMIA WITH HYPERLEUKOCYTOSIS: A RANDOMIZED CONTROL TRIAL

Manish Sharma, Amitabh Singh, Rachna Seth, Rajiv Kumar, Sushil Kabra, R.M. Pandey. All India Institute of Medical Sciences (AIIMS), New Delhi, Delhi, India

Background: Acute leukemia with hyperleukocytosis (total leukocyte count > 1,00,000/cu.mm) is an oncological emergency. Hyperleukocytosis forms a poor prognostic marker for treatment outcome. These patients are at risk of severe complications due to the hyper viscosity of blood. Increase risk of mortality in hyperleukocytosis is due to CNS hemorrhage or thrombosis, pulmonary leukostasis, metabolic derangement due to tumor lysis and renal failure. Hydroxyurea is often used to treat hyperleukocytosis, but evidence of its effectiveness is limited particularly in children.

Objectives: 1. To demonstrate that addition of hydroxyurea to conventional management causes a significant decline in total leukocyte count when compared to conventional therapy alone in newly diagnosed children of with acute leukemia and hyperleukocytosis 2. To demonstrate difference in complications (tumor lysis, pulmonary complications, CNS complications, hemorrhagic complications and mortality) and time taken for initiating chemotherapy in both groups.

Design/Method: 48 children were randomized in two groups. One group received conventional treatment (intravenous fluids 3 litre/m2 as 5% dextrose saline with 40meq/litre of sodium bicarbonate and oral allopurinol 300mg/m2/day). Other group in addition received hydroxyurea (75mg/kg/day).

Results: Treatment response in hydroxyurea group was seen in (83.3%) patients, in conventional group it was seen in (29.2%). The difference was significant (P value < 0.05). There was no significant difference in complications. Bleeding complications were petechiae (25%), ecchymosis (16.7%), melena (8.3%), epistaxis (6.3%), retinal hemorrhage (6.3%). Respiratory complications predominantly were tachypnea (41.7%), cough (22.9%), respiratory acidosis (10.4%), infiltrate on chest radiograph (10.4%), CNS complications were papilledema (8.3%), photophobia (8.3%), headache (4.2%), Median duration to start chemotherapy was less in hydroxyurea group (P value < 0.05). There was no significant adverse drug effects of hydroxyurea.

Conclusion: Addition of hydroxyurea to conventional treatment leads to rapid and early decline in TLC without any significant adverse drug effect. Hydroxyurea treatment should be given with standard conservative treatment including intravenous fluids, alkalinization and allopurinol.
INTEGRATIVE MOLECULAR CONCEPT MODELING OF HIGH AND LOW INITIAL WHITE BLOOD CELL COUNTS IN HIGH-RISK PEDIATRIC B-ALL PATIENTS

Jitsuda Sitthi-Amorn, Betty Herrington, Catherine Gordon, Gail Megason, Jeanette Pullen, Shirley Hogan, Ritika Ramani, Tejaswi Koganti, Childo Hicks. University of Mississippi Medical Center, Jackson, Mississippi, United States of America

Background: High initial white blood cell (WBC ≥ 50,000/µl) is a well validated high risk prognostic factor in pediatric B-precursor acute lymphoblastic leukemia (B-ALL). Despite considerable research effort, dissecting the molecular mechanisms underpinning high WBC remains a daunting challenge.

Objectives: To determine whether molecular perturbation significantly differs between exceptionally high risk B-ALL patients with high and low initial WBC, to elucidate the molecular mechanisms contributing to the differences, and to identify aberrant molecular networks and pathways.

Design/Method: We performed integrative analysis combing publicly available gene expression data derived from exceptionally high risk (based on age, WBC and sex-specific criteria following Shuster algorithm) B-ALL patients enrolled on Children’s Oncology Group P9906 with information on single nucleotide polymorphisms (SNPs) and genes derived from genome-wide association studies and the Kinome Project. Only samples without detectable recurring molecular abnormalities were analyzed (n=156 with 77 high and 79 low WBC). We compared gene expression levels between the two groups to identify significantly differentially expressed genes. The set of significantly differentially expressed genes without SNPs was combined with the sets of significantly differentially expressed SNP-containing and kinase genes. We then performed hierarchical clustering to identify functionally related SNP-containing and nonSNP-containing genes with similar patterns of expression. Finally, we performed network and pathway analysis to identify aberrant networks and pathways enriched for genes with SNPs and kinase genes. Multiple hypothesis testing was corrected with false discovery rate (FDR).

Results: Supervised analysis revealed 77 highly significantly (P < 10-5; FDR <0.005) differentially expressed genes, 14 and 10 significantly (P < 0.05; FDR 0.1) differentially expressed SNP-containing and kinase genes, respectively. Clustering revealed functional relationships and similarities in patterns of expression profiles among the three sets of genes. We identified aberrant molecular networks and biological pathways enriched for SNP-containing and kinase genes, including the B cell receptor signaling and ATM signaling pathways.

Conclusion: Molecular perturbation significantly differs between patients with high and low initial WBC in exceptionally high risk B-ALL patients. Integrative analysis holds the promise for delineating the molecular mechanisms accounting for variation and differences in gene expression between high and low initial WBC B-ALL patients.
UTILITY OF PERIPHERAL BLOOD IMMUNOPHENOTYPING BY FLOW CYTOMETRY IN THE DIAGNOSIS OF PEDIATRIC LEUKEMIA
Ryan Summers, Laura Williamson, Scott Gillespie, Sunita Park, Glen Lew, Frank Keller. Emory University School of Medicine, Atlanta, Georgia, United States of America

Background: Childhood acute leukemia is traditionally diagnosed via bone marrow aspiration (BMA). New-onset leukemia patients do not always have visible circulating blasts in the peripheral blood at diagnosis. Due to its high sensitivity, peripheral blood flow cytometry (PBFC) is one method used to assess minimal residual disease, but its role in initial diagnosis is unclear.

Objectives: To compare PBFC versus BMA in establishing or excluding a diagnosis of childhood leukemia.

Design/Method: We retrospectively identified 732 PBFC samples from 2008-2012. 340 were excluded, primarily due to lack of corresponding BMA. 43 patients had paired PBFC/BMA samples obtained in the absence of visible circulating blasts during evaluations for possible rheumatologic diagnoses.

Results: Among 392 samples, 92 had negative PBFC and negative BMA, 3 had negative PBFC and positive BMA, 295 had positive PBFC and positive BMA, and 2 had positive PBFC and negative BMA (see Table for summaries). Of the 298 with BMA-confirmed leukemia, 228 had ALL, 60 had AML, and 10 were considered ‘other’. There were no significant differences in sensitivity (100% vs. 99.0%; p=0.759) or specificity (97.1% v. 98.3%; p=0.681) of PBFC between those who did or did not undergo rheumatologic workup. Furthermore, PBFC had high positive (99.3%) and negative (96.8%) predictive values for the diagnosis of childhood leukemia.

Conclusion: PBFC (without BMA) has high sensitivity and specificity for the diagnosis of childhood leukemia. PBFC predictive value results hold true for those in whom visible circulating blasts are not present, and in whom a rheumatologic diagnosis is considered.

Table

<table>
<thead>
<tr>
<th></th>
<th>Total Patients (n=392)</th>
<th>Non-Rheumatologic Workup (n=349)</th>
<th>Rheumatologic Workup (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of Leukemia</td>
<td>76.0 (71.4-80.1)</td>
<td>82.8 (78.4-86.5)</td>
<td>20.9 (10.6-36.5)</td>
</tr>
<tr>
<td>PBFC Sensitivity</td>
<td>99.0 (97.1-99.8)</td>
<td>99.0 (97.0-99.8)</td>
<td>100.0 (66.4-100.0)</td>
</tr>
<tr>
<td>PBFC Specificity</td>
<td>97.9 (92.5-99.7)</td>
<td>98.3 (91.1-99.9)</td>
<td>97.1 (84.7-99.9)</td>
</tr>
<tr>
<td>PBFC PPV</td>
<td>99.3 (97.6-99.9)</td>
<td>99.7 (98.1-99.9)</td>
<td>90.0 (55.5-99.8)</td>
</tr>
<tr>
<td>PBFC NPV</td>
<td>96.8 (91.1-99.3)</td>
<td>95.2 (86.5-99.0)</td>
<td>100.0 (89.4-100.0)</td>
</tr>
<tr>
<td>PBFC FPP</td>
<td>2.1 (0.3-7.5)</td>
<td>1.7 (0.04-8.9)</td>
<td>2.9 (0.07-15.3)</td>
</tr>
<tr>
<td>PBFC FNP</td>
<td>1.0 (0.2-2.9)</td>
<td>1.0 (0.02-3.0)</td>
<td>0.0 (0.0-0.07)</td>
</tr>
</tbody>
</table>

CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; FPP: false positive probability; FNP: false negative probability
ONC201(TIC10) EXERTS CYTOTOXICITY IN PRECLINICAL MODELS OF PEDIATRIC LYMPHOMA: A NOVEL APPROACH
Mala Talekar, Joshua Allen, Wafik El-Deiry. Penn State Hershey Children’s Hospital and Medical Center, Hershey, Pennsylvania, United States of America

**Background:** Outcome for pediatric NHLs using conventional treatment standards remains unsatisfactory, particularly in advanced stage/relapsed disease. TRAIL, an endogenous protein, induces apoptosis selectively in cancer cells by binding to death receptors. Previous TRAIL-targeting strategies have demonstrated unfavorable properties that hamper efficacy such as poor biodistribution and pharmacokinetics. ONC201(TIC10) is a novel compound (JE Allen et al) that induces p53-independent TRAIL gene transcription and cell death in tumor cells (sparring normal cells) through dual inactivation of prosurvival kinases Akt and ERK. ONC201 has long half-life, stimulates TRAIL and death receptor expression, has lower production cost, ability to cross the intact blood-brain barrier, is orally active and has demonstrated potent anti-tumor efficacy in preclinical animal cancer models.

**Objectives:** Derive preclinical rationale for ONC201 as novel targeted therapy for pediatric lymphoma as monoagent or in combination.

**Design/Method:** Diverse sub-type panel of seven human lymphoma cell lines used to assess lymphoma sensitivity to ONC201. Luminescent cell viability assay to generate inhibition curves post-treatment (T/t) with ONC201 yielding IC50’s. Caspase-based Apoptosis assay to quantify sub-G1 DNA content. Surface TRAIL expression via FACS. Inhibition of ONC201-induced apoptosis using Pan-caspase inhibitor (Z-VAD-FMK) at 72H post-T/t. Western blot analysis of representative cell lines from three sub-types at 48H post-T/t with ONC201 to validate the mechanism of induction of apoptosis. Statistical analysis: student t-test, p<0.05 significant.

**Results:** Sharp dose-response curves at 72H post-T/t yielded IC50 values ranging from 1.3 to 5.06 micromolar. Significant levels of apoptosis were noted in dose-dependent manner with increase in sub-G1 content ranging 1.8-fold to 4.15-fold. Increase in surface TRAIL expression was noted in dose-dependent manner across representative cell lines correlating with increase in subG1 DNA content. ONC201-induced apoptosis was demonstrably inhibited using Pan-caspase inhibitor. Western blot analysis of ONC201-treated representative cell lines suggests ERK inhibition and Foxo3a recruitment as potential mechanism of apoptosis induction.

**Conclusion:** ONC201 is promising as monoagent in preclinical models of pediatric lymphoma and may be enhanced by combination with approved therapies to improve the standard of care for pediatric NHL. The ultimate goal of this project is to provide preclinical rationale for potential phase Ib trial of ONC201 as combination therapy in pediatric lymphoma.
PROLONGED HYPOGAMMAGLOBULINEMIA IN PEDIATRIC LYMPHOMA PATIENTS AFTER RITUXIMAB THERAPY

William Terry, Neerav Shukla, Thomas Renaud, Nancy Kernan, Jayanta Chaudhuri, Peter Steinherz, Kobos Rachel. Memorial Sloan Kettering Cancer Center, New York, New York, United States of America

Background: Rituximab, an anti-CD 20 monoclonal antibody, is commonly used in combination with intensive chemotherapy in CD 20 positive lymphomas. Patients typically receive 3 to 5 doses. Peripheral B cell depletion occurs 24-48 hours after the initial dose; with recovery occurring 6-9 months after completing therapy, and normal function returning in 9-11 months. Recent case studies have described adult patients with prolonged hypogammaglobulinemia following rituximab administration, necessitating IVIG therapy.

Objectives: To retrospectively evaluate B-cell function in pediatric patients with CD-20+ lymphomas who received rituximab and intensive combination chemotherapy.

Design/Method: B-cell function was assessed by immunoglobulin measurements and flow cytometry of naïve- and memory-B cells. Frequency of infection and need for replacement IVIG were also documented. Hypogammaglobulinemia was defined as IgG <500 mg/dL and switching deficiency identified as CD19+27+IgD+ switched B-cells <4% of total CD19+ cells by flow cytometry.

Results: From 2008-2012, 20 patients (ages 3-22 years) received a median of 4 doses of rituximab (range 2-5) with 4-8 cycles of intensive chemotherapy. They have been followed an average of 41 months (range 22-69 months) from their last rituximab dose. Persistent hypogammaglobulinemia, with no recovery of memory B-cells after 27-63 months after the last rituximab dose, has been noted in 6/20 (30%). They received a median of 4 doses of rituximab (range 2-5). Of these six patients, 4 have required IVIG replacement therapy for recurrent infections (salmonella septicemia, recurrent otitis, or recurrent pneumonia). These four received 2, 4, 4 and 5 doses of rituximab, with 8,8,8 and 6 cycles of intensive chemotherapy, respectively. For those 14/20 patients who recovered IgG levels to >500 g/dL, the median time to recovery was 14 months (range 4-43 months), with median time to recovery of memory B-cells 30 months (range 18-46 months).

Conclusion: Prolonged hypogammaglobulinemia occurs in a significant sub-set of patients receiving rituximab therapy in combination with intensive chemotherapy, and can persist for >60 months. Furthermore, these patients have subsequently developed clinically significant infections. Patients receiving rituximab need evaluation of immunoglobulin levels prior to therapy and until recovery. Further studies to elucidate the underlying mechanism for these deficiencies are warranted.
HEALTH-RELATED QUALITY OF LIFE ASSESSMENT IN CHILDREN AND ADOLESCENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): A REPORT FROM DANA-FARBER CANCER INSTITUTE (DFCI) ALL CONSORTIUM PROTOCOL 05-001

Lynda Vrooman, Traci Blonquist, Donna Neuberg, Uma Athale, Luis Clavell, Kara Kelly, Caroline Laverdiere, Bruno Michon, Andrew Place, Jennifer Welch, Stephen Sallan, Lewis Silverman. Dana-Farber Cancer Institute, Boston, Massachusetts, United States of America

**Background:** Maximizing health-related quality of life (HR-QOL) is an important consideration in the treatment of acute lymphoblastic leukemia (ALL). On DFCI ALL Consortium Protocol 05-001, children and adolescents with newly diagnosed ALL were randomized to receive either intramuscular (IM) E.Coli L-asparaginase weekly or intravenous (IV) PEG asparaginase every-other-week over 30 weeks in the Consolidation II Phase. HR-QOL was assessed before, during, and after the Consolidation II Phase.

**Objectives:** We aimed to compare HR-QOL in the context of a randomized clinical trial in children/adolescents with ALL receiving either IV PEG asparaginase or IM E. Coli asparaginase.

**Design/Method:** Patients enrolled on Protocol 05-001 were eligible for HR-QOL assessment. Patients aged 5-18 years and parents/guardians of patients aged 2-18 years completed a 24-item questionnaire composed of PedsQLTM modules measuring 6 domains: Treatment Anxiety, Procedural Anxiety, Emotional Functioning, Pain/Hurt, General Fatigue, and Sleep/Rest Fatigue. Questionnaires were administered at 3 time-points: 1) after induction, prior to start of the Consolidation II Phase, 2) between weeks 10-15 of Consolidation II, 3) one year (+/- 1 month) after ALL diagnosis. Results for each domain were compared by randomized treatment group.

**Results:** Between 2005-2010, 202 evaluable patients participating in the randomized asparaginase comparison underwent HRQOL assessment; 97 received IM-treatment, 105 IV-treatment. On parent-proxy report, there was significant difference in Treatment Anxiety at assessment time-point 2 (p=0.024), and in Procedural Anxiety at time-points 1 and 2 (p=0.029 and 0.0026), with greater anxiety reported on the IM-treated arm. On patient report, there was a significant difference in Procedural Anxiety at time-point 2 (p=0.029), with greater anxiety reported on the IM-treated arm, and in Sleep/Rest Fatigue, with greater fatigue reported on the IV-treated arm (p=0.005). There were no other statistically significant differences by randomized groups for other HRQOL domains. Overall, parent-proxy and patient reports displayed a moderate positive relationship.

**Conclusion:** In the context of a randomized trial, greater Treatment and Procedural Anxiety were endorsed by parent-proxy and/or patients undergoing therapy for ALL with IM asparaginase therapy compared with IV therapy. Further evaluation of all measured HR-QOL domains over the first year of therapy is planned with an expanded data-set.
THE EFFECTS ON LENGTH OF STAY DURING INDUCTION CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA ON READMISSIONS

Mary Wedekind, Sarah O'Brien, Terah Koch, Mollie Sturm, Robyn Dennis. Nationwide Children's Hospital, Columbus, Ohio, United States of America

Background: While the chemotherapeutic regimen for induction therapy in Acute Lymphoblastic Leukemia (ALL) is quite similar across the United States, the standard inpatient length of stay varies by institution. The effect of induction LOS on readmissions has not been well studied, nor has predictors of readmission after induction.

Objectives: To categorize US children’s hospitals by typical induction LOS, compare the number of readmissions and time in the pediatric intensive care unit (PICU) in the first 30 days of therapy, describe predictors of readmission, and the most common reasons for readmission.

Design/Method: We extracted data from the Pediatric Health Information System for ALL induction admissions in patients age 0-24 years, April 2007-March 2013. From that data, we obtained the initial admission date and first 30 days for each patient. Forty-two hospitals were placed into LOS categories of Short (2-7days), Medium (8-15days), and Long (16-30 days) based on each institution’s median LOS. Hospital categories were compared based on percentage of patients with readmissions and time in the PICU. A logistic regression was performed to obtain possible predictors of readmission.

Results: We identified 17 hospitals (3555 patients) as short LOS, 17 hospitals (2991 patients) as medium LOS, and 8 hospitals (1426 patients) as long. Short stay hospitals had 71% patients with no readmissions, 24.4% with 1 readmission, 4.6% with >1 admission. Medium stay category had 75.3% with no readmissions, 20.8% with 1 readmission, 3.9% with >1 admission. Long stay had 86.2% with no readmissions, 12.6% with 1 readmission, 1.3% with >1 readmission. There were significantly lower odds of readmission within 30 days of diagnosis in medium or long stay hospitals as compared to short LOS. We also found significantly lower odds of readmission within 30 days of diagnosis for patients initially admitted to the PICU. Finally we found that patients had significantly higher odds of being readmitted more than one time within 30 days if they were older and female.

Conclusion: For induction therapy in newly diagnosed ALL patients, median LOS varies widely by institution. Predictors of readmission include a short LOS hospital, older age(>13years), and female sex.
IDENTIFYING BARRIERS IN A PEDIATRIC ONCOLOGY POPULATION RETURNING TO SCHOOL
Joanna Wigfield, Erin Cockrell, Prasad Bodas. Akron Children's Hospital, Akron, Ohio, United States of America

**Background:** A cancer diagnosis has a significant impact on children’s psychosocial well-being. For many children, school constitutes their primary social outlet. Recommendations for returning to school vary among oncologists. Barriers for school re-entry may include clinic visits, hospitalizations, parental concerns, stamina, and concern for infection. To date there are very few studies to validate barriers in school participation and the impact it has on patients.

**Objectives:** The primary objective was to identify barriers that pediatric oncology patients have in school re-entry.

**Design/Method:** Patients aged 10-25 years, who receive care in a pediatric cancer survivorship clinic, were identified and asked in person or via mail to complete a 10 question survey. Teachers, identified through an email database of Ohio teachers, were asked to complete a 10 question survey.

**Results:** Thirty-six of 165 patients identified in survivorship clinic, responded to the patient survey. Barriers identified included increased risk of infection (64.5%), hospitalizations (61.3%), and physician preference (58.1%) as the primary reasons for not returning to regular school attendance. Decreased stamina was the most commonly identified concern after return to school. Ninety-four percent of the patients listed physician appointments as the primary cause of absences from school. Eighty percent of patients reported that their cancer treatment did not cause any deficiencies in their learning. Surveys were emailed to 1,399 teachers in Ohio. Of 265 respondents, 138 reported having students with cancer and completed the survey. Barriers identified included absences for doctor appointments (67.4%), decreased stamina (62.3%), and concern for increased infection risk (46.4%). Twenty-eight percent of respondents perceived that the child’s performance was worse after diagnosis/treatment, while 61% were unsure if performance had changed.

**Conclusion:** This study identified concern for infection, decreased stamina, and absences related to doctors visits as barriers to school re-entry. Further study is warranted in order to assess the impact of these barriers and to facilitate a safe return to school for our pediatric oncology patients.
FIRST INTERIM ANALYSIS OF THE ASPHO MENTORING PROGRAM

Sherif Badawy, Kerice Pinkney, Emily Meier, Kasiani Myers, Vandy Black, Caroline Hastings, Joanne Hilden, Patrick Zweidler-McKay, Linda Stork, Sarah Vaiselbuh, Theodore Johnson. Lurie Children’s Hospital Chicago - Northwestern University, Chicago, Illinois, United States of America

**Background:** Effective networking and mentorship are critical determinants of academic success. While mentoring programs already exist at the institutional and professional society level, these are often focused programs that create inherent gaps in meeting the full spectrum of mentoring needs for junior faculty and fellows. The Early Career Subcommittee of the ASPHO Professional Development Committee designed and implemented a novel mentoring program in 2013 that allows mentees to self-select their mentors from an internet-based list of mentor profiles.

**Objectives:** We present the first interim analysis of outcomes for the ASPHO Mentoring Program.

**Design/Method:** Target mentees are ASPHO members who are junior faculty within five years of fellowship or current trainees. Target mentors are ASPHO members who are well-established in their career tracks. Once a mentee self-selected a mentor from the list of mentor profiles posted on the ASPHO membership website, and the prospective mentor agreed to the pairing, they worked together to define written goals and plans for achieving their objectives. Outcomes and productivity of each mentee-mentor pair were determined using a semi-annual survey tool.

**Results:** Twenty-nine mentees and thirty-four mentors have been enrolled in the program, and twenty-three mentee-mentor pairs have been formed. Seven pairs were eligible to participate in the semi-annual outcome survey, and responses were received from five (71%) mentees and six (85%) mentors. We will present data pertaining to frequency of interactions, mode of communication, and overall satisfaction with the structure, expectations, and productivity of these relationships. The majority of mentees (73%) and mentors (67%) reported achieving at least some of their goals within this initial six month period, and more than eighty percent considered their experience to be rewarding. All of the mentees and most of the mentors (83.3%) planned to continue their mentoring relationship.

**Conclusion:** The ASPHO Mentoring Program provides an opportunity to meet the diverse professional development needs of a broad spectrum of ASPHO junior faculty and fellow members. This first interim analysis of the mentorship program suggests a clear benefit from career development guidance for Early Career ASPHO members. New mentees and mentors are encouraged to participate in the ASPHO Mentoring Program.
THE EFFICACY OF AN AYA PROGRAM ASSISTANT
Lynda Beaupin, Odochi Uwazurike. Roswell Park Cancer Institute, Buffalo, New York, United States of America

**Background:** Adolescents and young adults (AYAs), defined as those 15 to 39 years of age, have unmet psychosocial needs, complex cancer biologies, and treatment adherence issues. However, it remains challenging to connect with AYAs. Since our AYA program was established in 2011, less than 20% of all AYAs are referred to us, and continued follow-up is even rarer.

**Objectives:** To improve awareness about the program among AYAs, an AYA Program Assistant position was established. This position has proven to be beneficial to the AYA program.

**Design/Method:** The three main goals of the AYA Program Assistant are: 1. Meet with in-patient AYAs, introduce them to the AYA program and AYA team members, and follow up with them after discharge. 2. Manage and oversee the AYA program’s Facebook page. 3. Facilitate AYA social events and supportive workshops.

**Results:** Between July and December 2013, the AYA Program Assistant met with 39 AYAs. This nearly doubles the number of AYA referrals made the previous year. 25 of these survivors (64%) followed up with the program, or participated in an AYA event. A database of AYAs in the Western New York area has been established. Social events for AYAs are now offered monthly and have increasing participation each month. On the social media initiative, the number of people reached by Facebook increased from 79 individuals the first week to 866 the second week, indicating a 1000% increase, and increased to 2,400 people by the third week. Facebook continues to be a successful tool for engaging and interacting with AYAs, and is an effective means for increasing awareness about the program and AYA oncology. Due to increasing AYA feedback, a Young Adult Advisory Committee was established in December 2013 and is currently comprised of 14 dedicated survivors who meet monthly.

**Conclusion:** An AYA Program Assistant is an effective position for AYA programs. More AYAs are connected with the program and, in turn, learn about available AYA resources and have improved access to peers and AYA team members for psychosocial support. Our next steps are to measure patient outcomes and satisfaction with the AYA Program.
UNDERSTANDING THE EXPERIENCES AND SUPPORT NEEDS OF FATHERS OF CHILDREN WITH LIFE-LIMITING ILLNESSES

Mark Belletrutti, David Nicholas, Maru Barrera, Laura Beaune, Jonathan Blumberg. Stollery Children’s Hospital, Edmonton, Alberta, Canada

**Background:** Parents have reported that open and honest communication and social support (individual, family and community-based), are helpful in dealing with the adjustment and challenges of caring for a child with life-limiting illness. Clinical experience suggests that fathers of children with life-limiting illnesses experience substantial distress relating to their child's condition, and perceive limited social opportunities to deal with these issues. The majority of parental research has focused on mothers and has not determined if the needs of fathers in these circumstances are unique.

**Objectives:** This study sought to understand the experiences of fathers of a child with a life-limiting illness or fathers who are grieving the death of their child; and to describe the support needs of these fathers including (1) unique needs that may differ from mothers, and (2) the perceived potential use and benefit of online support for fathers.

**Design/Method:** Using qualitative methods, interviews and focus groups were conducted with 18 fathers (15 fathers of children with malignancy, 6 bereaved fathers). All interviews were digitally recorded, transcribed verbatim, and subjected to qualitative data analysis aided by NVivo analysis software.

**Results:** Participants conveyed a strong commitment to their families but also experienced profound stress associated with their child's condition. Identified concerns included their child's missed life experiences and developmental milestones due to illness, a potentially altered future for the child and family, the impact on siblings, financial burdens resulting from their child’s health situation, and impacts on parents’ marital relationship (positive and negative). Fathers described a need for improved support (clinical and community-based) and potential benefits of engaging in support (e.g. giving and receiving tangible support). They suggested improvements for care practices that would better serve the needs of all fathers, and offered thoughts about technology and peer-based tangible activities as a means of support.

**Conclusion:** The experiences described by fathers inform professional practice and influence the trajectory of future support for fathers who have a child with a life limiting illness. Implications for practice and program development include enhancing pre-existing programs to account for unique needs of fathers and offering support activities better suited to fathers.
NGOs ACTIVELY PARTICIPATE IN PEDIATRIC CANCER IN VENEZUELA
Adriana Bello. Hospital Domingo Luciani, Caracas, Distrito Capital, Venezuela

**Background:** In Venezuela, pediatric cancer represents 3.9 per cent of all malignant neoplasms. In 2005, the incidence for children under 15 was 1661 new cases, out of which 907 corresponded to hematologic cancers and 754 to solid cancers.

**Objectives:** There are renown and emerging NGOs that are engaging and actively adjusting to the necessity in care of pediatric cancer patients in Venezuela. Their participation has been of paramount importance in the overall management of these children.

**Design/Method:** Local organizations like Fundacion del niño con Cancer, Fundacion de padres de niños con cancer, Casa Ronald MacDonald, Fundacion Andrea. Even intergovernmental agreements with developed countries to transfer patients who need advanced treatments like hematopoietic stem cell transplantation. Also twinning with programs from St Jude, Memphis, that provide invaluable collaboration for education, diagnosis and management of such complex patients.

**Results:** Most of their contribution is directed at providing fundings for special tests, drugs, housing or through educational activities and opportunities for health providers from our country. Specially in a decentralized setting, where there is no single institution that embraces the great majority of them. Most activities include an active network from both sectors, private and public, that has been accomplished thanks to one single goal, that is benefit to the child and family. In this sense, we have been able to unite efforts to offer qualified care and good communication.

**Conclusion:** We hope to expand the participation of such organized NGOs and international collaboration to improve the care and survival of pediatric cancer patients in Venezuela.
FASTBREAK: OVERCOMING HURDLES TO PROMPT ANTIBIOTIC ADMINISTRATION
Jessica Foley, Lynn Stachel, Dianne Sinsabaugh, Elizabeth Hilton, Sharon Smith, Helen DeVos
Children's Hospital, Grand Rapids, Michigan, United States of American

**Background:** The prompt administration of antibiotics to febrile neutropenic patients with cancer improves outcomes and decreases mortality from sepsis. As an important quality initiative, decreasing time to antibiotics (TTA) became our focus for the children we care for, whether they were in the outpatient clinic, inpatient or in the emergency room. With the average TTA in these areas ranging from 93-193 minutes, it was important to develop a standard protocol that could easily be implemented by all, regardless of patient location. We recognized that such an initiative would need to appeal to a variety of stakeholders and be memorable and recognizable.

**Objectives:** Our global aim was to decrease TTA by introducing an easy-to-remember, consistent, hospital wide approach with antibiotic administration occurring within 60 minutes. Our Specific, Measurable, Achievable, Relevant and Time-bound (SMART) goal was to deliver antibiotics to 80% of patients within 60 minutes within four months.

**Design/Method:** After reviewing evidence-based literature and assessing our practice, we designed a multidisciplinary protocol for prompt antibiotic delivery. A key component was the plan to treat suspected neutropenia without CBC results. The term “Fastbreak” was used to market the protocol. Education of the staff proceeded and a Plan, Do, Study, Act (PDSA) approach was used to implement and improve outcomes. Run charts that demonstrate outcomes of the process change were shared at key institutional meetings.

**Results:** The “Fastbreak” protocol was implemented November, 2011. The TTA fell dramatically and was consistently below 60 minutes within four months and has persisted over time. The most recent averages for the outpatient clinic, the inpatient unit, and the emergency room, initially 111, 93, and 193 minutes respectively, were 32, 46 and 34 minutes. This correlates with a 71%, 50%, and 82% decrease in the time to antibiotic administration.

**Conclusion:** Using quality improvement methods we instituted a protocol that has been very effective in decreasing TTA for febrile neutropenic patients. The system-wide culture change using the “Fastbreak” protocol has positively affected timely administration of antibiotics to suspected neutropenic patients. We continue to track progress monthly and are redefining our SMART goals as we met our initial goals.
TRAINING PHYSICIANS ON ISSUES OF RACE AND RACISM TO IMPROVE HEALTH CARE EQUITY

Stephen Nelson, Heather Hackman, Children’s Hospitals and Clinics of Minnesota, Minneapolis, Minnesota, United States of America

Background: Disparities based on race are consistently reported in the management of many diseases. The barriers to health care equity are numerous and include racism and physician bias and stereotyping. Physicians receive little to no training on issues of race and racism. A study at our institution found that physicians received only 1.4 minutes/person-year of racism training.

Objectives: Per the recommendations of the Institute of Medicine, the goal of this pilot was to assess the effectiveness of our training module in improving physicians’ awareness of race and racism and in affecting physicians’ comfort in caring for people of color.

Design/Method: We developed a training module for physicians to address issues of race, racism, and whiteness. A group of physicians participated in three 2-hour sessions over a 3-month period. Participants completed a 5-point Lickert scale survey before and after the training. Results were compared using a two-sample t-test.

Results: Nineteen physicians completed the training course (5 males, 14 females). Ten identified as white, 7 Asian, and 2 black. The mean age was 31.9 years. The awareness level of issues of racism increased significantly in all participants, but was most striking in participants of color. The impact of racism on health care in general as well as individuals’ ability to deliver care was felt to have increased in all. White participants showed a significant decrease in feeling as effective in caring for patients of color when compared to white patients and they felt less equipped to care for patients of color following the training.

Conclusion: Awareness of racism and its impact on healthcare delivery is low. Following our training, awareness of this issue increased in all participants. This training was also successful in deconstructing white providers’ previously held beliefs about race and racism. This was evidenced by the fact that feelings of effectiveness in delivering equitable care went down significantly in this group. This is the first step in working on our own racism and unconscious biases. We recommend that all health care professionals receive training to help ensure equitable health care for all. Further study is warranted to define and refine the best training methods.
IMPROVEMENT IN RESIDENT EDUCATION IN PEDIATRIC HEMATOLOGY/ONCOLOGY
Irina Pateva, Connie Piccone, Hong Li. Rainbow Babies and Children's Hospital, Cleveland, Ohio, United States of America

Background: Resident education is a complex process which involves multiple teaching modalities. Didactic sessions, teaching during rounds and with direct patient care and self-directed learning are only some of the most frequently used modalities.

Objectives: To improve resident education in Pediatric Hematology/Oncology with review of pediatric board questions, didactic sessions, and self-directed learning.

Design/Method: The project was conducted during the 2012-2013 academic year. Participants were first and second year Pediatric residents at UH Rainbow Babies and Children’s Hospital in Cleveland, Ohio who rotated through our inpatient service. Pediatrics board review sample questions were compiled from preparation materials for the Pediatrics boards. Participants were given a pre-test with 29 questions at the beginning of their rotation. After the pre-tests were scored, the residents were provided with the correct answers and critiques for each question. Subsequently, a teaching session was conducted and the most commonly missed questions were reviewed. The residents also had the opportunity to discuss topics and the boards content covered in the material with attending physicians and fellows during their rotation. At the end of the rotation, residents were given a post–test with 29 questions. Overall improvement was examined using paired t test and difference between year of residency was compared using Wilcoxon test.

Results: 33 residents took the pre-test and 29 (88%) residents took both the pre- and post-test. Data was analyzed for those participants who completed both tests. 17 first-year and 12 second-year residents completed both pre- and post-tests. Percentages of correct answers were significantly increased after self-learning (76% before and 95% after, p<0.0001). Only 1 resident (3.4%) had all correct answers before, while 15 residents (52%) answered all questions correctly at the end of their rotation. The improvement in scores was similar between year 1 and year 2 residents.

Conclusion: Focused review of Pediatrics boards questions together with self-directed learning leads to improvement in residents’ knowledge in Pediatric Hematology/Oncology as demonstrated by a statistically significant increase in post-test compared to pre-test scores. The difference in test scores between residents at different levels of training was not shown to be statistically significant.
RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTION IN PEDIATRIC ONCOLOGY AND HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) PATIENTS
Mansi Sachdev, Melanie Comito, Robert Greiner, Lisa McGregor, Teresa Shapiro, George McSherry, Kevin Mulieri, Lindsay Trout, Brooke Soulier, Wallace Greene, Robert Tamburro. Penn State Hershey Medical Center, Hershey, Pennsylvania, United States of America

Background: RSV has been implicated as a major source of morbidity and mortality among pediatric cancer and HSCT patients. Therapies exist for the prevention and treatment of severe RSV infections, but they are expensive, labor intensive, and not without risks. Currently, there are no treatment guidelines for their use in this high risk population.

Objectives: To assess the guidelines established by a multidisciplinary working group for the treatment of RSV infections in pediatric oncology and HSCT patients

Design/Method: All cases of RSV in pediatric cancer and HSCT patients from 05/2006-present were reviewed. Data collected included demographics, oncologic diagnosis, HSCT status, chest radiographic findings and the use of RSV specific treatment. Criteria developed by the working group were used to categorize patients as high or low risk and as upper or lower respiratory tract disease. Treatment guidelines were outlined for each of four patient groups: high risk/upper tract, high risk/lower tract, low risk/upper tract, low risk/lower tract. RSV specific treatment consisted of ribavirin (oral and/or aerosolized) and palivizumab. Cases diagnosed before 09/2012 were assessed retrospectively, while cases diagnosed after that were assessed prospectively. Outcome variables included the need for PICU admission and survival. Odds ratios were determined to assess the association between adherence to the guidelines and survival.

Results: 28 pediatric cancer and/or HSCT patients with RSV infection were identified; the mean age was 83.2 ± 13.2 months. Treatment consistent with guidelines occurred in 21 patients (75%). Eleven (39%) patients were classified as high risk and 14 (50%) had lower respiratory tract disease. Four patients (14%) required transfer to the PICU. There were 2 deaths; both classified as high risk/lower tract disease. In neither case was treatment in accordance with suggested guidelines. Mortality among the high risk/lower tract disease group was 29%. The odds ratio for survival if guidelines were followed was 19.5 (95% CI:0.8, 468.8, p = 0.06).

Conclusion: Results of this single center study suggest that RSV treatment consistent with proposed guidelines may improve outcomes in pediatric cancer and HSCT patients. These data have provided the rationale for an ongoing multicenter analysis of these guidelines, results of which will be available soon for analysis.
**INTERVENTION TO PREVENT BURNOUT IN PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOWS**

Evan Shereck, Michael Recht, Nicole Steckler. Oregon Health & Science University, Portland, Oregon, United States of America

**Background:** Physician burnout is an important yet often neglected issue in the education of pediatric hematologists-oncologists. Burnout can lead to lack of empathy, decreased career and life satisfaction and poor patient care. Because burn-out causes an increase in medical errors (Shanafelt, 2010), decreasing physician burnout is important for a physicians’ well-being as well as patient safety.

**Objectives:** A pilot intervention was implemented for pediatric hematology-oncology fellows designed to prevent and mitigate burnout.

**Design/Method:** A curriculum was developed for pediatric hematology-oncology fellows to address topics including career choices (lab-based, clinical-based, academic, private), transition from fellow to attending role, work-life alignment, time management, and resiliency skills. All current fellows were invited and participated in the retreat. Given the demanding clinical schedule for fellows and faculty, a key component of the pilot design was negotiating call coverage to allow all fellows, program directors and key faculty participants to meet together offsite for a full day. Faculty candor in sharing their own experiences, external facilitation and confidentiality ground rules were used to create a safe space for candid reflection and learning. The retreat day combined individual written reflection exercises, small mixed-year structured conversations, and large-group discussion to achieve a balance of reflection and action-planning and to facilitate learning from peers as well as faculty. After the retreat, program evaluation feedback was sought via anonymous survey.

**Results:** Over the two-year pilot, fellow response rate to the evaluation survey was 94%. All respondents reported that the retreat was a valuable use of their time. Fellows found the following aspects of the retreat the most useful: life stories/career paths of faculty participants, peer mentoring, help with organizational skills, and resiliency skill practice.

**Conclusion:** Fellows reported value in a one-day retreat focused on the non-medical side of hematology/oncology training. Future studies will be conducted to determine if this curriculum decreases physician burnout.
YIELD AND COST EFFECTIVENESS OF SCREENING ECHOCARDIOGRAMS IN CHILDHOOD CANCER SURVIVORS TREATED WITH ANTHRACYCLINES AND CARDIOTOXIC RADIOTHERAPY

Michael Spewak, Rebecca Williamson, Ann Mertens, William Border, Lillian Meacham, Karen Wasilewski-Masker. Emory University/Children's Healthcare of Atlanta, Atlanta, Georgia, United States of America

Background: The Children’s Oncology Group’s Long Term Follow-Up (COG LTFU) guidelines for the screening of anthracycline- and radiotherapy-induced cardiomyopathy form a well-respected consensus. Childhood cancer survivors in the Aflac Cancer Survivor Program are screened with echocardiograms at risk-based intervals based on these guidelines.

Objectives: This study aims to investigate the incidence and yield of echocardiogram-derived left ventricular systolic dysfunction across multiple demographic groups and risk factors, as well as to estimate the cost per abnormal finding, in order to inform future COG LTFU guideline recommendations.

Design/Method: Survivors exposed to cardiotoxic therapy, diagnosed ≤21 years of age, and ≥2 years off therapy were included in the study. Patients with cardiac dysfunction <2 years off therapy were excluded. Demographics, treatment exposures, and screening echocardiogram results were extracted from the Cancer Survivor Database, and patients were stratified by COG LTFU risk category. Univariate and multivariate analyses were performed, and cost per abnormal echocardiogram was estimated.

Results: Of 1029 patients (56.3% male, 68.3% white, 20.3% black, mean diagnosis age 6.61 years) screened with 2025 echocardiograms, 64 patients (6.22%) had at least one abnormal test. Multivariate analysis confirms that increased time from diagnosis to first screening echocardiogram (OR 1.17, 95% CI 1.08 - 1.26, p < 0.01), male sex (OR 2.17, 95% CI 1.23 - 4.00, p = 0.01), cumulative anthracycline dose ≥300 mg/m2 (OR 7.35, 95% CI 2.10 - 35.19, p < 0.01), and any radiation dose are risk factors for an abnormal echocardiogram. There were no abnormal echocardiograms in patients exposed to <100 mg/m2 anthracycline dose without radiation exposure. Cost per abnormal echocardiogram was estimated at $391,450.15 for patients receiving <100 mg/m2 of anthracyclines versus $31,594.39 for ≥300 mg/m2.

Conclusion: This study confirms known risk factors for cardiac dysfunction including anthracycline dosage ≥300 mg/m2 and radiation therapy. Male sex and time from diagnosis to echocardiogram were also found to be risk factors. A more cost-effective risk stratification is proposed based on these findings with comparable diagnostic yield to current COG LTFU guidelines. Echocardiographic screening recommendations for patients who receive no radiation and <100 mg/m2 of anthracycline may need to be reevaluated.
CANCER DEATHS AVERTED AMONG CHILDREN, OLDER ADOLESCENTS, AND YOUNG ADULTS, 1975-2010
Eric Tai, Trevor Thompson, Cheryll Thomas, Temeika Fairley, Lisa Richardson. Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

Background: There has been significant improvement in cancer-related mortality in the United States in the past 35 years. However, improvements in cancer-related mortality have varied among children, adolescents, and young adults.

Objectives: The objective of this study was to determine changes in cancer death rates and the number of cancer deaths averted among children, adolescents, and young adults in the United States from 1975-2010.

Design/Method: We used 1975-2010 National Vital Statistics System data to measure cancer deaths averted among children (0-14 years), adolescents (15-19 years), and young adults (20-29 years). We calculated age-adjusted death rates and assessed trends in mortality from 1975-2010 using the average annual percentage change from Joinpoint regression models.

Results: Estimated deaths averted by reduction in cancer-related mortality since 1975 was highest among children (32,261) followed by young adults (29,829), and adolescents (11,035). Children consistently had the lowest age-adjusted death rates (3.2 per 100,000) and young adults had the highest (7.1 per 100,000). While mortality rates significantly decreased for all age groups, the magnitude of the decrease was the largest for children (-2.3%), followed by adolescents (-1.9%), and young adults (-1.5%).

Conclusion: While there have been decreases in cancer-related death rates in the United States over time across all three age groups, younger children consistently had the most improvement over time followed by adolescents and young adults. Increasing referral of adolescents and young adults to cancer centers optimized to treat these age groups and improving access to clinical trials for adolescents and young adults are needed to improve mortality.
STOP-PAIN-NOW PAIN PASSPORT: QUALITY IMPROVEMENT INITIATIVE TO IMPROVE HOME EDUCATION AND AWARENESS REGARDING SICKLE CELL PAIN MANAGEMENT FOR PEDIATRIC PATIENTS AND THEIR FAMILIES.

Maria Tama, Deena Maimone, Eleny Romanos-Sirakis, Sarah Vaiselbuh. Staten Island University Hospital, Children's Cancer Center, Staten Island, New York, United States of America

**Background:** Initial home managing of pain during a vaso-occlusive crisis (VOC) for pediatric sickle cell patients can be very challenging. Proper education can play a crucial role in crossing the narrow bridge between safe and adequate home management or an ED visit, with potential hospitalization.

**Objectives:** 1. To enhance early recognition of signs and symptoms of VOC at home 2. To improve education on initial pain management of a sickle cell vaso-occlusive event in the home environment 3. To include school nursing education as part of “the home environment management team" 4. To provide safe guidelines for best pain relief at home

**Design/Method:** Quality improvement Initiative: Patients, family, and school nurses will be provided with the educational tools necessary for initial management of new onset sickle cell pain outside of the hospital. Educational Tool Kit:1/ Home Education Packet • Education on Sickle Cell Disease and VOC • Step by step guidelines for home management of VOC • Pain self assessment scale with criteria for ED visit/ MD contact 2/ Pain Passport Booklet for self assessment and documentation (by the patient/family) of pain scale, location, time of onset, medications used, time of resolution or progression of pain for each pain episode at home.

**Results:** Pain passports will provide the physician with important clinical information documented at home between office visits, to observe trends in pain crisis, how well the patient’s pain is managed at home and reinforce at what point it will be necessary to go to the hospital if home management is unsuccessful. This home education improvement enhances patient autonomy and may increase compliance.

**Conclusion:** Ultimately, our goal is to improve education and awareness regarding pain management during a VOC in sickle cell disease by enhanced communication between the families, school nurses and the medical team. Early identification of pain and prompt initiation of treatment by the patient themselves can result in preventing symptoms from worsening and reduced number of visits to the emergency department.
THE IMPACT OF FEBRILE NEUTROPENIA GROUP EDUCATION FOR CAREGIVERS OF PAEDIATRIC ONCOLOGY PATIENTS ON CAREGIVER HEALTH LITERACY: A PILOT QUALITY IMPROVEMENT STUDY

Raman Tatla, Abby Bezant, Lisa Honeyford, Ashley Mehta, Angela Punnett. Hospital for Sick Children, Toronto, Ontario, Canada

**Background:** Febrile neutropenia (FN) is considered a medical emergency in paediatric oncology patients. Since fever can be the first and only sign of a life-threatening infection in this patient population, its timely recognition and management by caregivers can drastically improve their child’s health outcomes. Past studies have recognized institutional inconsistencies in definitions and significant knowledge deficits among caregivers related to FN knowledge and management behaviours in the paediatric oncology setting.

**Objectives:** To develop, implement and evaluate an FN curriculum for caregivers of paediatric oncology patients, which addresses caregiver health literacy issues related to FN recognition and management.

**Design/Method:** A pilot single-session group education class, which provides caregivers with interactive and formal teaching opportunities around FN education, was developed, implemented and evaluated using the PDSA Model within the Hospital for Sick Children (HSC). Curriculum content was finalized with input from the study population and healthcare providers (HCPs). Data collection tools were designed for: the (a) intervention group or caregivers attending the class, (b) control group, and (c) expert group. TEMPtEd was used to obtain further expert feedback on the developed curriculum as a patient education. A cross-sectional data analysis was performed between the intervention and control groups, in addition to cumulative evaluations from all three study groups.

**Results:** Four classes were administered, with 7 caregivers in the intervention group, 4 caregivers in the control group, and 7 HCPs in the expert group. The intervention and control groups showed differences in caregiver’s age, education level and the language used at home. The intervention group scored higher in caregiver health literacy and confidence scores after attending the class, compared to the control group. The curriculum received an above average TEMPtEd score from the expert group. The class received favourable evaluations from attendees, with unanimous recommendation for other caregivers of paediatric oncology patients.

**Conclusion:** This pilot QI study addresses the needs to improve caregiver health literacy related to FN, and is currently in the process of full implementation at HSC. The FN education classes will be given biweekly to caregivers of newly diagnosed paediatric oncology patients, with ongoing evaluation and feedback from stakeholders.
“MOST PARENTS TEACH THEIR CHILD HOW TO LIVE; WE TAUGHT OURS HOT TO DIE” – THE HOSPICE EXPERIENCE IN LATINO AND CAUCASIAN CHILDREN
Rachel Thienprayoon, Emily Marks, Maria Funes, Louizza Martinez, Simon Lee, Naomi Winick. University of Texas Southwestern Medical Center, Dallas, Texas, United States of America

Background: Fifty thousand children die annually, many following a protracted chronic illness. Hospice is an important provider of end of life (EOL) care. The quality of care received by children who enroll on hospice is poorly described. To our knowledge, there are no publications relevant to potential disparities in the hospice experience of Latino versus Caucasian children.

Objectives: The objective of this study was to explore parental perspectives of the hospice experience in Latino and Caucasian children.

Design/Method: We held semi-structured interviews with 20 parents or parent dyads of children who died of cancer and were enrolled in hospice. Interviews were conducted in the parents' primary language: 12 were in English and 8 in Spanish. An interview guide was developed based on literature review of parental decision making and cultural constructs at the EOL, and in consultation with a focus group of 8 bereaved parents. Interviews were recorded, transcribed, translated, and analyzed using accepted qualitative methods.

Results: Overall, emergent themes were similar between interviews. The importance of honest and direct communication by medical providers, multi-faceted caregiver burden, pain and symptom control were commonly discussed. Interviews were compared by parental primary language, not race/ethnicity. English speaking parents were more variable in their description of the quality of hospice care; some described "good" symptom control and appropriate hospice support, while others returned to the hospital for improved symptom management and supportive services. Spanish speakers generally reported high satisfaction with the quality of hospice care. English speakers focused on the benefit of child life services in hospice, while Spanish speakers commonly mentioned hospice support in terms of funeral planning. While both groups described anxieties surrounding the expectation of the moment of death, the comfort of being home and not in a hospital was a common theme in the Spanish interviews.

Conclusion: Hospice is an important provider of EOL care. While the intense grief associated with the loss of a child creates common shared experiences, we identified areas where Spanish and English-speaking parents describe their hospice experiences in different ways. More studies are warranted to explore how a family's culture impacts the pediatric hospice experience.
TIME TO ANTIBIOTIC ADMINISTRATION FOR FEBRILE, NEUTROPENIC PATIENTS IS SIGNIFICANTLY REDUCED BY USING A CLINICAL PATHWAY IN THE EMERGENCEY DEPARTMENT
Patrick Tomboc, Michael Henry. Phoenix Children's Hospital, Phoenix, Arizona, United States of America

Background: Fever with neutropenia (FN) is the most common oncologic emergency and a common cause of increased morbidity and mortality in the pediatric oncology population. Prompt identification and timely administration of broad-spectrum antibiotic therapy have been shown to decrease morbidity and mortality. Time-to-antibiotic administration (TTA) is a Quality-of-Care (QOC) measure that can be used to assess barriers to antibiotic delivery in the pediatric emergency department (PED).

Objectives: Decrease TTA to < 60 minutes after implementation of an evidence-based clinical pathway for pediatric patients presenting with FN to the PED and decrease associated length of stay (LOS). Our specific, measurable, attainable, relevant, and time-bound (SMART) aim was to attain a 30% decrease in TTA within six months of implementation of the clinical pathway (CP). Our global goal is to decrease TTA to <60 minutes in 75% of patients by December of 2014.

Design/Method: A retrospective chart review was performed on patients who presented to the PED in the 6 months prior to and 6 months after implementation of a CP for FN. Key drivers include percent reduction of TTA and LOS for each cohort.

Results: Number of patients with FN prior to initiation of the CP = 59, after initiation of the CP = 51. The average TTA prior to the CP was 141 minutes, and the average TTA after initiation of the CP was 103 minutes (p < 0.01). The time from ED arrival to antibiotic administration decreased from 78 minutes (prior to the CP) to 36 minutes (after CP implementation), for a 54% decrease (p < 0.000001). LOS was not significantly different before vs after CP implementation (5.9 vs 5.4 days, p = 0.67)

Conclusion: Implementation of a CP can decrease TTA for pediatric patients with FN and can assist in the identification of potential patient care workflows that can be optimized in the PED.
SIDEKICKS: A LONGITUDINAL PROGRAM PAIRING FIRST AND SECOND YEAR MEDICAL STUDENTS WITH PEDIATRIC HEM/ONC PATIENTS FOR PSYCHOSOCIAL SUPPORT, AND TO DEVELOP COMPASSION AND UNDERSTANDING OF CHALLENGES FACED BY PATIENTS AND FAMILIES

G Naheed Usmani, Fran Prunier, Michelle Pruchniewski. University of Massachusetts Medical Center, Worcester, Massachusetts, United States of America

Background: The UMMS Sidekicks program seeks to fill a void common to medical education: medical students are seldom allowed time and space to know their future patients as people first, before the science. Most are motivated by altruism, but during the initial 2 years of medical education there is a lack of opportunity to develop these qualities.

Objectives: The Sidekicks program seeks to develop medical students’ humanistic qualities, enhance their understanding of the complexities facing families navigating a challenging healthcare system and the need for compassionate, patient-centered care; and expose the students to pediatric hem/onc as a specialty early.

Design/Method: The program matches first/second year medical students as mentors/friends of children undergoing active treatment for hem/onc conditions. The program provides students with a rich variety of curricular and extracurricular experiences in their education. Students learn both in a discussion-based classroom setting and individually with pediatrics hem/onc patients. Students have attendance and visitation requirements, and are required to write a short reflective essay. Patients/families and medical students are surveyed about the program.

Results: 37 first/second year medical students were paired with patients from August'2011 to May'2013. Patient age range was 1.5 to 18 years, with median 11 years. The surveys were administered at the beginning of program in September and at the end of each academic year. We had a 43% return of surveys from patient/families, 100% of students completed the pre-surveys and 46% post-surveys. 100% of responding patients/families and students reported that this was a beneficial program and they would recommend it to other families and continue to participate in it. Students were perceived uniformly as good role models for children. Parents reported a substantial decrease in anxiety and depression coming to clinic and reported being more relaxed and less worried overall. All participating students reported improved understanding of the effects of chronic illness and less anxiety about loss of motivation and detachment. All students felt comfortable taking care of children with hem/onc diseases.

Conclusion: The SIDEKICKS program is simple and effective, provides support to our heme/onc patients, is a unique educational opportunity and encourages students into pediatric hematology oncology careers.
CONTRACEPTIVE RECOMMENDATIONS FOR ADOLESCENT AND YOUNG ADULT WOMEN DURING CANCER TREATMENT: EXAMINING CONTRACEPTIVE KNOWLEDGE OF PEDIATRIC ONCOLOGY CLINICIANS
Sloane York, Yasmin Gosiengfiao, Barbara Lockart, Sara Giordano, Kristin Smith, Jessica Kiley
Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States of America

**Background:** Adolescent and young adult women with cancer have specific reproductive health needs. They may seek recommendations and guidance for contraceptive care from oncology clinicians.

**Objectives:** To examine pediatric oncology clinicians’ reported recommendations for contraceptive use and knowledge on contraceptive safety and efficacy

**Design/Method:** Oncologists and oncologic advanced practice clinicians caring for women aged 13-45 completed an online survey, assessing reported recommendation for contraceptive use during cancer treatment. This secondary analysis reports on pediatric clinicians’ contraceptive knowledge. Participants identified typical failure rates of 10 contraceptives to assess contraceptive efficacy knowledge. Using 3 case scenarios of pediatric oncology patients, participants were asked to identify the safety of 4 hormonal contraceptives. Total knowledge score was determined by averaging the percent correct on safety and efficacy questions.

**Results:** 518 respondents were included in this analysis. Most were practicing pediatric hematologists/oncologists (52.3%) and 42.5% were advanced practice clinicians. Participants had practiced for a mean of 12.5 years, with most (64.1%) seeing 3-10 reproductive-aged female patients per month. Most (82.0%) reported regularly recommending a woman use contraception during cancer treatment. Over half (53.2%) stated they were comfortable with contraception counseling, 69.9% provided contraception in the past year, and 67.1% wanted more information on contraception. Almost half (47.3%) stated they do not discuss pregnancy planning with patients and 233 (45.0%) had cared for at least one pregnant cancer patient. Total knowledge score was 47.4% (95% CI: 45.8, 49.0). Participants identified 61.9% of contraceptives’ safety (95% CI: 60.0, 64.2). Most (87.1%) identified combined oral contraceptives (COCs) as unsafe following pulmonary embolism. For a young nulliparous woman with acute myeloid leukemia, 30.4% correctly identified the safety of the levonorgestrel intrauterine device (IUD) and 28.9% for the copper IUD. Participants identified 32.6% (95% CI: 31.0, 34.2) 10 contraceptives' efficacy. 19.4% correctly identified condoms' efficacy, 12% for oral contraceptive pills, and 34.8% for depot-medroxyprogesterone acetate. Most participants over-estimated the effectiveness of these contraceptives. Almost half correctly identified the failure rate of IUDs (46.1%) and contraceptive implants (41.1%).

**Conclusion:** Pediatric oncology clinicians report recommending contraception during cancer treatment, but may lack comprehensive knowledge for counseling their patients.
LONG TERM CLINICAL AND NEUROCOGNITIVE OUTCOMES OF HOMOZYGOUS ALPHA-THALASSEMIA SURVIVORS
Ali Amid, Catherine Segbefia, Vicky Breakey, Uma Athale, Karen Charpentier, Isaac Odame, Laura Janzen, Melanie Kirby-Allen. The Hospital for Sick Children, Toronto, Ontario, Canada

Background: Homozygous alpha-thalassemia was once considered a fatal disease with death occurring in-utero or shortly after birth. Improvements in the perinatal care with in-utero transfusions as well as chronic transfusions, iron chelation and comprehensive surveillance have resulted in improved survival. However, there are limited reports on the long-term clinical and neurocognitive outcomes of these patients.

Objectives: To present our experience on the long-term outcome of homozygous alpha-thalassemia children.

Design/Method: Comprehensive review of all homozygous alpha-thalassemia patients followed in our hemoglobinopathy programs at the Hospital for Sick Children (Toronto) and McMaster Children’s Hospital (Hamilton) in Ontario, Canada.

Results: Seven patients (four males, three females) were followed for a median of 14 years (range: 5.2-19.2 years). All received intra-uterine transfusions. Two patients had delayed intrauterine transfusion at 31 weeks gestation of which one was born premature at 32 weeks gestation while the rest were born at term. One patient had successful hematopoietic stem cell transplant at the age of six years with 12 month follow-up. Six patients are currently on chronic transfusions and iron chelation (4 deferasirox, 2 deferoxamine). Chelation was started at 16-26 months of age, Mean: 21 months). Four had dysmorphic features (urologic, cardiac, bone deformity). Observed complications included: early iron overload (all patients), deferoxamine-related ototoxicity (three of the six patients on deferoxamine), reduced bone mineral density (all five patients studied), and persistent short stature (all patients). When compared to 19 patients with HbH disease with same ethnic background, patients with alpha-thalassemia major had lower height percentiles. Four patients were old enough to undergo standardized neurocognitive assessments and generally average functioning was observed in three patients. Only one patient, who was born at term but had delayed initiation of intrauterine transfusions showed mild intellectual impairment and below average performance in most neurocognitive domains.

Conclusion: Good prenatal care, intrauterine/chronic transfusions, and comprehensive care may result in improvement of clinical and neurocognitive outcomes in patients with homozygous alpha-thalassemia but treatment-related complications and short stature may be observed. Delayed intrauterine transfusion may result in poor perinatal and neurocognitive outcomes. Early prenatal diagnosis and timely intrauterine transfusion as well as early iron chelation can lead to better long-term outcomes.
RISK FACTORS FOR EARLY VERSUS LATE TRANSCRANIAL DOPPLER FLOW VELOCITY CONVERSION IN PATIENTS WITH SICKLE CELL DISEASE: POSSIBLE EFFECT OF FUNCTIONAL SPLEEN
Ali Amid, Manroop Singh, Amanda Ciccolini, Suman Behera, Alan Daneman, Melanie Kirby-Allen
The Hospital for Sick Children, Toronto, Ontario, Canada

Background: Children 2-5 years of age are at the greatest risk for abnormal Transcranial Doppler (TCD) flow velocity and stroke but a small portion of older patients will have TCD conversion and stroke. While the risk factors for TCD conversion have been studied, their association with the age of TCD conversion (early versus late) has not been investigated.

Objectives: To investigate factors associated with TCD conversion (defined as change from normal to conditional/abnormal, time-averaged maximum velocity >170 cm/s) and the age of conversion.

Design/Method: Data on children 2-16 years with a diagnosis of HbSS or HbSβ0 who were followed in our center were reviewed. Patients who were on disease-modifying therapy were censored at the time of the start of therapy. Studied variables included: age, sex, baseline hemoglobin, HbF percent, LDH, platelet, WBC, and alpha-thalassemia status. In addition, in patients with TCD conversion, annual peripheral blood smears (when available) were reviewed for the assessment of the age of first Howell-Jolly Body (HJB) observation as a surrogate marker of asplenia and any association with the age of TCD conversion.

Results: Of 604 patients studied (1734 patient-year, 2150 TCDs), 132 (27%) had TCD conversions, of which 92 had either prior normal TCD velocities or were 2 years of age at the time of first conditional/abnormal TCD. The plotted Kaplan-Meier curve for conversion reached the plateau at 10 years with an estimated risk of conversion of <2% beyond 10 years of age. Age (p<0.001), alpha-thalassemia status (p=0.047), baseline hemoglobin (p=0.001), LDH (p=0.004) and WBC counts (p=0.01) were correlated with TCD conversion while HbF level was not (p=0.76). On multivariate regression analysis, age, LDH and WBC count were found to be independent predictors of TCD conversion. There was no correlation between these variables and the age of conversion, however, the age at time of TCD conversion was significantly associated with the age of first HJB observation (p=0.001).

Conclusion: In SCD patients, earlier TCD conversion was associated with earlier observation of HJB and not with other factors of disease severity. We hypothesize that a functional spleen may be protective against TCD conversion. This observation should be further investigated in future studies.
HEAD-TO-HEAD COMPARISON OF CURRENT CLINICAL IRON CHELATORS ON CELLULAR FERRITIN REGULATION IN HEPG2 CELL CULTURE MODEL

Monica Khurana, Elliott Vichinsky, Elizabeth Theil. Children’s Hospital Oakland Research Institute, Oakland, California, United States of America

Background: Chronic red blood cell (RBC) transfusions lead to fatal iron overload. Excess iron is mineralized inside intracellular protein ferritin cages (~4500 Fe/ferritin); however, hypertransfusion iron overwhelms iron homeostasis. Iron chelation prevents iron-induced, oxidative damage. Efficacy of current FDA-approved iron chelators (desferrioxamine [DFO], desferasirox [XJ], and deferiprone [L1]) is limited by patient compliance due to cumbersome administration, and toxicities that preclude dose escalation. Required is better understanding of chelator impact on cellular iron and ferritin to develop individualized chelation regimens for RBC transfusion-dependent patients.

Objectives: To develop a cell culture model yielding measurable changes in [iron] and [ferritin] during acute iron loading and chelation. To compare commercially-available chelators.

Design/Method: HepG2 cells, which model human hepatocytes that are the primary cells for iron storage, were iron-overloaded with ferric ammonium citrate (FAC; 100µM Fe) for 24hr followed by incubation with 100µM chelator (DFO, XJ, or L1) for 24hr. Samples of washed cells, lysed by repeated freeze/thaw cycles, and fractionated by sedimentation (10min; 13,000rpm) were analyzed for (1) intracellular and membrane iron (ng Fe/µL lysate) using emission spectrometry, and (2) intracellular ferritin protein (picomoles ferritin/ml lysate) using immunoblotting with chemiluminescent-tagged antibodies and densitometry, standardized to known concentrations of purified ferritin.

Results: FAC increased total cellular iron (p≤0.05) and ferritin protein expression compared to untreated/control cells; ~5x more iron localized to the membrane fraction compared to the intracellular fraction. Only DFO-treated cells significantly lowered intracellular and membrane [iron] by 40% and 33%, respectively, compared to the FAC-only group (p≤0.05). DFO and XJ significantly (p<0.05) decreased ferritin protein by 67% and 53%, respectively, but not L1. Only in DFO-treated cells did cellular [iron] and [ferritin] approach normal.

Conclusion: Intracellular ferritin protein is a sensitive marker of iron chelation. This first head-to-head comparison of DFO, XJ, and L1 at equal concentrations using intracellular ferritin protein as a reporter shows DFO is the most effective chelator. Our data support the use of DFO as a primary chelator in clinical practice. Further, the HepG2 cell culture/ferritin protein model will find use in testing/development of improved iron chelators, especially those targeting intracellular ferritin, the primary site of excess iron.
IMPACT OF ALPHA GLOBIN GENE DELETION ON SICKLE CELL DISEASE
Sasikumar Kilaikode, Sandeepkumar Kuril, Aditi Bagchi, Chittal Raulji, Aziza Sedrak, Swayam Sadanandan. The Brooklyn Hospital Center, Brooklyn, New York, United States of America

Background: Sickle Cell Disease (SCD) is a genetic disorder involving the beta globin gene which has multiple genotypes and variable clinical presentations. There are different variants of SCD like HemoglobinSS (HbSS), Hemoglobin SC (HbSC), HbS-betathalassemia (HbSβthal) and others. The diversity in clinical presentation may be influenced by genetic or environmental factors. Alpha thalassemia trait can coexist with SCD and potentially influence the hematological and clinical manifestations.

Objectives: To study the influence of alpha globin gene deletion (AGGD) on red blood cell (RBC) indices in SCD and its impact on the incidence of splenic sequestration crisis (SSC) and osteonecrosis.

Design/Method: 79 patients between 3 and 23 years with HbSS or HbSβthal were included in the study. Genetic testing was done as part of routine care. Results of genetic testing, mean RBC indices prior to initiation of Hydroxyurea and incidence of complications like SSC and osteonecrosis were reviewed. Data was analyzed using student t test based on the presence or absence of AGGD.

Results: 66(83.5%) Patients had HbSS and 13(16.5%) had HbSβthal, of which 5 were HbSβ0thal and 8 were HbSβ+thal. 24(36.4 %) patients with HbSS and 2(15.3%) with HbSβthal had one alpha gene deletion (–α3.7). None of the patients had 2 or more alpha gene deletions. Statistically significant lower MCV (P<0.01), MCHC (P=0.04), MCH (p<0.01), reticulocyte count (p<0.01) and higher hemoglobin (p<0.02) were seen in HbSS patients with AGGD but these findings were not significant in HbSβthal patients. Among HbSS patients, 25% with AGGD and 33.3% without AGGD had SSC (p=0.48). Osteonecrosis occurred in 12.5% with AGGD compared to 7.1% without AGGD (p=0.47). 50% of HbSβthal patients with AGGD had SSC compared to 27.2% without AGGD (p=0.48). None of them had osteonecrosis.

Conclusion: The incidence of coexisting AGGD (–α3.7) was similar to previous studies. Changes in RBC indices like lower MCV and MCHC noted in HbSS with AGGD may provide rheological advantage which can reduce sickling process and hemolysis. We observed that AGGD was protective against SSC in HbSS but not in HbSβthal. AGGD was not found to be protective against osteonecrosis in HbSS patients. These observations were not statistically significant. Further studies with larger number of patients are needed.
NEUROCOGNITIVE FUNCTIONING AND HEALTH-RELATED QUALITY OF LIFE OF CHILDREN WITH SICKLE-CELL DISEASE ON CHRONIC TRANSFUSION FOR ABNORMAL TRANSCRANIAL DOPPLER ULTRASONOGRAPHY: BASELINE RESULTS FROM THE TCD WITH TRANSFUSIONS CHANGING TO HYROXYUREA (TWiTCH) TRIAL

Margaret Lee, Melanie Bonner, Ofelia Alvarez, Lee Hilliard, Jennifer Rothman, Brigitta Mueller, Ifeyinwa Osunkwo, Sara Pressel, Barry Davis, Russell Ware. Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, United States of America

Background: Neurocognitive deficits are well-described in children with sickle-cell disease (SCD) who had history of stroke or silent cerebral infarcts. Data on neurocognitive and psychosocial functioning of those with abnormal transcranial Doppler (TCD) ultrasonography without documented stroke are limited.

Objectives: To examine the neurocognitive functioning and health-related quality of life (HRQL) of children with SCD on chronic transfusion for abnormal TCD velocities.

Design/Method: Participants in the TWiTCH trial completed standardized neurocognitive testing (Woodcock-Johnson Tests) and HRQL assessments (Children’s Health Questionnaire-50 and PedsQL) at study entry. Scores were summarized as means and standard deviations, and compared with known normative values.

Results: One hundred fifty-nine participants were enrolled from 27 centers (mean age 9.8 ± 2.9 years, 60% females, 98% HbSS, on chronic transfusion for 5.5 ± 2.0 years). Cognitive abilities were slightly below the normative mean of 100 ± 15 in general intellectual ability (92.3 ± 15.1), verbal ability (93.4 ± 13.3), processing speed (94.9 ± 15.9), working memory (97.1 ± 14.7), broad attention (95.5 ± 14.6), and executive processes (95.3 ± 11.8) but still within average range. Similarly, achievement scores were slightly lower than normative mean (100 ± 15) for broad reading (92.8 ± 15.9) and broad math (96.6 ± 43.0). For HRQL using CHQ-50, physical summary score (47.3 ± 9.0) was below healthy norms (53.0) but psychosocial summary score (53.3 ± 9.1) was comparable with healthy norms (51.2); both scores were above that previously reported in severe SCD (physical 28.0, psychosocial 44.3). With PedsQL, subjects and parent/caregiver proxy rated themselves below healthy norms in all subscales, particularly school functioning (Physical Health: Child 82.4 ± 16.3, Parent 79.9 ± 20.4, Norm 87.5; Psychosocial Health: Child 74.6 ± 17.0, Parent 76.7 ± 16.9, Norm 81.9; Total Score: Child 76.5 ± 15.9, Parent 77.5 ± 16.1, Norm 83.8; School Functioning: Child 65.1 ± 19.4, Parent 65.1 ± 22.6, Norm 81.1).

Conclusion: Neurocognitive functions in children with SCD on chronic transfusion for abnormal TCD enrolled in TWiTCH are only slightly lower relative to normative means in all domains. Quality of life is below normal but higher than predicted for clinical severity, perhaps reflecting benefits from chronic transfusion therapy.
CURRENT PRACTICE PATTERNS FOR PARTIAL VERSUS TOTAL SPLENECTOMY IN PEDIATRIC PATIENTS WITH CONGENITAL HEMOLYTIC ANEMIA
Sarah Leonard, Jennifer Rothman, Nirmish Shah, Courtney Thornburg, Henry Rice. Duke University Medical Center, Durham, North Carolina, United States of America

Background: Increasing evidence suggests a potential role for partial splenectomy in children with congenital hemolytic anemia (CHA), however current practice patterns for the use of total and partial splenectomy are poorly defined.

Objectives: This study was designed to understand current practice patterns of pediatric hematologists and surgeons regarding total and partial splenectomy for children with CHA.

Design/Method: We surveyed pediatric hematologists/oncologists registered as members of the American Society of Pediatric Hematology/Oncology (ASPHO) and surgeons participating in the Splenectomy in Congenital Hemolytic Anemia Consortium (SICHA). The anonymous, electronic survey consisted of 11 questions regarding demographic information, patient populations and clinical practices regarding partial or total splenectomy for children with CHA.

Results: 196 of 1712 ASPHO members and 9 of 16 surgeons in SICHA responded to the survey. Most respondents (81%) practice in a mixed inpatient/outpatient academic center, with 51% of ASPHO members and 78% of surgeons practicing >10 years. Twenty-five percent of responses were from sites reporting >400 patients age 0-18y with CHA seen annually. Of patients requiring spleen surgery, 80% of hematology/oncology providers report <10% undergo partial splenectomy compared to total splenectomy. In contrast, surgeons reported at least 10% of their patients had a partial splenectomy with 43% performing a partial splenectomy up to 25% of the time. Perceived benefits of partial splenectomy by all providers included preserved immune function (92%), decreased need for long-term antibiotics (38%) and vascular benefits (35%). Perceived risks of partial splenectomy included lack of surgeon’s experience (65%) and need for completion splenectomy (65%). Despite this understanding of risks and benefits, 48% of responders (33% of surgeons, 50% of hematologists/oncologists) were unsure if there were clear advantages for the use of partial splenectomy, versus total splenectomy, in children with CHA.

Conclusion: This survey of over 200 practitioners experienced in the care of pediatric patients with CHA suggests that providers are aware of the perceived benefits and risks of partial and total splenectomy. Notably, almost half of the surveyed clinicians are unsure of the advantages for use of partial splenectomy, emphasizing the need to further understand the risks, benefits and long-term outcomes of partial versus total splenectomy in children with CHA.
COMMUNICATING PROGNOSIS IN SICKLE CELL DISEASE: ADDRESSING THE FUTURE TO FACILITATE INFORMED DECISIONS
Lydia Pecker, Michael Roth, Sari Landman, Leslie Cunningham, Ellen Silver, Deepa Manwani.
Children's Hospital at Montefiore, Bronx, New York, United States of America

Background: Sickle cell disease (SCD) is clinically heterogeneous with an unpredictable course. Life expectancy for children with HbSS is in the fifth decade. Penicillin prophylaxis, hydroxyurea (HU), chronic transfusions and bone marrow transplant (BMT) contribute to improvements in SCD prognosis. Research shows affected adolescents’ and their parents’ understanding differs from physicians regarding the effect of SCD on their future. How prognosis is addressed in clinical practice is unknown.

Objectives: To understand how pediatric hematologists’ consider and communicate prognosis for patients with SCD.

Design/Method: Online survey emailed to 1,149 pediatric hematologists/oncologists.

Results: One hundred fifteen providers responded to the survey. Eight respondents were excluded because they did not care for patients with SCD. Participants had varied experience (58% practiced >10 years) and worked in diversely sized sickle cell programs (49% of respondents’ programs serve >250 SCD patients). Greater than 90% of respondents agreed that prognosis discussions should include patient health status, disease complications, BMT, and future expectations. Many respondents did not think life expectancy, transition of care, or friendships/teasing should be included. Respondents believed prognosis should be addressed at least annually (72%). Few physicians discuss life expectancy with adolescents or their parents (37% and 39%, respectively). The most common triggers for discussing prognosis were patient initiation (77%), changed clinical condition (72%), initiating HU (70%) and discussing BMT (64%). While 72% percent of providers have a clinical pathway for initiating HU, and 45% for offering BMT, only 24% have a pathway for discussing prognosis. Nearly all providers (92%) rate clinical pathways for communicating prognosis as somewhat to very important. Barriers to discussing prognosis are heterogeneity of SCD and time limitations. Respondents think routine re-visiting of prognosis might impact patients’ and parents’ willingness to start HU, initiate chronic transfusions, or undergo BMT.

Conclusion: Treatment decisions may affect prognosis for children with SCD; BMT offers a chance of cure. Standards for discussing prognosis with families do not exist. Ongoing studies assess patient, parent, and adult hematologist views on discussing prognosis in SCD. Clinical guidelines on how to address this issue will support patients and families in making informed decisions for medical care.
THE CHANGING EPIDEMIOLOGY OF SICKLE CELL DISEASE IN POST-WAR LIBERIA FOLLOWING EXTENSIVE INTERNAL DISPLACEMENT
Venee Tubman, Roseda Marshall, Wilhemina Jallah, Dongjing Guo, Wendy London, Matthew Heeney. Boston Children's Hospital, Boston, Massachusetts, United States of America

Background: Sickle cell disease (SCD) is most common in malaria endemic regions, many of which are low-income nations. In many of these countries, SCD remains underdiagnosed, poorly understood, and associated with extremely high mortality. In Liberia, a low-income country in West Africa, variant hemoglobins have been shown to cluster within specific ethnic groups and regions across the country. Emerging from a prolonged civil war that led to the internal displacement of over 300,000 people, the epidemiology of SCD should be re-established in order to describe a clinical care agenda that befits the changing population.

Objectives: To define the incidence of sickle cell trait and sickle cell disease through a pilot newborn screening program in Monrovia, the capital of Liberia.

Design/Method: This prospective descriptive epidemiologic study collected demographic information from mothers and dried blood spots from consecutively born infants delivered at a large hospital in the Monrovia area. Samples were analyzed by isoelectric focusing. Infants with sickle cell disease were referred to a preventive care program.

Results: The distribution of ethnic groups within the study population (n=2776) was similar to the rest of the country. Sickle cell trait occurred in 10.3% of infants screened. SCD was present in 1.2% (95% CI: 0.8%-1.6%) of infants screened with the most common phenotype being ‘FS’ (FS: 28/33, FSB: 2/33, FSA: 2/33, FSX 1/33). Other hemoglobin phenotypes ‘FC’ and ‘F’ were each present in 1:1000 infants screened. Sickle hemoglobin was significantly overrepresented in migrants from the north and underrepresented in migrants from the east.

Conclusion: The incidence of SCD and other hemoglobinopathies remain high in Liberia, though lower in post-war Monrovia than in earlier reports. This may be associated with internal migration and mixing of previously distinct groups. The high frequency of infants with phenotype ‘F’ suggest either a high incidence of beta-0-thalassemia alleles or hereditary persistence of fetal hemoglobin, both of which could impact the clinical phenotype of SCD in Liberia. A robust clinical care agenda for SCD in Liberia will be an important component to improving child health.
Background: Phase I trials play a key role in the early evaluation of novel targeted therapies for patients with advanced cancer. Pharmaceutical industry sponsored trials exclude patients less than 18 years of age in phase I clinical trials. Some investigator-initiated trials of combinations of US FDA approved agents allow patients less than 18 years.

Objectives: To determine the relationship between pre-enrollment clinical characteristics and survival outcomes of pediatric patients enrolled in adult-based phase I trials at the Department of Investigational Cancer Therapeutics at MD Anderson Cancer Center. To validate the Royal Marsden Hospital (RMH) score and the MD Anderson Cancer Center (MDACC) score as survival predictor tools in this population.

Design/Method: The medical records of 40 patients younger than 18 years treated in at least 1 phase I trial at MD Anderson between January 2005 and January 2013 were reviewed. Univariate and multivariate analyses were used to determine which baseline clinicopathologic characteristics were associated with increased or decreased overall survival (OS) and progression-free survival (PFS).

Results: The median OS was 8.5 months (95% CI, 5.5-13.2 months). In the multivariate analysis, age ≥15 was the only independent factor that predicted increased OS (P = 0.0065), and >3 prior therapies (P = 0.053) predicted decreased OS. The median PFS duration was 2.8 months (95% CI, 2.3-4.1 months). In the multivariate analysis, independent factors that predicted increased PFS were age ≥15 years (P < 0.001) and prior radiation therapy (P = 0.049); performance status >1 (P < 0.001) and >3 prior therapies (P = 0.002) predicted decreased PFS. RMH score ≥ 2 and MDACC score ≥ 3 were associated with decreased median OS (P = 0.029 and P = 0.031 respectively).

Conclusion: It is feasible to conduct phase I studies in pediatric patients based on adult protocols. A composite score using a larger number of patients needs to be developed using the RMH and MDACC scores in future trials. In the era of targeted therapy more trials should allow pediatric patients earlier in the drug development especially if deemed safe in adults in early phase trials.
SURVIVAL OF CHILDREN WITH MEDULLOBLASTOMA IN CANADA DIAGNOSED BETWEEN 1990 AND 2010

Donna Johnston, Daniel Keene, Maria Kostova, Douglas Strother, Lucie Lafay-Cousin, Christopher Fryer, Katrin Scheineman, Anne-Sophie Carret, Adam Fleming, Vanessa Percy, Samina Afzal, Beverly Wilson, Lynette Bowes, Shayna Zelcer, Chris Mpofu, Mariana Silva, Valerie Larouche, Josee Brossard, Eric Bouffet. Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

Background: Medulloblastoma is the most common malignant brain tumor in children. Published survival rates for this tumor are approximately 70%. We sought to determine the survival rate for medulloblastoma in Canada. The Canadian Pediatric Brain Tumor Consortium (CPBTC) is a group representing all the Canadian pediatric oncology centers and data collected by the CPBTC represents all cases of brain tumors in Canada.

Objectives: To determine the survival of children in Canada with medulloblastoma diagnosed between 1990 and 2010 and to determine if the survival changed over the time period studied.

Design/Method: All patients under the age of 18 years diagnosed with medulloblastoma from 1990-2010 inclusive in Canada were included. Data collected included date of diagnosis, age at diagnosis, gender, stage, pathology, treatment, recurrence and current status. Survival rates were determined for all patients.

Results: Data were obtained on 661 eligible patients. The overall survival for the study time period was 69.6±1.9%. The survival increased over the study time period with survival rates for the different time periods of: 1990-1995: 63.7±3.8%; 1996-2000: 72.9±3.9%; 2001-2005: 68.9±3.4%; and 2006-2010: 69.7±7.6%, p=0.03. The survival for different age groups for different stages and gender is shown in Table 1. Overall older patients had better survival than younger patients (age at time of diagnosis, p=0.001) and patients with lower stage disease had a higher survival than those with high stage disease.

Conclusion: This study showed that from 1990-2010 there was an increase in survival of Canadian children and adolescents with medulloblastoma, with older children having the best survival.

**Table 1 – Survival in different age groups based on overall survival, disease stage, and gender.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Overall</th>
<th>By Stage</th>
<th>By Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>M0</td>
<td>M1</td>
</tr>
<tr>
<td>&lt; 5 yrs</td>
<td>60.8±3.0%</td>
<td>68.5±4.0%</td>
<td>62.2±8.4%</td>
</tr>
<tr>
<td>5-14 yrs</td>
<td>76.1±2.7%</td>
<td>75.8±3.3%</td>
<td>78.2±8.7%</td>
</tr>
<tr>
<td>&gt; 14 yrs</td>
<td>81.8±6.5%</td>
<td>83.4±6.9%</td>
<td>100%*</td>
</tr>
<tr>
<td>Overall</td>
<td>67.7±2.0%</td>
<td>72.7±3.4%</td>
<td>70.5±5.9%</td>
</tr>
<tr>
<td></td>
<td>(n=389)</td>
<td>(n=65)</td>
<td>(n=94)</td>
</tr>
</tbody>
</table>

*N=3
POSITIVE β-hCG IN OSTEOSARCOMA: MYTH OR ACTUALITY
Nisha Ramani, Ajaykumar Morani, Najat Daw, Dennis Hughes, Cynthia Herzog. UT MD Anderson Cancer Center, Houston, Texas, United States of America

Background: β-hCG is a glycoprotein synthesized by the placental syncytiotrophoblasts during pregnancy. It is also secreted by gestational and germ cell tumors. There are few documented cases of elevated β-hCG in osteosarcoma.

Objectives: To evaluate whether elevated serum and/or urine β-hCG may be part of a paraneoplastic syndrome in osteosarcoma and speculate on its potential use as a marker of recurrent disease and for monitoring treatment response in cases with elevated levels.

Design/Method: From January 2000 to February 2013, all female patients, 0-25 years of age, treated for osteosarcoma and Ewing sarcoma at MD Anderson, were identified from the tumor registry and reviewed retrospectively. Those patients with elevated serum (S.) β-hCG level (>1 mIU/ml) or positive urine β-hCG were identified based on institutional laboratory reference values. Pregnant patients were excluded from the analysis. Pathology and radiology reports of these patients were reviewed in relation to positive β-hCG test.

Results: Of 359 patients, 263 had osteosarcoma and 96 had Ewing sarcoma. Of 96 patients with Ewing sarcoma, 36 had a β-hCG test done and none had positive serum or urine β-hCG. Of 263 patients with osteosarcoma, 138 had serum and/or urine β-hCG tests done. Forty patients had positive S. β-hCG, including 2 pregnant patients. The rate of elevated β-hCG, excluding the 2 pregnant patients, was 28% (N=38 of 136). All but 1 of these 38 patients had recurrent osteosarcoma at the time of testing, and 17 of them died of disease. In 4 patients, sequential S. β-hCG showed increasing level with disease progression, and in 1 patient it increased and decreased with progression and improvement in disease activity over time.

Conclusion: Osteosarcoma can present with paraneoplastic syndrome producing positive serum and/or urine β-hCG test. Awareness of this finding is important so that oncologists do not exclude such patients from treatment protocols and deny or delay treatment based on the erroneous thought that the patient is pregnant. Whether elevated β-hCG is associated with tumor recurrence or can serve as a tumor marker in osteosarcoma deserves further investigation.
SURGERY IS A FEASIBLE OPTION FOR SYMPTOM PALLIATION IN CHILDREN WITH ADVANCED LIMB SARCOMA
Meera Rayar, Alisha Kassam, Sevan Hopyan, Abha Gupta. Hospital for Sick Children, Toronto, Ontario, Canada

**Background:** Conservative surgical techniques that allow for extremity preservation represent the preferred surgical approach in extremity sarcoma. The use of amputation in adult patients with metastatic extremity sarcoma can provide effective symptom palliation. The use of amputations in children for this reason has not been explored.

**Objectives:** We present the first pediatric case series of palliative orthopedic surgery for advanced limb sarcoma.

**Design/Method:** The medical charts of 4 consecutive patients from 2008 to 2011 with advanced extremity sarcoma who underwent palliative orthopedic surgery at a large pediatric academic children’s hospital were reviewed. The patients had a median age of 14.5 years (range 14 to 16 years) and primary diagnoses of metastatic osteosarcoma (n=3) and malignant peripheral nerve sheath tumor (n=1). The dominant indication for surgery in each patient was severe pain (n=2), poor mobility (n=1) and tumor fungation (n=1). Qualitative assessment of mobility and pain for each patient was made based on documentation of pre and post pain scores, mobility descriptions and dosage of opioid/neuropathic medications used by patients.

**Results:** All procedures were done using general anesthesia with post-operative epidural. Two patients underwent a transfemoral amputation and one underwent a hip disarticulation for distal femur osteosarcoma. One patient with MPNST refused wide resection including internal sacrectomy, and suffered with a necrotic tumor fungating through the buttock for 4 months prior to undergoing debulking surgery. All patients tolerated surgery well without any significant intra-operative or post-operative complications. Severe phantom pain was not reported by any of the patients. Median post-operative hospital length of stay was 7 days (range 5 to 15 days). All patients had significant pain relief with reduction in opioid use, improved mobility, and improved quality of life. Median survival post surgery was 70 days (range 34 to 92 days).

**Conclusion:** Amputation can provide significant symptom relief in the context of metastatic sarcoma. Palliative orthopedic surgery should be considered early in children with refractory sarcoma who have failed non-surgical intervention. Further investigation using rigorous quality of life measures is needed to validate these results.
PULMONARY MICRONODULES DO NOT PREDICT SURVIVAL IN CHILDREN AND YOUNG ADULTS WITH OSTEOSARCOMA

Jason Romancik, Paul Kent, Cara Cipriano, Lauren Brockman, Jeff Ording, Robert Hartemayer, Steven Gitelis. Rush University Medical Center, Chicago, Illinois, United States of America

**Background:** Differentiating between localized and metastatic osteosarcoma (OGS) is necessary for making management decisions and determining prognosis. As part of staging workup, all patients undergo chest CT to screen for pulmonary metastases. The significance of subcentimeter nodules found on thin-slice CT remains unclear.

**Objectives:** The purpose of this study is to determine the effect of pulmonary micronodules (nodules <5mm) found at the time of presentation on the survival of OGS patients under age 50.

**Design/Method:** A chart review was performed for all patients age 50 or younger who were treated for OGS at our institution over a 10 year period. All patients were treated according to standard protocols. Patients with non-pulmonary metastatic disease at the time of diagnosis or a second malignancy were excluded. The results of the initial staging CT were used to separate these patients into a group with no nodules at presentation and a group with any number of nodules <5mm. Kaplan-Meier analysis was performed to compare the survival of the two groups.

**Results:** 61 patients met inclusion criteria. Median follow-up is 65.44 months (range 5.3-147.2). Group 1 consisted of 39 patients (63.9%) with no pulmonary nodules at presentation. Group 2 contained 22 patients (36.1%) who presented with nodule(s) <5mm. Survival at median follow-up for Group 1 is 75.5% compared to 86.4% for Group 2 (p=0.75).

**Conclusion:** In osteosarcoma patients age 50 or younger, the presence of any number of pulmonary nodules <5mm at presentation is not predictive of survival at 65 months.

![Influence of Pulmonary Nodules in Osteosarcoma Patients Under Age 50](image)

*Figure 1: Survival of osteosarcoma patients according to presence of pulmonary nodules. At median follow up of 65.4 months there is no statistically significant difference in survival between the two groups.*
METHOTREXATE INFUSION DIRECTLY INTO THE FOURTH VENTRICLE FOR TREATMENT OF RECURRENT MALIGNANT FOURTH VENTRICULAR BRAIN TUMORS: A PILOT CLINICAL TRIAL

David Sandberg, Soumen Khatua, Michael Rytting, Wafik Zaky, Mary Tomaras, Marcia Kerr, Leena Ketonen, Uma Kundu, Bartlett D. Moore, Grace Yang. University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America

**Background:** Children with recurrent malignant brain tumors have a poor prognosis despite salvage therapies. We hypothesize that chemotherapy infusions directly into the fourth ventricle can potentially treat both recurrent tumors in the fourth ventricle as well as leptomeningeal metastases. Prior experiments in piglets and non-human primates demonstrated safety and favorable pharmacokinetics.

**Objectives:** Under an IRB-approved and FDA IND-exempt protocol, methotrexate was infused into the fourth ventricle in patients with recurrent malignant fourth ventricular tumors. We present preliminary results of this study, which marks the first human clinical trial of direct chemotherapy administration into the fourth ventricle.

**Design/Method:** Patients with recurrent, malignant tumors originating within the fourth ventricle underwent catheter placement into the fourth ventricle with simultaneous tumor resection if clinically indicated. The catheter was attached to an Ommaya reservoir. After confirmation of cerebrospinal fluid flow by CINE MRI, methotrexate (2 mg) was infused. Each cycle consisted of 4 consecutive daily infusions. Serum and cerebrospinal fluid (CSF) methotrexate levels and CSF cytology studies were obtained daily, and MRI scans of the brain and total spine were obtained after the 1st and 3rd cycles and every 3rd cycle thereafter. Neuropsychological evaluation was performed before and after intraventricular chemotherapy.

**Results:** To date, 3 patients have received 13, 6, and 1 cycles, respectively. Median serum methotrexate level was 0.04 micromoles/liter, and median trough CSF level was 15.06 micromoles/liter (range 0.53-212.36). None of the patients had any adverse events or even minor side effects, and no leukoencephalopathy was noted on MRI scans. The first patient, a 19 year-old boy with recurrent medulloblastoma, had a partial response, with decreased tumor in the posterior fossa and spine and fewer malignant cells on cytology analysis. The second patient, an 8 year-old boy with recurrent ependymoma, had stable disease after 3 cycles and partial response after 6 cycles, with decreased leptomeningeal disease in the brain. The third patient, a 12 year-old boy with recurrent medulloblastoma, has had 2 cycles to date and has imaging scheduled after the next cycle.

**Conclusion:** Direct infusion of methotrexate into the fourth ventricle is safe and may represent a promising new means of treating recurrent malignant fourth ventricular brain tumors.
AUTOPHAGY AS A MECHANISM OF RESISTANCE IMPlicated IN OSTEOSARCOMA RESPONSE TO GEMCITABINE

Janice Santiago-o'Farrill, Mario Hollomon, Eugenie Kleinerman, Nancy Gordon. The University of Texas-MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Despite improvements in the treatment of osteosarcoma (OS), overall survival has remained unchanged in the last 15 years. One of the limitations of OS treatment is acquired resistance. Therefore, there is an increasing interest in understanding the molecular mechanisms implicated in OS resistance to chemotherapy in order to improve survival of patients.

Objectives: We had previously demonstrated that aerosol Gemcitabine (GCB) has a significant therapeutic effect against OS lung metastases. However, the presence of residual tumor at the end of therapy suggests a possible acquired resistance mechanism against aerosol GCB. Autophagy, an alternative survival mechanism that cells use in response to stressful conditions, has been associated with tumor cells resistance to chemotherapy. GCB-induced autophagy in OS has not been studied. We investigated the role of autophagy in OS lung metastases resistance to aerosol GCB.

Design/Method: Human LM7 cells were treated with GCB and Western blot analysis, Acridine Orange (AO) staining and Electron Microscopy (EM) images were used for detection of autophagy. Phosphorylation of the AKT/mTOR pathway was evaluated as one of the main mechanisms implicated in autophagy regulation. Additionally, to confirm that autophagy induction decreases LM7 cells sensitivity to GCB we tested the effect of combination therapy using GCB and hydroxychloroquine (HCQ), an autophagy inhibitor, or treated Beclin1 knockdown LM7 cells with GCB.

Results: We demonstrated GCB-induced autophagy as indicated by an increase in protein expression of the autophagy markers: microtubule-associated light chain 3 (LC3I/LC3II) conversion, Beclin 1 (BECN1) expression and acidic vesicular organelles formation. In addition, GCB treatment of LM7 cells resulted in degradation of the signal adaptor protein sequestosome 1 (p62/SQSTM1), further indicating autophagy induction. Additionally, electron microscopy images showed increase in autophagosome formation. Furthermore, we have evidence to demonstrate the inhibition of the Akt-mTOR pathway, as a mechanism involve in the induction of autophagy. Finally, we show that blocking autophagy resulted in increased LM7 cells sensitivity to GCB.

Conclusion: GCB induces autophagy in LM7 human OS cells. Autophagy induction by GCB in LM7 OS cells decreases tumor cells sensitivity. Modulation of autophagy may be an alternative approach for the treatment of OS, possibly by using combination therapy with an autophagy inhibitor.
BRIDGING THE GAP: IMPROVING HEALTH KNOWLEDGE GAPS IN PROVIDERS OF CHILDHOOD CANCER SURVIVORS THROUGH A CONTINUING EDUCATION PROGRAM

Mukta Sharma, Sripriya Raman, Wendy McClellan, Mary Beth Warren, Eve-Lynn Nelson, Robin Ryan, Kristin Stegenga, Kathy Davis, Jennifer Klemp, Joy Fulbright. Children's Mercy Hospital, Kansas City, Missouri, United States of America

Background: Among the U.S population, about 1:680 between ages 20 and 50 is a survivor of pediatric or adolescent cancer. The need for long-term follow-up care of childhood cancer survivors has been well established and guidelines now exist to help providers monitor for late effects of treatment. However, there continues to be a knowledge gap among health care providers in several topics related to monitoring and early diagnosis of long-term effects of cancer treatment.

Objectives: The goals of this project are to assess and improve health care providers’ knowledge on the unique needs of childhood cancer survivors.

Design/Method: We presented evidence based curriculum providing salient information on essential areas of survivorship care at a one day conference. Participants completed an anonymous 20-point pre- and post-test questionnaire at the beginning and end of the conference to assess knowledge and understanding. Fourteen of the 20 questions (70%) covered general information about long term effects including areas of secondary malignant neoplasm (SMN), cardiovascular and lung diseases.

Results: Thirty-one pre-conference and 29 post-conference questionnaires were returned from 35 participants (13 MDs, 12 RN/APN, 2 SW, 8 allied health), majority of which were oncology providers. There was an overall improvement from the pre-conference survey results to the post-conference survey results. Pre-conference, 100% of the participants demonstrated awareness of the critical information to be included in the treatment summaries and what common late effects are. Participants demonstrated significant improvement in knowledge regarding risk factors for development of a SMN (39% correct on pre-test and 79% correct on post-test, p =0.0014) and recognition of the most common SMN after chest radiation for Hodgkin’s Lymphoma (48% correct on pre-test and 90% correct on post-test, p <0.001).

Conclusion: Even though cohort of health care providers had baseline knowledge of the importance of monitoring for late effects, improvement in specific knowledge was demonstrated on the post conference survey. We will be providing additional continuing education through web conferences in the next year and assessing ongoing impact.
Poster # 3095

BRAF V600E MUTATION IN A PATIENT WITH METASTATIC ANAPLASTIC GLIONEURAL TUMOR
Archana Sharma, John Glod. Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, United States of America

**Background:** BRAF V600E has been described in some brain tumors but at a very low rate. This is an interesting case of a patient with an aggressive brain tumor with BRAF V600E expression.

**Objectives:** to describe an usual case with unusual genetic results

**Design/Method:** Patient is a 13 year old girl who presented in March 2012 with headaches and was noted to have a right frontal extra-axial mass. Partial resection of the mass was performed on March 22, 2012 and pathology showed a hemangiopericytoma. Her course was then complicated by bleeding from the tumor with left-sided hemiparesis. Due to rapid progression, another resection was performed and she had started external beam radiation therapy. A second opinion on the tumor pathology from another institution was anaplastic glioneuronal tumor (WHO IV). Daily temozolomide was added to her therapy once this information was obtained. Subsequently, the patient developed back pain and was found to have glioma infiltrating her bone marrow and right cervical lymph nodes and then her left hip. She was treated with irinotecan and vincristine with minimal response in the lymph nodes, but worsening back and hip pain. She then received cyclophosphamide, vincristine and dactinomycin and additional started external beam radiation to the left hip as well as the lumbar spine. Tumor DNA sequencing showed a BRAF V600E mutation and she was started on vemurifanib. After approx 4 weeks of Vemurifanib, the patient was having more hip pain. Vincristine, dactinomycin, and cyclophosphamide was given again but she continued to progress on therapy. She had decreasing activity and more seizures and subsequently expired.

**Results:** BRAF V600E is a known mutation in high grade gliomas. The rapidly metastatic nature of this tumor suggests that DNA sequencing may yield additional therapeutic options.

**Conclusion:** DNA sequencing of brain tumors may yield information for therapeutic choices. Targeted therapy for BRAF V600E should be considered in rapidly progressing tumors.
A FEASIBILITY TRIAL USING MOLECULAR GUIDED THERAPY IN NEUROBLASTOMA
Giselle Sholler, Jeffrey Bond, Genevieve Bergendahl, Akshita Dutta, Julie Dragon, Kathleen Neville, William Ferguson, William Roberts, Don Eslin, Jacqueline Kraveka, Joel Kaplan, Deanna Mitchell, Nehal Parikh, Takamaru Ashikaga, Gina Hanna, Melinda Merchant, Matt Huentelman, Jason Corneveaux, Jeffrey Trent, Helen DeVos Children's Hospital, Grand Rapids, Michigan, United States of America

Background: Neuroblastoma is the most common extracranial solid tumor in children, and treatment options for recurrent neuroblastoma are limited. Using molecular profiling to target the molecular vulnerabilities of neuroblastoma with existing therapeutic agents may result in a rational, data-driven approach with potential to improve clinical outcomes.

Objectives: The primary objective of this study was to evaluate the feasibility of creating real-time treatment decisions in a molecular tumor board through predictive modeling of genome-wide mRNA gene expression data from neuroblastoma tumor biopsies.

Design/Method: Feasibility was defined as completion of tumor biopsy, histopathological evaluation, RNA extraction and quality control, gene expression profiling within a CLIA-certified laboratory, bioinformatic analysis, generation of a drug prediction report, molecular tumor board review yielding a formulated treatment plan, independent medical monitor review and treatment initiation within a 2-week period. RNA sequencing and DNA exomes was performed on all patients.

Results: Fourteen patients with multiply relapsed or refractory neuroblastoma were enrolled between July 2011 and November 2012. All biopsies passed histopathology and RNA quality control. Generation of gene expression data and its analysis (3-8 days), reports which linked this data into medically actionable drug candidates (0-3 days), molecular tumor board (1-6 days) and independent medical monitor review (1 -4 days) were all completed in real-time. The average time was 12.4 days from biopsy to initiation of treatment. There were no unexpected serious adverse events. RNA Sequencing of all patients correlated with RNA expression profiling.

Conclusion: This study shows that it is feasible and safe to create therapeutic treatment plans based on genomic profiling in less than 13 days within a molecular tumor board. Further testing should be pursued to evaluate additional molecular profiling components in order to make individual therapeutic treatment plans more robust as well as to further streamline the process from tumor biopsy through initiation of treatment.
PRIMARY EWING SARCOMA/PERIPHERAL NEUROECTODERMAL TUMOR OF THE KIDNEY: A SINGLE INSTITUTION EXPERIENCE

Nidale Tarek, Sung Kim, Tina Suki, Najat Daw. UT MD Anderson Cancer Center, Houston, Texas, United States of America

Background: Ewing sarcoma (ES)/primitive neuroectodermal tumor (PNET) of primary renal origin is a rare entity. Limited information is available on these tumors, their clinical behavior and treatment.

Objectives: To describe the clinical characteristics, treatment, and outcomes of patients with primary ES/PNET of the kidney.

Design/Method: We retrospectively reviewed the records of all patients who were treated for primary ES/PNET of the kidney at MD Anderson Cancer Center from 1990 to 2013.

Results: Of 277 patients diagnosed with ES/PNET, 19 (6.8%) had primary tumors arising from the kidney. The median age at diagnosis was 29.7 years (range, 14 to 46 years). Twelve were male; 12 were White, 6 Hispanic, and 1 Asian. The most common presenting symptoms were hematuria, pain, and abdominal distension. Of the 10 tested tumors, 8 had EWS gene rearrangement. Ten patients (53%) with metastasis to lung (n=5), bone (n=4), or liver (n=1) were treated with surgery and chemotherapy. Of the 7 patients with metastatic disease on whom data was available, 1 was alive with disease 4 years after diagnosis and 6 died of disease. Five patients with loco-regional disease underwent initial nephrectomy, 4 had tumor thrombus in the renal vein or inferior vena cava (IVC) and 2 of them developed pulmonary embolism after surgery. One patient with tumor invasion into the perinephric adipose tissue had a local recurrence. All 5 patients developed distant metastasis within 2 months after nephrectomy alone (n=3) or 2 years after adjuvant chemotherapy (n=2). Survival data was available on 4 patients, 2 of whom were alive (with disease) 2 years and 5 years after diagnosis. Four patients with tumor confined to the kidney underwent initial nephrectomy followed by adjuvant chemotherapy. All 4 patients were alive a median of 6 years after diagnosis (range, 1.5 to 10 years).

Conclusion: ES/PNET of the kidney may involve the renal vein or IVC. Approximately half of the patients present with metastasis at diagnosis, and have a poor outcome. Patients with disease confined to the kidney may survive long-term after nephrectomy and adjuvant chemotherapy. Patients with loco-regional disease may benefit from neoadjuvant chemotherapy and possibly radiation therapy.
Background: Retinoblastoma (RB) is a rare embryonic tumor that represents 1/16,000 births in France. In Mali, a study showed the characteristics of a hospital series of cases seen in Bamako in the Pediatric Oncology Unit of Gabriel Touré Teaching Hospital and in the African Institute of Tropical Ophthalmology (IOTA) between January 2005 and June 2007. Median age was 4 years versus 2 years in France for unilateral disease. Near two third of children with RB had extra-ocular extension at diagnosis, which is now exceptional in France. Only 11% were bilateral versus 35% in France. Cure rate was around 50%, but it is estimated only on the cases arriving in Bamako and with at least 20% lost for follow-up. Cure rate is over 95% in France within an exhaustive register.

Objectives: This is why, the World Alliance Against Cancer (AMCC), the Curie Institute in Paris, which is the referral center in France for RB, and teams in Bamako were proposing a program to help the development of early diagnosis, treatments, including eye preservation, and rehabilitation of children with RB in sub-Saharan Africa in collaboration with the Franco-African Pediatric Oncology Group (GFAOP).

Design/Method: Information and training of physicians and health personnel on retinoblastoma. Developing retinoblastoma program awareness with the realization of audio-visual spots, facilitation of access to diagnostic exams and chemotherapy. Strengthening histology, coordinate enucleation, conservative treatment and rehabilitation of patients.

Results: The official launching of this program was held in Bamako November 4th, 2011 for Mali and the surrounding countries. After this first experience, this program is now implemented in Senegal, Ivory-coast and democratic republic of Congo. This program will be installed in Madagascar in 2014.

Conclusion: It is possible to develop the treatment of retinoblastoma in sub-Saharan Africa. Better coordination of efforts would be necessary to achieve this goal.
The Role and Efficacy of Retinoic Acid (RA) and the FLT3 Inhibitor as combination Therapy for High Risk Neuroblastoma

Urmila Uparkar, Kay Gurley, Kirstin Robinson, Emily Girard, Kyle Pedro, Julie Park, Christopher Kemp, Carla Grandori. Fred Hutchinson Cancer Research Center, Seattle, Washington, United States of America

**Background:** Neuroblastoma is the most common pediatric extra-cranial solid tumor resulting in the highest infant cancer related mortality. Despite advancements in targeted therapy, 40% of High Risk patients have refractory or relapsing disease. Small molecule inhibitors are successful in other pediatric tumors, but their use in neuroblastoma remains investigational.

**Objectives:** To identify targeted therapies to be utilized in combination with Retinoic Acid (RA) to reduce recurrence of high risk neuroblastoma.

**Design/Method:** We developed a High Throughput screening (HTS) to identify genetic targets whose knockdown would sensitize neuroblastoma cells to RA therapy. FLT3 was identified as a gene. We selected AC220, FLT3 inhibitor which is already utilized drug in pediatric oncology to validate the effect of combination therapy for neuroblastoma. We used escalating doses AC220 alone and in conjunction with RA in 12 neuroblastoma cell lines. Fixed concentrations of RA and DMSO were used as controls. Cell viability was assessed with Promega’s Cell titer glow. Drug responses were normalized to RA and area under the curve (AUC) analysis was performed. Patient derived xenograft model, by injecting 7x10^6 neuroblastoma cells into the flank of Nude/Nude mice was developed. The mice were divided into 4 arms: 1) Control was the drug solvent oil and 5%HBC 2) 60mg/kg of RA in oil 3) 10mg/kg of AC220 in 5%HBC 4) 10mg/kg AC220 in 5%HBC + 60mg/kg RA in oil. Tumor growth was used to assess drug response compared to control.

**Results:** In vitro analysis showed decreased cell survival with the combination therapy. AUC analysis in 10 out of 12 cell lines showed that the ratio of AC220 to combination was greater than 1.7 (1.5-2.3), indicating that the combination of AC220 with RA was superior to single agent therapy. In vivo results show tumor growth was not significantly different in the 3 treatment arms and single agent AC220 activity similar to that of RA alone in neuroblastoma.

**Conclusion:** The result of our screen pinpointed FLT3 as a new gene target for therapeutics to be used in combination with RA in neuroblastoma. FLT3 inhibition limits cell growth when combined with RA in vitro, but further work is necessary to establish parameters allowing in vivo effectiveness.
PRECLINICAL EVALUATION OF NANOPARTICLE ALBUMIN-BOUND PACLITAXEL FOR TREATMENT OF PEDIATRIC BONE SARCOMA
Lars Wagner, Hong Yin, David Eaves, Mark Currier, Timothy Cripe. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

Background: The combination of docetaxel and gemcitabine is frequently used to treat recurrent bone sarcoma. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is less toxic and more active than either docetaxel or paclitaxel for breast cancer patients, and may be particularly beneficial for patients whose tumors express the matricellular protein SPARC, which is hypothesized to facilitate intratumoral accumulation of the drug. Nab-paclitaxel has dose-dependent activity against osteosarcoma xenografts, perhaps related to ubiquitous expression of SPARC in this tumor type. SPARC expression in Ewing sarcoma has not been thoroughly investigated. Recent studies demonstrate synergy between nab-paclitaxel and gemcitabine, and the drug pair is now FDA-approved for treatment of pancreatic cancer.

Objectives: We assessed the extent of SPARC expression in Ewing sarcoma tumor tissue, and then investigated the activity of nab-paclitaxel as a single-agent in a mouse model of Ewing sarcoma, and in combination with gemcitabine in an osteosarcoma model.

Design/Method: Immunohistochemistry was performed to identify SPARC expression in a panel of archival Ewing sarcoma tumors. Established subcutaneous xenograft models of Ewing sarcoma and osteosarcoma were used to test the activity of nab-paclitaxel alone and with gemcitabine. When the implanted tumor reached 200-300 mm3, athymic nu/nu mice received the previously established dose of nab-paclitaxel 30 mg/kg iv for days 1-5, and in the osteosarcoma model mice also received gemcitabine 100 mg/kg iv twice weekly.

Results: SPARC was expressed by immunohistochemistry in 52% of the 25 Ewing sarcoma tumors, including all 7 recurrent tumors. The combination of gemcitabine and nab-paclitaxel prolonged survival in mice bearing 143.98.2 osteosarcoma cells compared to nab-paclitaxel alone (p = 0.0311). Significant growth inhibition and improved survival compared to saline control was seen in mice bearing A673 Ewing sarcoma cells following a single- 5-day course of nab-paclitaxel (p < 0.0001).

Conclusion: Nab-paclitaxel showed single-agent in vivo activity against Ewing sarcoma, and was additive with gemcitabine against osteosarcoma. These findings, coupled with the documented expression of SPARC in bone tumors and the tolerability of this commercially available drug combination in adults, provide rationale for further study of nab-paclitaxel in pediatric bone sarcoma.

Supported by a grant from Celgene Corporation.
CROSSTALK: A SYSTEMATIC REVIEW OF ADHERENCE INTERVENTIONS TARGETING PEDIATRIC TUBERCULOSIS TREATMENT IN LOW- AND MIDDLE- INCOME SETTINGS WITH APPLICATIONS FOR PEDIATRIC SOLID TUMOR OUTCOMES

Meaghann Weaver, Catherine Lam. St. Jude Children's Research Hospital, Memphis, Tennessee, United States of America

**Background:** Cure requires sustained treatment, but, failure to complete indicated treatment (treatment abandonment) occurs in up to one quarter of pediatric tuberculosis cases and half of pediatric oncology cases in some low- and middle- income settings (LMIS).

**Objectives:** This systematic review assesses the design, delivery and outcomes of adherence interventions utilized in pediatric tuberculosis in LMIS, and evaluates the potential application of these interventions for pediatric oncology treatment adherence.

**Design/Method:** A protocol was drafted in alignment with PRISMA standards and registered with PROSPERO. 412 reports published between 2003 to 2013 were identified from PubMed, COCHRANE bibliographies, hand-searching including of the grey literature, and expert consultation. 163 reports qualified for full-text review. Randomized control, quasi-experimental, and observational studies that utilized an intervention specific to treatment completion, adherence, prevention of refusal, or family-efficacy with a reported adherence-related outcome for pediatric-age populations (< 19 years) in LMIS (defined by World Bank) were included. Studies were categorized for utilization of educational, psychosocial support, care delivery, health systems, or social protective/financial interventions. Adherence outcomes included referral to care, prevention of refusal, appointment attendance, medication adherence, self-efficacy, and treatment completion. 14 studies (10 countries) were included in synthesis. Risk of bias was systematically assessed.

**Results:** Four randomized and eight non-randomized studies were included (8 prospective), representing urban outpatient (n=4), rural outpatient (n=3), township (n=2), rural camp (n=1), and mixed settings (n=4). Interventions targeting adherence education (n= 2), counseling (n=2), decentralization of care delivery (n=7), support clubs (n=1), social franchising (n=1), and social protection/financial provision (n=1) were feasible across diverse, rural/urban settings, and demonstrated to impact on tuberculosis treatment adherence outcomes in 13 studies, and equivocal in 1 studies. This study incorporates critical analyses of comparative pediatric oncology outcomes in the same countries, relevant to solid tumor diagnoses. Findings were also applied to generate a preliminary model to stimulate further trans-sectoral collaborations.

**Conclusion:** These findings highlight needs and next steps for rigorous methodology with attentiveness to implementation and cost analyses to examine effectiveness, local acceptability, feasibility, affordability, and sustainability of successful treatment completion interventions in the context of pediatric solid tumor therapy completion in LMIS.
INCIDENCE OF SUBSEQUENT MALIGNANCIES IN PEDIATRIC THYROID PATIENTS FOLLOWING RADIOACTIVE IODINE THERAPY
Ashley Weiner, Perry Grigsby, Todd DeWees, Stephanie Perkins, Washington University School of Medicine, Saint Louis, Missouri, United States of America

**Background:** Well-differentiated thyroid cancer (WDTC) is a rare occurrence in the pediatric population. Patients typically present with more advanced disease than adults, and many of these children are treated with radioactive iodine (RAI) therapy. Despite often presenting with advanced disease, overall survival for these patients is excellent. The risk of subsequent malignant neoplasms (SMNs) following treatment with RAI is therefore important to evaluate in this population with excellent long-term survival.

**Objectives:** To evaluate the rates of subsequent malignancies in pediatric patients with WDTC who have received RAI.

**Design/Method:** Using the National Cancer Institute’s Surveillance, Epidemiology and End-Results (SEER) database, we identified a cohort of pediatric patients aged 4-21 years who were diagnosed with WDTC between 1973-2005. All patients in this cohort were treated with RAI and survived a minimum of 5 years after diagnosis. Cumulative incidence of SMNs and standardized incidence ratios (SIRs) of observed to expected SMNs were calculated.

**Results:** A total of 695 patients were included in the analysis consisting of 586 females and 109 males. Median age was 18 years old. Follow-up ranged from 5-37.3 years with a median follow-up of 14.3 years. Overall survival at 20- and 30-years was 96.9% and 94.1%, respectively. During the study period, 15 patients developed a subsequent malignancy (3 breast, 2 melanoma, 2 parotid, 2 cervical, 1 endometrial, 1 renal, 1 ovary, 1 brain, 1 sarcoma and 1 lymphoma). The cumulative incidence of subsequent malignancy at 30 years was 4.9%. The expected incidence of malignancy in this cohort was 10.5, yielding an SIR of 1.42 (95% CI 0.8-2.34). Two patients developed parotid malignancy, which was increased over the expected incidence. Both patients were alive 5 and 7 years after diagnosis of the parotid tumor.

**Conclusion:** Pediatric WDTC patients treated with radioactive iodine did not experience an overall statistically significant increased risk of SMNs. Two patients developed a parotid malignancy, which was greater than the expected incidence in this cohort. Many children with WDTC require treatment with RAI due to advanced disease, and it appears that risk of SMN following RAI is low.
THE ROLE OF FGFR4 IN NEUROBLASTOMA
Sarah Whittle, Melissa Du, Linna Zhang, Sarah Woodfield, Michael Scheurer, Fatih Okcu, Peter Zage.
Baylor College of Medicine, Houston, Texas, United States of America

**Background:** Neuroblastoma is the most common extra-cranial solid tumor of childhood. Many children present with high-risk disease characterized by rapid tumor growth, resistance to chemotherapy, and widespread metastasis, and novel therapies are needed. A germline polymorphism resulting in a substitution of arginine in place of guanine in codon 388 in the FGFR4 gene is associated with increased incidence, treatment resistance, and poor outcomes for many cancers. Recent studies have also shown that this FGFR4 variant protein demonstrates both reduced degradation and sustained activation and signaling.

**Objectives:** We aim to determine the incidence of the FGFR4 polymorphism in neuroblastoma patient samples, determine the significance of the polymorphism on disease severity and patient outcomes, and evaluate the degradation and trafficking of the FGFR4 protein.

**Design/Method:** We screened DNA from 129 neuroblastoma patients collected through an IRB-approved protocol for the FGFR4 genotype using RT-PCR analysis. Allele frequencies were determined and compared to the allele frequencies in a representative control population as reported in HapMap (release 27, NCBI build 36). In order to evaluate the degradation rate of FGFR4 in neuroblastoma tumor cells, neuroblastoma tumor cell lines were starved in serum-free media and then treated with ligand to induce receptor endocytosis. Western blots using antibodies against individual receptors were performed and relative expression levels were determined.

**Results:** We identified an association with patient genotype for the FGFR4 polymorphism and neuroblastoma incidence. Logistic regression analyses suggested an association between having the variant allele and having neuroblastoma (p<0.05), with a 3.3-fold increase in patients homozygous for the arginine allele having neuroblastoma compared to those homozygous for the more common glycine allele. Additionally, the FGFR4 protein does not undergo ligand-induced degradation as seen with EGFR, consistent with increased FGFR4 stability.

**Conclusion:** We have shown that neuroblastoma patients disproportionately possess the FGFR4 variant allele and that neuroblastoma tumor cell lines have reduced FGFR4 degradation. Ongoing studies are underway to determine the association of the FGFR4 polymorphism with neuroblastoma patient clinical features and outcomes and the association of the FGFR4 genotype with the responses to FGFR kinase inhibitors.
THE ROLE OF UBE4B AND GROWTH FACTOR RECEPTOR TRAFFICKING IN NEUROBLASTOMA
Peter Zage, Sarah Woodfield, Rongjun Guo, Sandra Indiviglio, Linna Zhang, Angela Major, Emporia Hollingsworth, Natalie Sirisaengtaksin, Andrew Bean, Dolores Lopez-Terrada. Baylor College of Medicine, Houston, Texas, United States of America

Background: The UBE4B gene, found in the chromosome 1p36 region commonly deleted in neuroblastoma tumors, encodes an E3/E4 ubiquitin ligase. We have previously observed a direct interaction between UBE4B and Hrs, a protein required for growth factor receptor (GFR) trafficking, suggesting a link between GFR trafficking and neuroblastoma pathogenesis. However, the mechanisms underlying the role of UBE4B in neuroblastoma are not known.

Objectives: We analyzed the roles of UBE4B in the outcomes of neuroblastoma patients and the association of UBE4B with neuroblastoma tumor prognostic features, GFR trafficking and downstream signaling.

Design/Method: We obtained neuroblastoma tumor tissue microarrays from the Children's Oncology Group and both formalin-fixed paraffin embedded (FFPE) tissue and fresh frozen tumor samples from the Texas Children's Hospital pathology department and tissue bank. We screened neuroblastoma tumor cell lines and tumor samples for UBE4B protein expression and for GFR expression and downstream signaling using immunohistochemistry and Western blots.

Results: Out of 29 neuroblastoma tumor samples initially screened, twenty one cases were poorly differentiated or undifferentiated and eight cases were differentiating. UBE4B expression was diffusely or focally reduced in eighteen cases (51.4%). Reduction of UBE4B expression was only seen in poorly differentiated or undifferentiated neuroblastoma tumors or the poorly differentiated component of intermixed neuroblastomas. UBE4B expression was associated with GFR expression and downstream signaling in neuroblastoma tumor cells.

Conclusion: We have demonstrated associations between UBE4B expression and neuroblastoma patient outcomes and between UBE4B and GFR expression in neuroblastoma tumor samples. In this study, reduced UBE4B expression in neuroblastoma tumors was associated with a lack of differentiation in neuroblastoma tumors. Therefore, immunohistochemistry for UBE4B expression is a reliable approach to addressing heterogeneity of neuroblastoma. This link between a known cytogenetic risk factor, GFR trafficking, and neuroblastoma tumor histology suggests UBE4B-mediated GFR trafficking may contribute to the poor prognosis of neuroblastoma tumors with 1p36 deletions.
NOTCH IN NEUROBLASTOMA: TUMOR SUPPRESSOR MECHANISM AND RESISTANCE.
Riitta Nolo, Mandy Hall, Patrick Zweidler-McKay. UT MD Anderson Cancer Center, Houston, Texas, United States of America

Background: We have previously shown that activation of Notch signaling results in neuroblastoma growth inhibition and death. We have found that Notch signaling leads to dysregulation of multiple oncogenic pathways, including profound downregulation of CD24. CD24 (HSA) is a cell adhesion and signaling molecule that is expressed in the majority of neuroblastoma samples and has been linked to neuroblastoma proliferation, metastasis and tumor initiation. We have also found that neuroblastoma cells express Notch2 mutants whose function is currently unknown.

Objectives: To define the role of CD24 down-regulation as a mechanism of Notch-mediated tumor suppression in neuroblastoma, and to test the function of Notch2 mutants.

Design/Method: JAG1 ligand-mediated Notch signaling was used to measure mRNA (RNA-seq, QRT-PCR), cell surface protein (flow cytometry), and total cellular protein (immunoblot) in neuroblastoma cell lines SHEP and SH-SY5Y. Notch2 variants were cloned from these neuroblastoma cell lines.

Results: Upon Notch activation via exposure to JAG1 ligand or expression of constitutively-activated Notch2, CD24 mRNA and cell surface protein expression were profoundly down-regulated (RNA-seq, 10-fold QRT-PCR, and >100-fold flow cytometry). Importantly CD24 siRNA enhanced JAG1-mediated growth arrest, while CD24 overexpression partially rescued the ligand-induced effects and increased neuroblastoma proliferation. Consistent with other tumor models, CD24 knockdown decreased SRC activation (p-SRC T416). Notch2 point mutant P2168L and splice variant deletion of exon 17-18 (del17-18), along with wildtype Notch2 were cloned from neuroblastoma lines. Expression of wtNotch2 in Notch-resistant SY5Y cells led to Notch2 expression at the surface, restored sensitivity to JAG1 ligand, and reduce CD24 expression. The P2168L mutant was also expressed at the cell surface and led to modest decreases in CD24 expression. In contrast, the del17-18 splice variant, which removes extracellular EGF repeats, was not present at the cell surface, despite high levels of expression, and did not induce ligand sensitivity or CD24 down-regulation.

Conclusion: CD24 downregulation plays a critical role in Notch-mediated tumor suppressor effects in neuroblastoma. However, Notch2 mutants and splice variants may lead to escape from Notch ligand-mediated signaling and resistance to this mechanism. Thus combined targeting of Notch resistance and CD24 may represent a novel therapeutic approach in neuroblastoma.
EPIDEMIOLOGY OF PAEDIATRIC HAEMATOPIETIC STEM CELLS TRANSPLANTS – AN ASIAN PERSPECTIVE
Ah-Moy Tan, Christina Ha, Chun Fu Li, Goffrey Chan, Vincent Lee, Poh Lin Tan, Suradej Hongeng, Kleebsaibai Sanpaki, Anselm Lee, Hai Peng Lee, Maria del Rosario, Jing Chen. KK Women's & Children's Hospital, Singapore, Japan

Background: Haematopoietic stem cell transplant (HSCT) is an established treatment for many malignant and nonmalignant childhood conditions. Because of regional difference in disease spectrum and donor availability, transplant approaches may vary in Asia.

Objectives: The Viva-Asia Blood and Marrow Transplantation (VABMT) Group was established in 2009 to address the specific transplant issues for children in the Asian region.

Design/Method: Data were collected from each center on a yearly basis and compiled before the annual VABMT group meeting. Members of this working group perform paediatric HSCTs in 6 Asia countries, including 3 centers in Singapore, 2 in Hong Kong, 2 in mainland China, 2 in Thailand and 1 each in Malaysia and Philippines.

Results: A total of 1790 haematopoietic stem cell transplantations (HSCT) for children were performed in these 11 centers during the 12-year period from 2000 to 2011 inclusive. In that period, 1407 (78.6%) were allogeneic HSCTs and 383 (21.4%) were autologous HSCTs. Among the allogeneic HSCTs, majority (54.9%) were for nonmalignant conditions while 45.1% were for malignant conditions. Main indications for malignant conditions were acute leukaemia (lymphoid and myeloid), chronic myeloid leukaemia and myelodysplastic syndrome. The nonmalignant conditions were haemoglobinopathy, acquired/congenital bone marrow failure syndrome, primary immunodeficiency disorders and metabolic diseases. Unrelated sources of stem cells contributed 48% while related sources accounted for 52%. Within related HSCT, bone marrow was the main source of stem cells (58%), while among unrelated HSCT, peripheral blood was the main source (44.3%). Unrelated cord blood accounted for 28.9% of stem cells source, and it showed a rising trend over the years. The number of children receiving allogeneic HSCT increased from average 79 cases/yr in early period 2000-2005 to 155 cases/yr in the recent period 2006 to 2011.

Conclusion: The study gives us the opportunity to understand the different pattern of HSCT in Asia. Nonmalignant conditions surpass malignant conditions for allogeneic HSCT. Some diseases like SAA and haemoglobinopathy are more prevalent in this part of Asia. The number of unrelated allogeneic HSCT is almost equal to related HSCT. Unrelated cord blood is a growing source of stem cells for children in this part of Asia.
A RETROSPECTIVE REVIEW OF THE USE OF INTRAVESICULAR CIDOFOVIR FOR BK HEMORRHAGIC CYSTITIS IN PEDIATRIC PATIENTS AFTER HSCT

Jennifer Foster, Ngoc-Yen Nguyen, Meng-Fen Wu, Caridad Martinez. Baylor College of Medicine, Houston, Texas, United States of America

Background: BK virus hemorrhagic cystitis (BKVC) is a common complication of hematopoietic stem cell transplantation (HSCT), resulting in significant morbidity requiring prolonged inpatient management. Current treatment strategy is symptomatic support, with limited medical treatment options. Response to intravenous cidofovir is varied and has a risk of serious side effects. Intravesicular cidofovir is a promising therapy, as it has not been associated with systemic side effects. The scant literature available report experience in adults, with most of the patients experiencing symptomatic improvement with variable reduction in BK viruria. We now report the first series of pediatric patients with BKVC after HSCT treated with intravesicular cidofovir.

Objectives: The objectives of this study are to determine the safety and efficacy of intravesicular cidofovir administration in pediatric patients with BKVC after HSCT.

Design/Method: In this retrospective chart review we abstracted from electronic medical records baseline and post treatment data on pediatric patients treated for BKVC with intravesicular cidofovir (5mg/kg intravesicular for 1 hr) from 2008 to present.

Results: Data was available and reviewed on 5 patients. All patients were treated with systemic antivirals prior to intravesicular cidofovir without resolution of symptoms. BK hemorrhagic cystitis was diagnosed at a median interval of 25 days from HSCT (range, 18-604 days) and treated with a median of 6 doses (range, 2-13). There was no significant decrease in urine or plasma BK pcr (2.32x10^9±4.30x10^9 vs 3.52x10^8±2.87x10^8 and 6544.75±11905.58 vs 21400±41733.84, P=0.66, respectively). Four patients had pain score data available. Three of the 4 patients had decrease in pain on days 3 and 7 after intravesicular cidofovir was given. The median pain scores on days 0, 3, and 7 are as follows: 8.5 (range, 2-10), 4.5 (range, 2-8) and 1 (range, 0-7). There was no significant decrease in pain score on days 3 (P=0.38) and 7 (P=0.25). The average morphine(mg) used during this period was 40.18±37.03 vs 30.09±32.45 (P=0.19). No patients receiving intravesicular cidofovir experienced side effects associated with systemic cidofovir.

Conclusion: Intravesicular cidofovir appears to be safe and effective for symptomatic treatment of BKVC in pediatric patients after HSCT but further studies are needed to confirm our findings.
Predicting Transfusion Requirements in Pediatric Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Ahmed Qawasmi, Bulent Ozgonenel, Sureyya Savasan, Yaddanapudi Ravindranath. Children's Hospital of Michigan, Wayne State University, Detroit, Michigan, United States of America

Background: Patients who receive hematopoietic stem cell transplantation (HSCT) go through a certain recovery period until engraftment occurs. During this period, the patient needs transfusion support for anemia and/or thrombocytopenia. Providing blood components to such patients is a daunting task for the blood bank, and predicting such requirements is crucial for planning ahead.

Objectives: To identify the requirements for packed red blood cell (RBC) and platelet transfusions in the first 12 weeks after allogeneic HSCT.

Design/Method: We reviewed the transfusion records of patients undergoing allogeneic HSCT treated at Children's Hospital of Michigan over a 5-year period. We collected information on RBC and platelet transfusions during the first 12 weeks after HSCT.

Results: There were 38 allogeneic transplantations in 36 patients during the study period, after exclusion of an outlier. Median age at transplantation was 6 years old (range 0-19 years). The patients required (mean ± standard deviation) 6.6 ± 6.4 RBC transfusions and 14.9 ± 13.4 platelet transfusions during the first 12 weeks after HSCT. Both RBC and platelet transfusions peaked during the second week of the transplantation (1.4 ± 1.1 transfusions for RBCs and 3.5 ± 2.2 for platelets, p<0.001 for both). The figure shows total RBC and platelet transfusions per post-transplant week.

Conclusion: Blood banks should anticipate high RBC and platelet transfusion requirements during the first weeks after HSCT. Despite individual variability between patients, the transfusion requirements after an allogeneic HSCT were consistently noted to be highest during the second post-transplant week.
Pediatric Blood and Marrow Transplant Consortium Posters
Poster # 5000

HAPLOIDENTICAL BMT USING FULLY MYELOABLATIVE CONDITIONING, T CELL REPLETE GRAFTS, AND POST-TRANSPLANT CYCLOPHOSPHAMIDE (PT/CY) HAS LIMITED TOXICITY AND PROMISING EFFICACY IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH HIGH RISK HEMATOLOGIC MALIGNANCIES
Heather Symons, Dean Lee, Allen Chen, Lawrence Cooper, Rick Jones, Richard Champlin, Ephraim Fuchs, Stefan Ciurea. The Johns Hopkins University, Baltimore, Maryland, United States of America

Background: Promising results have been demonstrated for adults with hematologic malignancies using T cell-replete haploidentical bone marrow and post-transplantation cyclophosphamide (PT/Cy).

Objectives: Here, we report the results using such an approach specifically for pediatric patients treated after October, 2009 on two institutional [Johns Hopkins Hospital (JHH) and MD Anderson Cancer Center (MDACC)] phase II clinical trials for subjects with high risk hematologic malignancies (n=47).

Design/Method: Conditioning at JHH consisted of IV Busulfan (pharmacokinetically adjusted) and Cy (50 mg/kg/day) except for patients with ALL or lymphoblastic lymphoma who received Cy (50 mg/kg/day) and total body irradiation (300cGy /day) days –3 to 0. Conditioning at MDACC consisted of melphalan 140 mg/m2, fludarabine 40 mg/m2/day and thiotepa 10 mg/kg. Postgrafting immunosuppression consisted of Cy (50 mg/kg/day) on days 3 and 4, followed by mycophenolate mofetil for 30-100 days and tacrolimus for 4-6 months.

Results: Donor engraftment at Day 60 occurred in 42/43 evaluable patients (98%). Median time to engraftment of neutrophils >500/μL was 25 days (range 17-39, N=43) and platelets >20,000/μL was 32 days (range 18-122, N=40). Cumulative incidences of acute GVHD grades II-IV and grades III-IV at day 100 were 23% and 7%, respectively, and chronic GVHD at 6 months was 13% and at 1 year was 27%, with 4/9 classified as moderate-severe per NIH consensus criteria. The cumulative incidence of NRM at 6 months was 5%. With median follow-up of surviving patients of 403 days (range 113–1383), actuarial overall survival (OS) is 84% at one year and 77% at 2 years and progression-free survival is 67% at one year and 55% at two years for patients in complete remission or with chemo-sensitive lymphoma. The cumulative incidence of relapse at 1 year for patients with leukemia in complete remission or chemo-sensitive lymphoma is 28%.

Conclusion: For pediatric and young adults with high-risk hematologic malignancies, myeloablative HLA-haploidentical T-cell replete BMT and PT/Cy is associated with excellent rates of engraftment, GVHD, OS, and NRM, similar to myeloablative matched transplants. It is therefore a feasible option for high risk pediatric and young adult patients who lack timely access to an HLA-matched donor.
ACUTE GUT GRAFT VERSUS HOST DISEASE (AGGVHD) IS ASSOCIATED WITH SIGNIFICANTLY HIGHER INCIDENCE OF ENTERIC BACTERIA BLOOD STREAM INFECTION (EB-BSI) IN PEDIATRIC ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT (ALLOHCT) RECIPIENTS

Kerice Pinkney, Anya Levinson, Zhezhen Jin, Prakash Satwani. Columbia University, New York, New York, United States of America

Background: Septicemia continues to be the leading cause of mortality and morbidity following AlloHCT. Recent murine studies have not only demonstrated that aGGVHD is associated with significantly higher incidence of EB-BSI, but also with an increase in mortality. The impact of aGGVHD on incidence of EB-BSI in humans is not well described.

Objective: Our study aimed to investigate the relationship between aGGVHD and the development of EB-BSI in pediatric AlloHCT recipients.

Design/Methods: We performed a retrospective review of electronic data collected between day 0 and +180 on pediatric AlloHCT recipients from 2000-2012. We hypothesized that a temporal relationship should exist between onset of aGGVHD and EB-BSI and calculated the infection density before and after the onset of aGGVHD, acute liver and skin GVHD (aLS-GVHD) and in patients without aGVHD.

Results: Two hundred sixty four children underwent AlloHCT for malignant (n=162, 61.4%) and non-malignant (n=102, 38.6%) disorders. Median age was 9 years, M/F ratio was 64/36%, and donor sources included matched family donors (n=107, 40%) and matched unrelated donors (n=157, 60%). Patients with EB-BSI (n=122, 46.2%) and without EB-BSI (n=142, 53.8%) were comparable (age, p=0.18; sex, p=0.8; disease type, p=0.13; donors, p=0.26; conditioning regimen, p=0.19; use of alemtuzumab, p=0.8 and ATG, p=0.4). The incidence of aGVHD was 44% (n=115): aGGVHD (28%) and aLS-GVHD (16%). In the aGGVHD cohort, the EB-BSI infection density was 0.952 infections/person-year prior to the onset of aGGVHD vs. 2.258 infections/person-year after onset of aGGVHD (p-value=0.022). The EB-BSI infection density in patients after onset of aGGVHD was 2.258 vs. 1.557 in non-aGVHD patients (p-value=0.035).

Conclusion: Our results indicate that aGGVHD predisposes patients to EB-BSI. To our knowledge, this is the first study to demonstrate that aGGVHD significantly increases the risk for EB-BSI in pediatric AlloHCT recipients. Prophylactic strategies such as probiotics and/or antibiotics that may potentially prevent EB-BSI in patients after onset of aGGVHD should be studied prospectively. We are further investigating the morbidity and mortality associated with EB-BSI in patients with aGGVHD.
HAPLO TRANSPLANT FOR FANCONI ANEMIA - MULTI-CENTER STUDY
Monica S. Thakar, Carmem Bonfim, Mark Walters, Ricardo Pasquini, Rainer Storb, Brenda M. Sandmaier, Ann Woolfrey, Hans-Peter Kiem, Medical College of Wisconsin, Milwaukee, Wisconsin, United States of America

Background: Given our prior experience that Fanconi Anemia (FA) patients can tolerate CY 60 mg/kg in a transplant setting with minimal toxicity1, we adapted the Luznik and O’Donnell simple approach for in vivo T-cell depletion using post-transplant cyclophosphamide (CY)2.

Objective: To develop a strategy to transplant patients with Fanconi Anemia having marrow failure using human leukocyte antigen (HLA)-haploidentical donors.

Design/Method: Prospective, Phase II Multi-Center Clinical Trial

Results: Between April 2008-Sept 2012, six patients with FA having marrow failure and poor donor searches underwent HLA-haploidentical hematopoietic cell transplantation (HCT). Patients fell in two categories based on their referral to transplant – “delayed” (n=2) and “early” (n=4), with the former presenting with significant iron overload from heavy transfusion dependence (n=2) or severe virilization due to androgen use (n=1). The latter were in excellent health with minimal transfusion burden. Patients were transplanted at a median of 1.9 (range, 0.6 -7.3) years after diagnosis at a median age of 11.1 (range, 6.9-13.9) years. Conditioning consisted of fludarabine (150 mg/m2) and 2 Gy total body irradiation. CY (10 mg/kg) was initially added to the conditioning regimen in the first two subjects enrolled but later removed to decrease mucositis. Marrow was infused on day 0, followed by CY (25 mg/kg/day, days +3, +4), cyclosporine, and mycophenolate mofetil (MMF) for post-grafting immunosuppression (oral MMF was only available in “delayed” group). All patients engrafted. One patient with iron overload (ferritin >14,000) died at day +37 due to disseminated toxoplasmosis/CMV. Of the remaining five patients, three developed acute GVHD (grade I, n=2; IV, n=1) of which the latter progressed to chronic extensive GVHD. With a median follow-up of 1 year (range, 37 days – 5 years), five patients are alive with 100% donor chimerism and are transfusion independent. The patient with chronic extensive GVHD is still being treated with multi-agent immunosuppression.

Conclusion: Our results confirm that post-HCT CY can be used in patients with FA to facilitate engraftment across HLA-disparate barriers. Our findings emphasize that early treatment prior to developing co-morbidities, and the availability of IV immunosuppressive drugs, is critical for the success of this alternative donor approach.

1 Bonfim et al, BBMT, 2007
2 Luznik et al, BBMT, 2008
CD34-SELECTED, T CELL-DEPLETED ALTERNATIVE DONOR STEM CELL TRANSPLANTATION FOR PEDIATRIC NON-MALIGNANT DISEASES

Michael J. Eckrich, Stacy Epstein, Carrie Barnhart, Javier Oesterheld, Darci Grochowski, Tracy Fukes, Mark Cannon, Maria Lacaria, Alexis Teplick, Andrew L. Gilman, Levine Children’s Hospital, Charlotte, North Carolina, United States of America

**Background:** Hematopoietic stem cell transplant is indicated for many pediatric non-malignant disorders, but may be complicated by limited donor availability, graft rejection, transplant-related mortality (TRM), and graft-versus-host disease (GVHD). Many pediatric patients have neither a matched sibling nor a matched unrelated donor. Successful use of alternative donors including mismatched family members could provide a donor for nearly all patients.

**Objective:** We examined the ability of CD34-positive selection using the CliniMACS® to prevent severe acute GVHD (aGVHD) in recipients of reduced-intensity alternative donor peripheral blood stem cell (PBSC) transplant.

**Design/Methods:** Between 2009-2013, seventeen patients underwent alternative donor CD34-selected, Tcell-depleted PBSC transplantation on an IRB-approved protocol. Ten patients had mismatched-related and seven had unrelated donors. Diseases included sickle cell anemia (6), HLH (3), SAA (3), immunodeficiency (2) and bone marrow failure syndromes (3). Conditioning regimen: melphalan, thiotepa, fludarabine, and rabbit-ATG with no post-transplant immunosuppression. Seven patients received rituximab during conditioning. Seven received planned donor lymphocyte infusion (DLI) between days 30-42 with methotrexate prophylaxis on a companion study. End points were engraftment, TRM, GVHD and survival.

**Results:** Median age at transplantation was 10 years (range 0.3-18). Median PBSC dose was 21x10^6 CD34/kg (range 11-25); all received 500 at a median of 14 days (range 9-16) and platelets at a median of 18 days (range 14-22). One had primary graft failure but engrafted following CD34-selected transplant from another parent, one with late graft failure was re-transplanted from the original donor, and one had second transplant for pancytopenia. The incidence of primary graft failure was 6%. Grade II-IV aGVHD occurred only after therapeutic DLI; one stage 3 skin, and two grade IV GI. One patient developed chronic GVHD. Overall survival at day 100 was 94%, 2-year was 81% with median follow-up of 15 months (range 0.5-52). TRM occurred in three patients due to GVHD/infection in two and infection in one. Other complications included post-transplant lymphoproliferative disorder, viral reactivation, and bacterial infections. None receiving full-dose rituximab developed PTLD.

**Conclusion:** A reduced-intensity conditioning regimen followed by CD34-selected, Tcell-depleted alternative donor transplantation provides reliable engraftment and a low incidence of GVHD for pediatric patients with non-malignant diseases.
Background: X-linked lymphoproliferative disease (XLP) is a rare inherited immunodeficiency characterized by hypogammaglobulinemia, frequent infections, susceptibility to Epstein-Barr virus (EBV) and a predisposition for lymphoma. The majority of cases are caused by mutation in the SH2D1A gene which codes for the signaling lymphocyte activating molecule (SLAM)-associated protein (SAP), while a smaller subset of patients carries mutations in XIAP, which codes for the X-linked inhibitor of apoptosis protein. Patients may remain asymptomatic until primary infection with EBV, at which time they may develop fulminant infectious mononucleosis, secondary hemophagocytic lymphohistiocytosis or B-cell lymphomas. Treatment consists of immunoglobulin replacement therapy, aggressive treatment of EBV infection with rituximab, and appropriate therapy of HLH or lymphoma. Hematopoietic stem cell transplantation (HSCT) is the only curative therapy, and without transplant, the majority of patients will die before the age of twenty. Although myeloablative conditioning regimens have been used in the treatment of XLP, they are associated with significant toxicities. More recently, non-myeloablative, or reduced intensity conditioning (RIC) regimens have been utilized with promising results, though the incidence of graft rejection and mixed donor chimerism is higher.

Objective: We present here four XLP patients who were successfully treated with a reduced intensity conditioning regimen.  

Results: Patients ranged in age from 9 months to 7 years. All patients had confirmed mutations in SH2D1A. 2 patients were treated after the development of Burkitt’s lymphoma, while 2 patients were transplanted prior to the development of complications of XLP. 3 of the patients received alemtuzumab, fludarabine, thiotepa and melphalan conditioning, while 1 received anti-thymocyte globulin, fludarabine and melphalan. The stem cell source was unrelated cord blood in 3 of the patients and unrelated bone marrow in 1 patient. All 4 patients tolerated transplant well with minimal complications and currently remain with 100% donor engraftment and no acute or chronic GVHD with a median follow-up of 28 months (range 9-45 months).

Conclusion: Our results suggest that reduced intensity conditioning is well tolerated and can produce successful and durable engraftment for patients with XLP undergoing HSCT.
A RANDOMIZED PHASE II STUDY COMPARING TWO DIFFERENT INTENSITY CONDITIONING REGIMENS PRIOR TO ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) IN CHILDREN WITH JUVENILE MYELOMONOCYTIC LEUKEMIA (JMML): A CHILDREN’S ONCOLOGY GROUP REPORT

Christopher C. Dvorak, Prakash Satwani, Stephan A. Grupp, Lu Chen, Mitchell A. Cairo, Donna A. Wall, Samir B. Kahwash, Betsy Hirsch, Parinda A. Mehta, Todd Cooper, Micah Skeens, Mignon Loh.

University of California, San Francisco, San Francisco, California, United States of America

Background: JMML is a rare disease of young children, and generally only curable with HCT, with event-free survival (EFS) rates of ~50% (1) Optimal conditioning regimen is unknown. We hypothesize that HCT accomplishes long-term remission in some patients with JMML due to the provision of alloreactive graft-versus-leukemia activity and that the conditioning regimen’s sole role is to facilitate donor cell engraftment. More intensive regimens may be detrimental due to increased risk for transplant-related mortality (TRM).

Design/Methods: The primary aim of the study is to compare the Day 100 TRM incidence and 18-month EFS of the reduced-toxicity, but myeloablative, preparative regimen busulfan-fludarabine to the more intensive busulfan-cyclophosphamide-melphalan. This randomized phase II design will determine the preferred regimen for future trials. Eligibility is based on central review of specimens utilizing the revised diagnostic criteria (2) including detection of mutations in RAS pathway genes (PTPN11, NRAS, KRAS, CBL, NF1). When applicable, mutations will measure minimal residual disease burden before and after HCT at defined time-points. Once a donor is identified, patients are randomized, with anti-thymocyte globulin added for patients with unrelated or umbilical cord blood (UCB) donors. Patients are stratified by PTPN11 status and donor type. In addition to conventional transplant endpoints, the study will assess whether genetic and biochemical alterations can be used to improve risk-stratification and identify novel targets. Stopping rules are in place for excessive graft failure, relapse, or TRM.

Results: The study activated June 2013. To date, 6 patients have been enrolled; 5 have proceeded to HCT. The median age at enrollment is 1.94 years (range 0.85-12.4). All patients have had diagnostic mutations or cytogenetic abnormalities identified: PTPN11 (n = 2), KRAS (n = 3), and Monosomy 7 (n = 1). HCT donors include: matched sibling bone marrow (n = 1), unrelated bone marrow (n = 3), UCB (n = 1). Enrollment will continue until 108 patients have undergone randomized HCT.

Conclusions: The trial is in progress and open for enrollment. Clinical Trial Information: NCT01824693.

Supported by CTEP-NCI, with a BIQSFP grant, and support of JMML Foundation.

References:
WITHDRAWAL OF IMMUNESUPPRESSION SUCCESSFULLY INDUCES REMISSION IN POST BMT RELAPSE OF FANCONI ANEMIA WITH MYELODYSPLASTIC SYNDROME

Arunkumar Modi, Aron Flagg, Rabi Hanna. Cleveland Clinic Children’s, Cleveland, Ohio, United States

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for patients with Fanconi anemia (FA) with ~50% long term survival. Cytogenetic abnormalities in FA can lead to development of myelodysplastic syndrome (MDS) or leukemia, and early treatment is essential for better outcome.

Objective: We describe an 11-year-old male with pancytopenia, bone marrow hyper-cellularity with trilineage dysplasia and 3.5% myeloid blasts with Auer rods. He was classified as having MDS, refractory anemia with excess blasts-2 (RAEB2) per WHO2008 classification. He had persistent disease after a reduced intensity allogeneic 9/10 HLA-matched BMT from his brother. He underwent a second transplant after recovery; reduced intensity allogeneic 9/10 HLA-matched (A-antigen mismatch) from his mother, but continued to have persistent disease. At our institution, he was evaluated for worsening MDS, increased bone marrow blasts, and extramedullary hematopoiesis. Genetic evaluation revealed FANC-complete type C with genetic mutation [165 (+1) G>T] with cytogenetic abnormalities of 48,XY,+i(1)(q10),+19,add(19)(p13.3)x2. He was treated with mini-FLAG (fludarabine, cytarabine, G-CSF) decreasing blasts from 19% to 4%. He then received a reduced intensity conditioning regimen (fludarabine, TBI) followed by peripheral blood HSCT from his mother, using cyclosporine and mycophenolate mofetil for graft versus host disease (GVHD) prophylaxis. He had neutrophil engraftment on day +10 and platelet engraftment on day +33, with 100% donor cells. On day +87 bone marrow showed abnormal cytogenetic with reappearance of abnormal clone (48,XY,+1,i(1)(q10),+19,add(19)(p13.3)x2[1]/46,XX. We weaned his immune suppression causing severe acute GVHD (grade III liver and gut), but his repeat BMA showed no evidence of disease by morphology, flow cytometry and cytogenetics.

Method/Design: Clinical history and pertinent studies were obtained from medical records and literature review of similar cases was performed.

Results: Patient achieved and remained in remission after treatment of GVHD with steroids, sirolimus and infliximab. He is currently in remission at 21 months after his transplant and 18 months after relapse of MDS.

Conclusion: Relapse of abnormal cytogenetic abnormalities pose a challenging question after third HSCT in FA patients. We present a unique case of successful remission after withdrawal of immune suppression in a patient with post-HSCT cytogenetic relapse of FA and MDS.
HEMATOPOIETIC STEM CELL TRANSPLANT FOR FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) IN PEDIATRIC PATIENTS AT THE MEDICAL UNIVERSITY OF SOUTH CAROLINA
Hawazen Alsaedi, John Lazarchik, Jennifer Jaroscak. Medical University of South Carolina, Charleston, South Carolina, United States of America

**Background:** Hemophagocytic lymphohistiocytosis (HLH) is a rare disease that is fatal if untreated. Familial HLH usually presents in infancy. Patients present acutely ill with a febrile illness, and a high index of suspicion is required to make the diagnosis. Criteria to diagnose HLH include: genetic mutations consistent with HLH or 5/8 of the published criteria.

**Objective:** Review case series of pediatric patients transplanted for FHLH at our institution.

**Design/Method:** Chart review of FHLH diagnosed and treated with Bone Marrow Transplantation (BMT) from January 1999 to December 2013. We evaluated time to diagnosis, time to BMT, and BMT outcome measures for FHLH patients.

**Results:** Five patients were identified with familial HLH at the Medical University of South Carolina. All cases have an identified gene mutations. Median age of presentation is 11 weeks. All patients are minorities. Time from the diagnosis to transplant is 2 months. Four patients out of 5 are surviving (80%). All patients engrafted. Two patients are siblings from consanguineous parents, and both had severe GI complications (perforation and profound feeding intolerance). Another infant developed renal failure during his primary hospitalization and underwent successful renal transplant 10 months after BMT.

**Table 1. Summary of FHLH BMT patients.**

<table>
<thead>
<tr>
<th>Dx</th>
<th>Tx</th>
<th>onation regimen</th>
<th>cations</th>
<th>l</th>
</tr>
</thead>
<tbody>
<tr>
<td>h</td>
<td>h</td>
<td>P2</td>
<td>/ATG/Steroid</td>
<td>HD perforation</td>
</tr>
<tr>
<td>h</td>
<td>h</td>
<td>P2</td>
<td>/Etop</td>
<td>VHD placed</td>
</tr>
<tr>
<td>h</td>
<td>h</td>
<td>n1</td>
<td>/Etop/ATG</td>
<td>d Gut GVHD transplant</td>
</tr>
<tr>
<td>h</td>
<td>h</td>
<td>n1</td>
<td>th/Flu/Mel</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>h</td>
<td>P2</td>
<td>th/Flu/Mel</td>
<td>d Gut GVHD placed</td>
</tr>
</tbody>
</table>

**Conclusion:** Various conditioning regimens resulted in stable donor chimerism in survivors. These patients experienced unusual BMT complications and further investigation of GI complications seen in patients with STXBP2 gene mutation should be considered.
RESULTS OF A PROSPECTIVE MULTI-CENTER TRIAL OF REDUCED INTENSITY TRANSPLANTATION FOR PEDIATRIC SEVERE APLASTIC ANEMIA USING ALEMTUZUMAB FOR IMMUNE SUPPRESSION

Alexander Ngwube, Lisa Murray, Robert Hayashi, Brett Loechelt, Jignesh Dalal, Jennifer Jaroscak, Shalini Shenoy, Washington University in St. Louis and St. Louis Children’s Hospital, St Louis, Missouri, United States of America

**Background:** Stem cell transplantation (SCT) is curative for severe aplastic anemia (SAA) with disease free survival (DFS) of 70-90%. SCT is considered upfront from matched sibling donors (MSD) or if immunosuppression fails, from unrelated donors (URD). Transplant outcomes are influenced by graft rejection, GVHD, organ toxicity/infection, and treatment related mortality (TRM). We present results from a prospective multi-center trial of reduced intensity transplantation (RIT) for SAA. The rationale for this approach was avoidance of radiation and high dose chemotherapy.

**Methods:** Fourteen children (median age 11 years; range 4-17) underwent RIT following alemtuzumab (48 mg) IV (days -22 and -19), fludarabine (30 mg/m2/day) (days -8 to -4), and melphalan (140 mg/m2) (day -3) at 4 centers. GVHD prophylaxis was tacrolimus tapered after day 100, and methotrexate (7.5 mg/m2 on days 1, 3 and 6). URD recipients received prednisone (1 mg/kg/day) tapered after day +28. Invasive infections rendered patients ineligible. Infection prophylaxis consisted of ciprofloxacin and itraconazole until day +180. GCSF was administered from day +7 until neutrophil recovery.

**Results:** Recipients underwent MSD (n=7) or URD (7-8/8 match) (n=14) SCT from PBSC (1), cord (1) or marrow (12). The median nucleated cell dose was 3.43 x 10^8/kg (range 0.2 to 19.1). The median times to neutrophil and platelet engraftment was 14 (range 10-27) and 19.5 (range 11-60) days respectively. All patients had 100% donor chimerism with median follow up of 61 months (range 6-128). The 2-year Kaplan-Meier survival probability estimate was 86% (95%CI: 56-97). The incidence of grade II-IV and III-IV acute GVHD was 36% (95%CI: 16-61) and 21% (95%CI: 7.5-47.5) respectively. The cumulative incidence of limited and extensive chronic GVHD at 1 year was 21% and 21% respectively. At two years, all except 1 recipient were off immunosuppression. DFS was 100% in MSD transplants. TRM in 2 patients was due to due to complications of GVHD on day +173 and day +346 respectively.

**Conclusions:** Allogeneic HCT using this RIT approach is feasible, and effective for SAA transplants from related and unrelated donors.
OPTIMIZATION OF ECULIZUMAB THERAPY IN CHILDREN TREATED FOR HSCT-ASSOCIATED THROMBOTIC MICROANGIOPATHY
Sonata Jodele, Tsuyoshi Fukuda, Alexander Vinks, Kana Mizuno, Benjamin L. Laskin, Jens Goebel, Kasiani C. Myers, Jack Bleesing, Michael Grimley, Sharat Chandra, Christopher E. Dandoy, Stella M. Davies. Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, United States of America

Background: Hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA) is a challenging post-transplant complication with mortality >90% in severe cases and no effective therapy available. We recently observed that dysregulation of the complement system may be involved in the pathogenesis of HSCT-TMA suggesting that the complement inhibitor eculizumab could be a potential therapeutic option for this complication.

Objective: To examine eculizumab efficacy and required dosing in children with HSCT-TMA.

Methods: We treated twelve children with severe multi-visceral HSCT-TMA using eculizumab. Eculizumab dosing schedule was adjusted by measuring drug in serum to maintain therapeutic level of >99 µg/ml based on recommendations for children with aHUS. Total hemolytic complement activity (CH50) and membrane attack complex (sC5b-9) were measured during therapy as pharmacodynamic markers of complement blockage. Pharmacokinetic and pharmacodynamics analyses were performed to correlate eculizumab levels with clinical response and the degree of complement blockade as measured by CH50 and sC5b-9.

Results: To date, seven children achieved complete resolution of HSCT-TMA and recovery of organ function and were able to discontinue therapy after receiving a median of 9 doses of eculizumab (range 4-19), and remain clinically well with median follow up time of 1 year. One patient is still receiving eculizumab therapy. All responding patients required higher eculizumab doses and/or more frequent infusions to achieve therapeutic drug levels and complement blockage than currently recommended for children with aHUS. Four critically ill patients failed to reach therapeutic drug levels even after dose escalation and died. There were no side effects attributable to eculizumab. CH50 activity <5% directly correlated with therapeutic eculizumab level, but there was a 3-4 week time lag to normalization of sC5b-9 and clinical response.

Conclusion: Eculizumab is a promising therapeutic option for pediatric patients with severe HSCT-TMA, but HSCT patients appear to require higher medication dosing than recommended for other conditions and respond better when therapy is initiated early in the disease course. CH50 monitoring can aid in timely eculizumab dose adjustments, especially in highly catabolic patients, and sC5b-9 normalization reflects time to clinical response. Controlled studies of this approach in both children and adults after HSCT are warranted.
LONG TERM SURVIVAL CAN BE ACHIEVED WITH SECOND STEM CELL TRANSPLANTS IN CHILDREN WITH RELAPSED HEMATOLOGIC MALIGNANCIES

Allison Pratt, Courtney Spiegel, David Delgado, Jamie Renbarger, Jodi Skiles, Paul R. Haut, Kent A. Robertson, W. Scott Goebel, Riley Hospital for Children at IU Health, Indianapolis, Indiana, United States of America

Background: Children with hematologic malignancies, immune disorders, and genetic diseases can be cured with hematopoietic stem cell transplantation (HSCT). From 20% to 60% of HSCT fail due to relapse or graft rejection. Second HSCT for patients relapsing following initial HSCT remains controversial due to concern for high transplant-related mortality (TRM).

Objective: We report the outcomes of children who have undergone second HSCT for relapsed hematologic malignancies at a single institution.

Design/Method: A retrospective analysis of all patients with hematologic malignancy at Riley Hospital for Children at IU Health who have undergone a second HSCT from January 1997 to May 2011 was performed. Patients were excluded if second HSCT was due to graft failure. Age, disease, donor type, remission status, TRM and disease-related mortality were assessed.

Results: Thirteen patients received second HSCT following disease relapse. Median age at first transplant was 2 years (range 1-17), and 5 years (range 2-20) for second transplant. Three patients had ALL, six had AML, two had CML, and one had MDS. For the first transplant, six patients (46.2%) received bone marrow, seven (53.8%) received cord blood, and none received peripheral blood stem cells (PBSC). For the second transplant, seven (53.8%) received bone marrow, three (23.1%) received cord blood, and three (23.1%) received PBSC. Six patients had matched-related donors and seven had unrelated donors for the first transplant. Four patients had matched-related donors and nine had unrelated donors for the second transplant. 7/13 patients received cells from the same donor for both transplants. All patients received ablative preparative regimens for the first transplant, whereas two patients received nonmyeloablative conditioning for the second. 69% of patients were in remission at both the times of first and second transplant. 7/13 patients are still alive (range 2-16 years after second HSCT). The cause of death in all patients who died after second HSCT was disease relapse, with no patients dying from TRM.

Conclusion: We conclude second HSCT in children can be successfully and safely performed in patients who relapse following an initial HSCT. Our data suggest the major cause of mortality remains disease relapse, with less risk of TRM.
SAFE AND EFFECTIVE PROPHYLAXIS WITH INTRAVENOUS PENTAMIDINE IN THE PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT POPULATION

Emily R. Levy, Lisa Musick, Thomas Lang, Peggy S. Weintraub, Christopher C. Dvorak. University of California, San Francisco, San Francisco, California, United States of America

**Background:** Without prophylaxis, Pneumocystis Jiroveci pneumonia (PCP) develops in 5-15% of pediatric hematopoietic stem cell transplant (HCT) patients with mortality rates above 50%. Trimethoprim-sulfamethoxazole is standard PCP prophylaxis, however, intravenous (IV) pentamidine is frequently used to avoid bone marrow suppression. Monthly IV pentamidine has variable efficacy in HCT pediatric patients with PCP infection rates of 0-10%, and higher breakthrough in those <2 years old. To increase efficacy, UCSF administers prophylactic IV pentamidine every 2 weeks, as pharmacokinetic studies demonstrate a 10-14 day elimination half-life.

**Objective:** To quantify the efficacy and toxicities of bi-monthly IV pentamidine PCP prophylaxis in the pediatric HCT population.

**Methods:** We retrospectively reviewed records of all pediatric patients 12/1/2006 – 1/1/2012 who received IV pentamidine. We identified HCT patients and collected data regarding demographics, clinical course, rationale for pentamidine, laboratory values, and adverse events.

**Results:** Over 5 years, 267 pediatric patients underwent HCT, of which 85 (with a total of 112 HCTs) received IV pentamidine as PCP prophylaxis (95 individual courses; 482 total doses; 241 patient-months). Twenty-three (27%) patients were ≤2.0 years old at pentamidine initiation. No patients were diagnosed with PCP at any time during or after IV pentamidine; 3 patients underwent bronchoalveolar lavage with negative silver stain. The average course was 2.5 months (5 doses; st dev 6). The most common initiation reason was myelosuppression and the most common discontinuation reason was resolved myelosuppression. Four patients (4.7%; 0.8% doses) experienced a major side effect, all involving infusion-related hypotension (1 anaphylaxis, 1 with altered mental status). Five patients (5.8%, 1.0% doses) experienced a minor side effect prompting discontinuation (2 infusion reactions, 1 nausea, 1 rash, 1 anemia) and 2 patients (2.4%; 0.4% doses) developed pancreatic dysfunction prompting pentamidine discontinuation for possible contribution. No courses were discontinued based on only renal or liver laboratory values.

**Conclusion:** Bi-monthly IV pentamidine for PCP prophylaxis has comparable safety in the HCT pediatric population to previously described toxicities of monthly IV pentamidine. It should be considered as the 2nd line option to trimethoprim-sulfamethoxazole as it trended towards higher prophylactic efficacy than previous reports for monthly IV pentamidine, particularly in the very young.
ENGRAFTMENT SYNDROME (ES) IN CHILDREN UNDERGOING AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (ASCT) - INCIDENCE, CLINICAL CHARACTERISTICS AND EVALUATION OF STEROID USE: SINGLE INSTITUTION EXPERIENCE

Chenue Abongwa, Rolla Abu-Arja, Shawki Qasim, Ali Suliman, Stephen Rumelhart, Ghada Abusin.
University of Iowa- Carver College of Medicine, Iowa City, Iowa, United States of America

Background: ES remains a significant complication following ASCT and important cause of morbidity and mortality in children. It is characterized by non-infectious fever, skin rash and capillary leak in the peri-engraftment period. There is lack of uniform diagnostic criteria and guidelines for steroid therapy.

Objectives: To describe ES in children undergoing ASCT for malignant diseases and evaluate the use of steroids in preventing complications.

Design/Method: Data were collected retrospectively from transplants done in the University of Iowa Children's Hospital between 2001 and 2012. ES was defined using as the presence of fever and diarrhea or skin rash or pulmonary infiltrates 24 hours prior to or any time after the first appearance of neutrophils (>500/mm³) in the peripheral blood (Miliano criteria).

Results: Analysis was done on 89 ASCT from 65 patients, 48 patients underwent single ASCT, 8 patients double and 9 triple. One patient in the double and another one in the triple transplant groups did not complete the full intended tandem sequence. Underlying diagnoses included neuroblastoma (45%), brain tumors (23%), bone tumors (14%), others (12%), thirty-seven patients (57%) were in complete remission prior to ASCT. ES was diagnosed in 16/89 (18%), fourteen of which were single ASCT. Melphalan-based regimen was found to be significant risk factor to the development of ES (p<0.05). Steroids were used in 30/89 (33%) of transplants (86% of single). There was no significant difference in hyperglycemia, hypertension and/or infections between the steroid and non-steroid groups. Clinical improvement was observed within 24 hours in most patients. Forty two patients were alive at the end of the study period. The overall survival (OS) at 5 years was significantly higher in patients with complete response (80%) when compared to patients with partial response (30%) (p<0.05). There was a trend towards worse long-term OS in the group with ES (50%) when compared to that without ES (64.7%).

Conclusion: ES is a common complication in children following autologous stem cell transplantation and Miliano criteria can be used to guide effective short course steroid burst.
HEALTH RELATED QUALITY OF LIFE FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR SICKLE CELL DISEASE

Monica Bhatia, Elissa Kolva, Laura Cimini, Zhezhen Jin, Prakash Satwani, Diane George, James Garvin, Eduvigis Cruz-Arrieta, Stephen Sands. Columbia University, New York, New York, United States of America

Background: Sickle Cell Disease (SCD) is a hereditary hemoglobinopathy that affects over 100,000 people in the United States. Patients with SCD are known to experience suboptimal Health-Related Quality of Life (HRQoL). In addition to the physical manifestations of SCD, patients experience psychological stress secondary to the chronicity of the disease and its complications. While medical therapy of SCD has improved, allogeneic hematopoietic cell transplant (alloHCT) remains the only curative therapy.

Objectives: To measure HRQoL pre- and post-alloHCT by assessing physical, psychological, social and school functioning in patients with SCD who have undergone reduced toxicity conditioning (Busulfan/Fludarabine/Alemtuzumab) followed by alloHCT.

Methods: Patients less than 21 years of age undergoing alloHCT (matched siblings and unrelated donors) for SCD and their primary caregiver were enrolled using either the English or Spanish version of the PedsQoL 4.0. Data were collected at six time points: pre-alloHCT and days 100 and 180, as well as 1, 2, 3 and 4-years post-alloHCT. The change in HRQoL from baseline was assessed with unadjusted and adjusted mixed effects models in which subjects were treated as random effects, and variance component structure was used.

Results: Twenty-one patients and primary caregivers were enrolled and reported a mean overall HRQoL of 64.59 (SD=15.19) and 69.89 (SD=16.16) at baseline, respectively. Consistent improvements were seen in patients and primary caregivers after two years, which continued at 4-years post-alloHCT. In the analysis with unadjusted mixed effects models, the estimated improvements were 16.41 (SE=5.76, p=0.007) at two-years and 26.32 (SE=7.22, p=0.002) at four-years for patient-reported overall HRQoL, and 11.74 (SE=5.28, p=0.03) at two-years and 20.73 (SE=8.0, p=0.012) at four-years for primary caregiver-reported overall HRQoL respectively. Similar results were found across physical, social, school, and psychological HRQoL domains. In the analysis with mixed effects models after adjustment of demographic and medical variables, the significance of improvements remained.

Conclusions: In addition to the alleviation of clinical manifestations of SCD, these patients demonstrated significant improvement in all aspects of HRQoL post-alloHCT. These data represent the longest follow-up period of HRQoL within this population and should be integrated into the decision-making process when contemplating alloHCT in patients with SCD.
ACUTE KIDNEY INJURY AFTER HSCT - ARE YOUR PATIENTS AT RISK?
Petr Cigner, Rolla Abu-Arja, Rupesh Raina, Beth Vogt, Robert Cunningham. University Hospitals Case Western Medical Center, Cleveland, Ohio, United States

Background: AKI is a common comorbidity in the pediatric population following HSCT. The incidence of AKI in children after HSCT is 25-50%, whereas that of the other hospitalized children in the US is 0.39%.[1]

Objective: To review of the incidence, risk factors, morbidity and mortality of AKI in children and AYA, undergoing HSCT at our center.

Design / Methods: Retrospective data collection was performed on all pediatric and AYA patients who underwent HSCT at our center. From 9/11 to 9/13 39 allogeneic and autologus HSCT were performed in 33 patients. AKI was defined and stratified using the modified pediatric RIFLE criteria (pRIFLE), Creatinine clearance was calculated using the updated (IDMA radiolabeled) Schwartz formula for children: eCCl = (0.413 x ht in cm) / SCr.[2]

Results: Twenty out of 33 (61%) patients developed AKI (14-60 days after HSCT) per (pRIFLE). Nine patients (26.5%) developed Severe (Grade 3) AKI. Six out of 9 patients developed Sinusoidal Obstructive Syndrome (SOS) and were managed with Continuous Veno-Venous Hemofiltration (CVVH). Indications for CVVH use included diuretic-resistant FO >5% and oligo/anuric AKI. Four of 6 patients (66%) had full resolution of AKI and SOS symptoms (mean recovery time 5 days). Two patients (34%) died - one due to SOS, one due to systemic CMV infection. CVVH was initiated within 4-16 hrs after diagnosis of FO or oligoanuric AKI. Average time on CVVH machine was 9 days. Fluid overload (>20%) and multisystem organ failure were the risk factors associated with mortality in patients with grade III AKI.

Conclusion: Early initiation of CVVH may be a useful modality to prevent progressive fluid overload and maintain electrolyte and acid base balance in patients with FO/ severe AKI and SOS.

POST-TRANSPLANT CYCLOPHOSPHAMIDE DOES NOT CHANGE INCIDENCE OR SEVERITY OF HC IN PEDIATRIC PATIENTS
Diana Steppan, Jeffrey Huo, Heather Symons. The Johns Hopkins University, Baltimore, Maryland, United States of America

Background: Hemorrhagic cystitis with or without BK virus following HSCT is widely recognized with reports of 2-40%, but its incidence and severity after high dose post-transplantation cyclophosphamide (PT/Cy) has not been described.

Objectives: To better characterize the incidence and severity of HC after BMT with PT/Cy, we retrospectively analyzed data from 94 (70 adult and 24 pediatric and young adults ≤25y) HSCT recipients treated on an institutional IRB approved myeloablative haploBMT protocol between 2008 and 2013.

Design/Method: All patients had high risk hematologic malignancies and received myeloablative preparative regimens consisting of busulfan/Cy or Cy/TBI. T-cell replete haploidentical bone marrow with PT/Cy on Days +3 and +4 after transplant (50mg/kg/dose/day). Out of the 24 ≤25yo, median age was 13.5y (2y-25y). Testing for BK viruria, viremia, and adenoviruria was performed at the onset of urinary symptoms and/or hematuria in the majority of patients. Serum creatinine, therapeutic interventions for HC, and transplant outcomes were also collected.

Results: Overall, we identified 21 patients (22%) with documented HC. 9/24 (37.5%) pediatric and young adult patients developed HC (Grade 1=1, Grade 2=3, Grade 3=2, Grade 4=3). General transplant outcomes for those ≤25y on this trial include a cumulative incidence of NRM of 8% at 1 year, aGVHD 4% at 100 day, cGVHD 4% at 6 months and 25% at 1 year 25%. All pediatric and young adult patients with HC tested positive for BK viruria via RT-PCR, but only 1 patient developed BK viremia (peak copy number 691). Median time to development of HC was 68d (5-302d). 3/9 patients developed BK+ HC prior to engraftment (<7days post transplant), with symptoms persisting >1 month. Patients received a variety of therapies depending on severity including IVF, continuous bladder irrigation, IV cidofovir, bladder cauterization, and hyperbaric O2 therapy. There was no relationship between aGVHD and HC and 1 patient receiving systemic therapy for cGVHD developed HC. There were no deaths related to HC.

Conclusion: The incidence and severity of HC in patients receiving PT/Cy is comparable to that previously described literature. Prospective data is needed to confirm this and determine screening/intervention strategies to decrease HC associated morbidity.
TREATMENT OF HEPATIC SINUSOIDAL OBSTRUCTIVE SYNDROME IN CHILDREN FOLLOWING HEMATOPOIETIC CELL TRANSPLANTATION

Seema Rao, Jens C Eickhoff, Christian M Capitini, Kenneth B DeSantes. University of Wisconsin at Madison, Madison, Wisconsin, United States of America

Background: Hepatic sinusoidal obstructive syndrome (SOS) remains a serious complication of hematopoietic cell transplantation (HCT). It usually presents within the first 21 days after HCT. Current management consists mostly of supportive care, with no agents to date approved for the treatment.

Objective: To assess the outcome of SOS after no therapy, Antithrombin III (AT III) therapy alone, Defibrotide (DF) alone or combined DF and ATIII therapy following hematopoietic stem cell transplantation in our institution.

Method: We conducted a retrospective chart study of 103 pediatric patients who had undergone HCT between August 2003 to June 2013 in our institution. 13 out of 103 children who developed SOS (based on either Seattle or Baltimore criteria) had a mean age of 6 yrs, mean peak direct bilirubin of 3.5 mg/dl, and mean weight gain of 10 %. 7 out of 13 patients received ATIII therapy alone, 1 received DF therapy alone, 2 of them received both ATIII and DF therapy, 1 patient received ATIII followed by DF and 2 of them received no therapy for SOS. All 13 children had received prophylaxis (either ursodiol or heparin drip or both) against SOS.

Results: Of the 7 patients who received ATIII therapy alone, 6 of them had complete resolution of SOS. The patients who received DF therapy alone, combination therapy with ATIII and DF as well as no therapy had progression of SOS leading to multi-organ failure and eventually died. One patient who received ATIII initially followed by DF had complete resolution of SOS once DF therapy was initiated. There was a significant difference in the survival rate between subjects who received ATIII treatment and subjects who received DF (alone or in combination with ATIII) (86% vs. 0%, p=0.0152). There were no records of treatment related adverse events.

Conclusion: ATIII was safe and successfully prevented the progression of hepatic SOS following HCT in the majority of children treated at our center. Larger prospective multi-center trials are needed to establish whether ATIII replacement therapy should be used as a front line treatment for SOS.
MOBILIZED PERIPHERAL BLOOD STEM CELLS COMPARED WITH BONE MARROW AS THE STEM CELL SOURCE FOR TRANSPLANTATION IN PEDIATRIC PATIENTS

Juan Carlos Jaime. Institute of Hematology and Immunology, Havana, Cuba

**Background:** Hematopoietic stem cell transplantation (HSCT), is the infusion of these cells to a recipient who has previously been prepared to receive the graft. There are different sources of hematopoietic progenitors such as bone marrow (BM), peripheral blood (PB) and umbilical cord. In several studies it has been shown that the PB offers advantages over the BM, as it produces a more rapid hematopoietic recovery, which significantly reduces morbidity and mortality of transplantation with no significant adverse effects on donor which can be both adults and children.

**Objectives:** To determine the efficacy of PB transplants and compare the results with those obtained when using BM.

**Material and Methods:**
All patients under 18 years old who received HSCT at the Institute of Hematology and Immunology from June 1986 to April 2008 were included in the work. Two groups were formed: one with the BM transplant and another with PB and various variables were compared them.

**Results:** The BM was the source used in 23 cases (62%). Thirteen patients (56.5 %) received autologous transplant and 10 (43.4%) allogeneic. The PB was the source of cells in 14 patients (37.8 %), seven (50 %) were allogeneic and 7 (50 %) were autologous.
Platelets reached values greater than 20 x 10⁹ / L , in the absence of platelet concentrate transfusion, more quickly when the PB was used and three patients had severe thrombocytopenia . Patients receiving PB required less packed red cells transfusions. The frequency and severity of acute GVHD was similar in both two groups. In the PB group chronic GVHD was more severe. Death occurred more often in the BM group.

**Conclusions:**
1. A higher number of mononuclear cells were obtained when PB was used
2. Hematologic recovery was faster in the PB group.
3. Transfusion requirements were lower in the PB group
4. Infectious complications were lower in patients receiving PB.
5. Acute GVHD was similar in the two groups, both in frequency and severity, while chronic GVHD was equal frequency but higher severity in patients receiving PB.
6. Early mortality was similar in both sources.
THE ROLE OF SCREENING SINUS CT IN PEDIATRIC HEMATOPOIETIC STEM CELL PATIENTS
Hema Dave, Avi Oppenheimer, Izlem Izbudak, Heather Symons. Children's National Medical Center, Washington, Distric of Columbia, United States of America

Background: Sinusitis is common in pediatric hematopoietic stem cell transplant patients (HSCT). Presence of radiographic abnormalities alone can predict the risk of developing sinusitis and guide treatment for neutropenic fever.

Objective: To evaluate the role of screening sinus CT scans pre-HSCT as a predictor of sinusitis post-HSCT and correlate CT findings with clinical sinusitis. We also sought to identify clinical risk factors related to HSCT as a predictor for sinusitis.

Method: Retrospective chart review of 100 patients who received a screening sinus CT prior to HSCT from 2006-2010. We evaluated pre- and post-transplant CT sinus findings using the Lund-MacKay system and “common-practice” radiology reporting based on air-fluid levels, frothy secretions, and sinus opacification. Seventy patients underwent CT scans post-HSCT.

Results: Average age of the patients at the time of transplant was 10.7 years (range 8 months to 22 years). Seventy received allogeneic transplants, 21 received autologous transplant and 9 patients received high dose cyclophosphamide. Clinical characteristics of patients are described in Table 1. Eight out of 56 patients with a normal screening CT developed post-transplant sinusitis, compared with 8 out of 35 patients with radiographic abnormalities and 2 out of 9 with clinical sinusitis, not statistically significant. Sensitivity of CT findings for the presence of clinical sinusitis ranged between 19% and 56%. Except for mucosal thickening (71% specificity), other findings had a specificity between 92 and 97%, highest in the presence of multiple abnormalities. A significant difference was found in Lund-MacKay score change from baseline, with a change ≥10 associated with 2.8 times higher likelihood of having clinical sinusitis (P < 0.001).

Conclusion: Screening CT can serve as a baseline for post-HSCT comparison to identify patients at risk of sinusitis.