PB=25, CBU=2). At the time of 2nd HSCT, 24 had RIC, 8 had MAC and 12 had no conditioning. 31 patients engrafted after the 2nd HSCT. The overall survival for patients who underwent a 2nd HSCT was 61% (27/44) with a median overall survival of 3.8 years (range: 0.2yrs to >10 yrs) and better survival for patients with non-malignant (21/30) versus malignant disease (6/14). There was no difference in survival between patients with primary versus secondary graft failures. Infection was the primary cause of death (9/17). For 13 patients who failed to engraft after 2nd HSCT, 3 patients died and 10 patients received a 3rd HSCT of whom 5 patients survive. Thus 61% of pediatric patients can achieve graft salvage from a second transplant, and half of the continuing graft failures can be rescued by a third HSCT.

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Optimizing Cyclosporine Dosing Regimen to Achieve Therapeutic Levels at the Time of Allogeneic Bone Marrow Transplantation: A Pediatric Quality Improvement Intervention

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Several studies have demonstrated that a therapeutic Cyclosporine (CsA) concentration within one week following graft infusion correlates with a reduced risk of grade III-IV acute graft versus host disease (aGVHD). Therefore, to begin a quality improvement (QI) project we performed a retrospective chart analysis to determine when, using our standard approach to initial CsA dosing, our allogeneic bone marrow transplant patients first achieved therapeutic CsA levels (Trough=150-250ng/ml). Fifty three allogeneic transplants were performed during the period assessed, of which 47 were eligible for evaluation. Patients were excluded from analysis due to alternate GVH prophylaxis or major drug interactions. In this historical cohort, CsA prophylaxis was initiated as follows: loading with Cyclosporine, 2mg/kg/dose IV Q 12 hrs for two days (day -2 and day-1) then decreasing to 1.5mg/kg/dose IV Q 12 hrs. Using this approach, 34% of patients had therapeutic levels within the first 3 days following transplant. Following this baseline analysis, we initiated a QI intervention aimed at achieving a therapeutic trough CsA level in at least 80% of patients by Day +3. To accomplish this, the following new CsA regimen was instituted. Patients 5 years or older received Cyclosporine at 2.5mg/kg/dose IV Q 12 hrs beginning on day -3, and patients less than 5 years of age received Cyclosporine at 2.5mg/kg/dose IV Q 8 beginning on day -3. If the trough level was subtherapeutic (below 100 NG/ML) on day 0, we gave an extra 2mg/kg/loading dose IV, then increased the basal dose by20%. If the level was between 100 and 149, we increased the basal dose by 20% without an additional loading dose. The impact of this intervention on the percentage of patients achieving therapeutic CsA levels between Day 0 and Day + 3 was then assessed. To date, we have performed 28 transplants under the new CsA regimen. Of these, 23 patients were evaluable. Five patients were excluded per the previous criteria. Using the new dosing guidelines, 87% of patients achieved therapeutic CsA levels in the Day 0 to Day +3 window. This represent a statiscally significant improvement over our previous dosing regimen in which 34% of patients achieved therapeutic CsA levels by Day +3 ($P < .0003$). No patients had supratherapeutic CsA levels, defined as greater than 400 ng/ml within the first 3 days post transplant. One patient did exhibit nephrotoxicity, defined as a persistent doubling of the serum creatinine by Day +10. This patient also had Adeno and BK viruria at Day 0 which confounds assessment of causation. Overall, the revised dosing regimen is both well tolerated and more effective in achieving the targeted CsA level in $\geq$ 80% of cases (95% confidence interval, 68-95%). Following completion of this project, we plan further analyses to determine whether this practice change has impacted rates of aGVHD in our patient population.

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The Risk Factors Associated with Liver Injury and the Impact of Liver Injury on Transplant Related Mortality in Pediatric Recipients of Allogeneic Hematopoietic Stem Cell Transplantation

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In adults, hepatic complications following allogeneic hematopoietic stem cell transplantation (AlloHSCT) are associated with significant morbidity and transplant related mortality (TRM). However, there is a paucity of parallel data on the incidence of, and risk factors for, liver injury (LI) and the impact of LI on TRM in pediatric AlloHSCT recipients.

Methods: We compared total bilirubin, direct bilirubin and alanine aminotransferase values pre-AlloHSCT and at 1month, day +100 and 12 months post-AlloHSCT in 248 patients following myeloablative conditioning (MAC) or reduced toxicity/reduced intensity conditioning (RTC/RIC). Liver injury was defined as $\geq$ Grade 2 toxicities according to the NCI CTCAE 3.0/4.0 or total bilirubin 1.95mg/dL (1.5 times above upper limit of normal). Univariate and multivariate logistic regression models were used to identify risk factors for the incidences of LI and TRM.

Results: 248 eligible patients received MAC (n=109) or RTC/RIC AlloHSCT (n=139). The incidence of LI at 1 month post-AlloSCT was significantly higher in MAC vs. RTC/RIC AlloHSCT based on total bilirubin levels (21.9% vs. 7.8%; $P = .0067$). There was no significant difference in LI pre-AlloHSCT, LI at day +100 and 12 months post-AlloHSCT between the two groups. The TRM among patients with LI at 1 month post-AlloHSCT was as 64.2% (CI_{95} 49%, 79.4%)

compared to 19% (CI_{95} 11.8, 26.1%) ($P < .0001$) for those who did not have LI at 1 month post- AlloHSCT. On multivariate analysis, only bloodstream bacterial infections ($P = .0059$) and invasive fungal infections ($P = .0020$) were significant risk factors for developing LI at 1 month. On multivariate analysis for risk factors for TRM, only LI at 1 month post-AlloHSCT ($P = .0001$), primary graft failure ($P = .0096$) and bloodstream bacterial infections ($P = .0328$) were significant. However, LI prior to AlloHSCT conditioning was not associated with higher TRM.

Conclusions: TRM among pediatric patients with LI at 1 month post-AlloHSCT is extremely high, with infections being the primary risk factor for LI.

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The Safety and Tolerability of the Novel Therakos Cellex Machine for Extracorporeal Photopheresis in the Treatment of GVHD in Children

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Extracorporeal photopheresis (ECP) is an established second line treatment option for graft versus host disease post hematopoietic progenitor cell transplant. At our center the Therakos Cellex has replaced the UVAR-XTS machine for ECP since 2009. We reviewed the records of 385 procedures using the Therakos Cellex. Nine patients underwent ECP for GVHD. The median age was 13.5 years (range 3.7 to 24) and weight was 49.2 kg (range 18.5-86.3). ECP was initiated at a median of 7.5 months (range 0.3-34.8) from the onset of GVHD. The mean duration per procedure was 106 minutes (range 60-205). Fifteen (3.9%) procedures were cancelled and 10 (2.6%) were delayed with central venous line (CVL) issues being the most frequent problem. Instillation of prophylactic tissue plasminogen activator (tPA) in the CVL lumens prior to a procedure was instituted 6 months before the end of study period, to reduce the incidence of CVL related occlusions and sluggish returns. With change in practice, fewer CVL related occlusions were observed (4.7% vs. 2.3%). There was one episode of CVL-associated thrombosis and one episode of delayed bleeding (mild and spontaneously resolved). There were four episodes of viral reactivation, 4 CVL-associated infections (1142 catheter days) and 1 episode of systemic inflammatory response syndrome. No patient experienced hypotension that required medical intervention. Although no additional adverse events were noted, there was considerable blood exposure in the smallest patients because of the need for machine blood prime. The Therakos Cellex appears to be safe and well-tolerated in 385 procedures performed in our institution. This is the first report regarding the safety and tolerability of this device for ECP in children and young adults.

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CNS Disease at Diagnosis May Predict Relapse of Hematologic Malignancies in Pediatric Patients After Allogeneic Hematopoietic Cell Transplantation (AlloHCT)

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Background: Relapse is the primary cause of treatment failure post alloHCT. We sought to identify risk factors that predict relapse of hematologic malignancies after allogeneic hematopoietic cell transplantation (alloHCT) to identify those at highest risk of relapse who may benefit from novel therapies.

Design: This was a single institution, retrospective cohort study of children with acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), mixed phenotypic acute leukemia (MPAL) and myelodysplastic syndrome (MDS) who had undergone alloHCT between 1/1/2003 and 12/31/2010. Relapse was defined as any evidence of increasing disease post-alloHCT, including minimal residual disease (MRD). Relapse-free survival (RFS) was estimated by the Kaplan-Meier method and the log-rank test used to assess univariate associations with various characteristics. A Cox proportional hazards model was used to identify factors jointly associated with RFS.

Results: Of 70 children who underwent a myeloablative HCT for MDS or acute leukemia in complete remission at the time of HCT, 24 (34%) relapsed at a median of 214 days (range 1 month- 57 months) post-HCT. Relapse rates by disease were 14/31 (45%) for ALL; 7/26 (27%) for AML; 3/9 (33%) for MPAL; 0/4 (0%) for MDS. Univariate analysis demonstrated that black race, central nervous system (CNS) disease at diagnosis (Figure 1), greater number of regimens given to induce remission and MRD pre-HCT were associated with higher relapse probability. In a Cox model, either two or more regimens needed to achieve remission or the presence of both pre-HCT MRD and CNS disease were approximately equally predictive of increased relapse risk. In patients with ALL, CNS disease was more highly associated with relapse risk than MRD. For those who were MRD negative, based on 19 total patients, the presence of CNS disease at diagnosis (n=2) was significantly associated with higher relapse risk ($P < .0001$).

Conclusion: We identified CNS involvement at diagnosis as a novel risk factor associated with relapse risk after alloHCT. This may be due to inherent biologic differences leading to higher risk disease, or as a sanctuary site, the CNS may be less amenable to an allogeneic effect. These patients may benefit from earlier or more intensive CNS-directed therapy to reduce relapse risk. Validation of these risk factors in a larger population and development of a prognostic score to identify those at highest risk of relapse in addition to a biology study to evaluate for MRD in the CNS using flow cytometery is planned. The goal is for prospective use of this prognostic tool in the development of relapse prevention trials.

Table 1
Relapse rates, by MRD

Disease	MRD ≥0.01%	Total (n)	Relapse (n)	Relapse Rates
Acute lymphoblastic leukemia	No	20	7	35%
	Yes	11	7	64%
Acute myelogenous leukemia	No	15	3	20%
	Yes	11	4	36%
Mixed phenotype acute leukemia	No	8	3	38%
	Yes	1	0	0%