values >0.9 were acceptable. Precision and mean bias <15% were acceptable.

24 children (0.4-17.2 years) participated. Most patients (18) received cyclosporine and methotrexate. Mean actual dose infusion time was 121 ± 5.9 min. Mean AUC-all after the first cyclosporine dose was 2397 ± 713 h•μg/L. Sufficient data were available to validate the LSSs in 16 (3, 4 & 5-point LSSs) and 15 (6-point LSS) patients. Values of AUC predicted by all but the 5-point LSS were strongly associated with AUC-all.

The 3-point LSS (2, 6 and 8 hours) is likely suitable for determining AUC following the first cyclosporine dose given as 2-hour infusion to children undergoing HSCT. Further validation in a larger number of patients is required. The relationship between acute GVHD and cyclosporine AUC at different time periods after HSCT merits further study.

Sample times		Mean bias	Precision
(hours after start of infusion)	Adjusted r^2	(%; range)	(%)
2, 6 and 8	0.9504	− 0.7 (−13.7 to 12.4)	6.0
2, 2.5, 6 and 8	0.9547	−2.7 (−16.6 to 7.7)	6.0
2, 2.5, 4, 6 and 8	0.8896	−4.7 (−25.6 to 0.8)	9.1
2, 2.5, 4, 6, 8 and 10	0.9062	−4.7 (−24.2 to −0.1)	8.5

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KIDNEY INJURY (KI) IN PEDIATRIC RECIPIENTS OF ALLOGENEIC STEM CELL TRANSPLANT (ALLOSCT): RISK OF KI IS GREATER WITH MYELOABLATIVE CONDITIONING (MAC) THAN WITH REDUCED INTENSITY CONDITIONING (RIC) IN FIRST MONTH FOLLOWING ALLOSCT

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Background: Pediatric alloSCT patients are at substantial risk of developing KI, which contributes to transplant-related morbidity and mortality (Holthe et al, Pediatr Nephrol., 2002).

Objective: To compare the incidence and outcomes of KI in pediatric recipients following RIC vs. MAC AlloSCT in 1st year post-AlloSCT.

Methods: Among 170 pediatric patients, we used the Schwartz equation to estimate creatinine clearance (eCCl) at ≤ 2wks pre- and 1,3,6,9 and 12 mo post-alloSCT with RIC or MAC. We categorized patients whose eCCI dropped ≥ 50% from baseline as having KI. Pts received Tacrolimus and MMF for GVHD prophylaxis (Osunkwo/Cairo et al. BBMT, 2004). Other nephrotoxic exposures included Ambisome at 3 mg/kg from day 0-100 (Roman/Cairo et al. PBC, 2008) and CMV prophylaxis with Foscarnet/Ganciclovir (Shereck/Cairo et al. PBC, 2007). Including risk factors significant at 0.1 level based on χ-square tests, we developed multivariable logistic regression models of predictors of kidney injury, and Cox models of overall survival.

Results: 76 pts (median 10;0.3-22 yrs) received RIC-alloSCT; 94 pts (median 8;0.3-22 yrs) received MA-AlloSCT. At 1 mo post alloSCT, A total of43/94 (45.7%) MAC recipients but only 13/76 (17.1%) RIC recipients had KI ($p < 0.0001$). The two groups did not differ in risk of KI at 3, 6, 9 or 12 months post-alloSCT. In univariate analysis, p-values were >0.1 for the association of KI at 1 mo with age, sex, CMV at risk status, and fungal infections. Associations with p-values ≤0.1were MAC (odds ratio {OR}-4.1, 95% CI 2.0-8.4,$p = 0.0001$), poor disease risk status (OR-1.8,95% CI 0.8-4.0, $p = 0.1$),VOD (OR-4.9, 95% CI 0.5-46.0, $p = 0.1$), and UCB (OR-1.8,95% CI 0.9-3.6, $p = 0.1$). In logistic regression, only MAC was an independent predictor of KI (OR-3.5, 95% CI 1.6-7.7, $p = 0.0001$).

In the Cox model, all-cause mortality hazard ratios (HR) were: RIC vs. MAC (HR = 0.3) $p = 0.0007$, poor vs. average risk disease status (HR = 2.2) $p = 0.002$, UCB vs. MSD and MUD (HR-2.2) $p = 0.02$, and KI vs. no KI (HR = 2.0) $p = 0.006$).

Conclusions: In the first month after alloSCT in children, MAC was strongly associated with risk of KI, and overall, MAC and KI were independent predictors of mortality. Avoiding KI in the first month post-alloSCT might improve OS.

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SINGLE VS DOUBLE DOSE PALONOSETRON FOR THE PREVENTION OF ACUTE AND DELAYED NAUSEA AND VOMITING IN PATIENTS UNDERGOING HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION

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Objectives: The vast majority of patients (pts) undergoing high dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT) still experience major acute and delayed chemotherapy-induced nausea and vomiting (CINV), showing how emesis control in the ASCT setting remains sub-optimal. Palonosetron (PALO), a new 5-hydroxytryptamine receptor antagonist with long half-life and high receptor binding affinity, achieves a significant control of CINV in pts receiving moderately/highly emetogenic chemotherapy. We prospectively evaluated the efficacy of a single or double i.v. dose PALO in pts undergoing HDT and ASCT.

Methods: A total of 60 pts (M/F = 32/28), median age 45 yrs (r16-64), with diagnosis of lymphoma (29), myeloma (24), sarcoma (5), acute leukemia (1), breast cancer (1) were accrued. The first cohort (30 pts) received a single iv PALO dose (0.25 mg) plus 8 mg of dexamethasone (DMS) 30' before starting of HDT while in the second cohort (30 pts) the first dose was followed by a further PALO (0.25 mg)/DMS (8 mg) injection 48 h after HDT. The distribution of conditioning regimens (high-dose melphalan = 28, BEAM = 25, MitoMel = 6, ThioEpiCTX = 1) was comparable between the two cohorts. Acute (24 h) and delayed (120 h) CINV episodes were rated by the visual analogic scale (MASCC/MAT) while CINV impact on daily activities was self-assessed by pts (at 120 h from starting of HDT), through the Functional Living Index-Emesis (FLIE) tool.

Results: No significant differences between the two groups (single vs double PALO) emerged as to acute CINV evaluation (MAT) since 98% of pts achieved a complete response (CR = no emesis, no need for rescue therapy) with only 17 pts (28%) experiencing moderate nausea (median intensity = 5, r1-10). Double-dose PALO displayed a trend for a better control of delayed nausea which occurred in 53% vs 77% of pts ($p = 0.0581$). In addition, double PALO dosing had a highly significant impact on nausea-related modifications of daily activities. FLIE nausea score was of a median value of 55.26 (r47.5-58.9) in pts receiving two doses of PALO vs 40.92 (r35-45.2) for pts treated with the single PALO dosing ($p = 0.0009$).

Conclusion: Our results indicate that double dose PALO achieves an optimal control of acute/delayed CINV and significantly reduces the detrimental impact of nausea on daily activities in patients undergoing HDT. The impressive activity of PALO in the ASCT setting might be possibly improved by combination with NK1 receptor antagonists.

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END-OF-LIFE EXPERIENCE OF CHILDREN UNDERGOING STEM CELL TRANSPLANTATION FOR MALIGNANCY: PARENT AND PROVIDER PERSPECTIVES AND PATTERNS OF CARE

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Background: The end-of-life (EOL) experience of children who undergo stem cell transplant (SCT), intensive therapy delivered with curative intent, may differ from other children with cancer.

Objectives: To evaluate parent and physician perspectives and patterns of EOL care for children after SCT.
Methods: Retrospective, cross-sectional survey of 141 parents of children who died of cancer, and primarily received care at one of two tertiary care pediatric institutions (response rate 64%). Chart review provided additional information. Children for whom SCT was the last cancer therapy (n = 31) were compared with those for whom it was not (non-SCT, n = 110).
Results: The SCT group included 22/31 (71%) allogeneic and 9/31 (29%) autologous SCT. The median (IQR) interval between last cancer treatment and death was 65 (30-127) days (SCT group) and 25 (8-59) days (non-SCT) ($p < 0.001$). SCT children were more likely to die from toxicity ($p < 0.001$). SCT parents and physicians recognized no realistic chance for cure (RCC) later than their non-SCT peers (Table 1) and were more likely to have a primary goal of cure/life extension at death (parents $p < 0.001$, physicians $p = 0.02$). SCT children were more likely to die in the ICU ($p < 0.001$), with less opportunity for location of death to be planned ($p < 0.001$) or hospice to be involved ($p < 0.001$). For SCT children, resuscitation discussions occurred later ($p < 0.001$) and resulted in fewer DNR orders ($p = 0.028$). SCT children were more likely to suffer highly from their last cancer therapy ($p = 0.034$), and experienced more physical and psychological symptoms ($p < 0.009$ and <0.007, respectively). For the 13 SCT children whose parent and physician recognized no RCC >7 days before death, intubation was less likely ($p = 0.05$) and resuscitation discussion and LOD planning more likely (both $p = 0.02$). SCT parents who recognized no RCC ≥ 7 days before death along with the physician, were more likely to prepare for EOL and if their primary goal was to reduce suffering, to achieve this ($p < 0.001$).
Conclusion: SCT is associated with significant suffering and less opportunity to recognize and prepare for EOL. Given the high morbidity and mortality associated with SCT and the shorter timeframes, children and families undergoing SCT may benefit from ongoing discussions regarding prognosis, goals and opportunities to maximize quality of life.

Parent and Physician Understanding of Prognosis: Duration of recognition of no realistic chance for cure*

	SCT (n = 31)	non-SCT (n = 110)	P†
Parents	4 (1-822)	83.5 (29-237)	<0.001
Physicians	15.5 (2-30)	84 (29-166)	<0.001

*Reported as median (inter-quartile range) number of days before death.
†P values correspond to logistic regression models adjusting for time since death.

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ALTERNATE DAY MICAFUNGIN ANTI-FUNGAL PROPHYLAXIS IN PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT): A PHARMACOKINETIC (PK) STUDY

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Disseminated fungal infection is a major cause of morbidity and mortality in children undergoing HSCT. Prophylaxis with amphotericin B can be limited by it's renal toxicity. Oral triazoles are limited by poor absorption, large inter-individual PK variability and hepatic toxicity, leading to breakthrough infections. Intravenous micafungin has a distinct advantage due to its better safety profile specifically in terms of hepatic and renal toxicity, and lack of drug-drug interactions with common medications used in the HSCT setting. We hypothesized that higher dose micafungin (3 mg/kg) every other day will provide drug exposure similar to standard dose (1 mg/kg) given daily, and improve patient compliance at reduced administration costs. Both animal and adult patient data support the use of this approach.

Fifteen children (M/F = 11/4, age ≤10 y; mean 3.9 y, range 0.6-10 y) with various hematological, metabolic and immune deficiency disorders undergoing HSCT received a single dose of Micafungin (3 mg/kg) intravenously over 1 hour. Dose selection was based on published PK data in pediatric patients (Seibel et al. ntimicrob Agents Chemother, 2005), and exploration of different dosing regimens using Monte Carlo PK/PD simulation. Blood samples were drawn around this dose (pre-dose, at the end of infusion (1 h), and at 1.5, 2, 4, 6, 10, 24, 36 and 48 h post dose) and PK analysis was conducted using standard non-compartmental methods. In addition, we evaluated free AUC/MIC (minimum inhibitory concentration) and Peak/MIC ratios as target pharmacodynamic indices.

Micafungin at 3 mg/kg dose was well tolerated in all patients. Measurable plasma concentrations were present in all cases at 48 hours (Table 1). Half-life and clearance observed were comparable to previous pediatric PK data, with clearance being higher than adults as expected. Volume of distribution was higher in our patients compared to published pediatric data, likely due to a larger proportion of very young children in our study cohort (<2 yrs, n = 3; 2-5 yrs, n = 9; 5-10 yrs, n = 3).

Our data show measurable plasma levels at 48 hours after a single 3 mg/kg dose of Micafungin. After correction for protein binding, concentrations at the end of the dosing interval during maintenance treatment will remain well above the MIC of most common fungal pathogens. This finding suggests that alternate day Micafungin dosing, as described here, may provide an attractive alternative for antifungal profylaxis in HSCT patients.

Table 1. Plasma Micafungin Pharmacokinetic Parameters

Parameters (unit)	Mean	Standard Deviation (SD)	Range
Cmax (mg/L)	12.5	2.7	8.25 – 18.69
Cmin (mg/L at 48 hr)	0.8	0.5	0.27 – 1.99
AUC0-24 (hr*mg/L)	128.5	35.9	79.29 – 229.18
AUC0-48 (hr*mg/L)	164.4	50.7	97.46 – 305.16
AUC0-INF (hr*mg/L)	180.8	62.2	104.18 – 352.87
Cl (ml/hr/kg)	17.7	5.8	7.89 – 29.62
T ½ (h)	13.0	2.1	9.45 – 16.84
Vss (L/kg)	0.3	0.1	0.22 – 0.48

Cmax - peak plasma concentration; Cmin - trough plasma concentration, AUC0-24 area under the plasma concentration-time curve at 24hrs, AUC0-48 area under the plasma concentration-time curve at 48hrs, AUC0-INF area under the plasma concentration-time curve extrapolated to infinity, Cl total body clearance, T ½ elimination half-life, Vss volume of distribution.

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DRUG INTERACTION BETWEEN ORAL CALCINEURIN INHIBITORS (TACROLIMUS AND CYCLOSPORINE A) AND ORAL VORICONAZOLE IN THE RECIPIENTS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Although drug interaction between calcineurin inhibitors such as tacrolimus and cyclosporine A (CsA) and voriconazole has long been recognized, it has not been systemically evaluated. Based on the limited data, a uniform dose reduction of calcineurin inhibitors on initiating voriconazole (1/2 for CsA, 1/3 for tacrolimus) is recommended. To date, the administration route (i.v. or oral) on the drug interaction has not been the main subject of evaluation and discussion. In the present study, the drug interaction between calcineurin inhibitors and voriconazole were evaluated in recipients of