Background: Human breast milk contains anti-inflammatory proteins and oligosaccharides that maintain infant intestinal homeostasis. We hypothesized that children receiving human milk would have lower plasma inflammatory cytokines and maintain a more diverse stool microbiome after bone marrow transplant (BMT).
Methods: Children 0-5 years of age were randomized 2:1 to receive either donor human breast milk formulated specially for the study (Prolacta Bioscience, Duarte, CA) or standard feeding with formula. Both arms were supervised by an expert BMT dietician. Babies who were breastfeeding at the time of BMT were enrolled on the human milk arm without randomization. Human milk was started on day –3 and continued until day +14 after BMT. We observed children for acute graft versus host disease (GVHD) and blood stream infections (BSI) until day +100. Metagenomic shotgun sequencing of stool and plasma cytokine analyses by Luminex were performed for samples at enrollment and day +14 after BMT. Ratios of day +14: baseline cytokines were compared between 2 groups.
Results: Forty-two children were enrolled and 23 were randomized to receive human milk while 10 were controls. Nine babies were breastfed at the time of BMT and enrolled to receive maternal milk. Four controls withdrew from study and 2 controls obtained human milk from alternate sources, and were unevaluable. Twenty-four patients received at least 60% of total goal breast milk (determined by enteral feeding volumes or breastfeeding time in minutes), and were included for analysis. We performed an as-treated analysis to assess biological activity of our intervention. Five patients within the human milk group developed engraftment syndrome (n = 4) or sepsis (n = 1) on day +14 and were excluded from cytokine analyses.
There were no differences in the median age among the human milk cohort (1.25 years; range .3-4.9 years) and controls (1 year; range .5-1.6 years). All 4 controls and 23/24 of human milk cohort received an allogeneic BMT. Eighteen of the 23 human milk recipients and all 4 controls were unrelated donor transplants. Sixteen human milk recipients and 3 controls were HLA 8/8 matched.
IL6, IL8, IL10, IFNγ and SIL2 were decreased in the human milk cohort compared to controls (Figure 1). Principal coordinate analysis of stool microbiome showed differences in beta diversity in the human milk cohort compared to controls ($P = .07$) (Figure 2) Specifically, decrease in *Streptococcus* spp. abundance at day +14 was observed in the human milk cohort compared to controls ($P = .04$).
Four children developed acute GVHD in human milk cohort compared to 3 controls ($P = .04$). Incidence of blood stream infections was 3/100 line days in the human milk cohort compared to 9/100 line days in controls ($P = .09$).
Conclusions: Our data suggest that human milk administration modifies the intestinal microbiome and might reduce inflammation and GVHD (Figure 3).

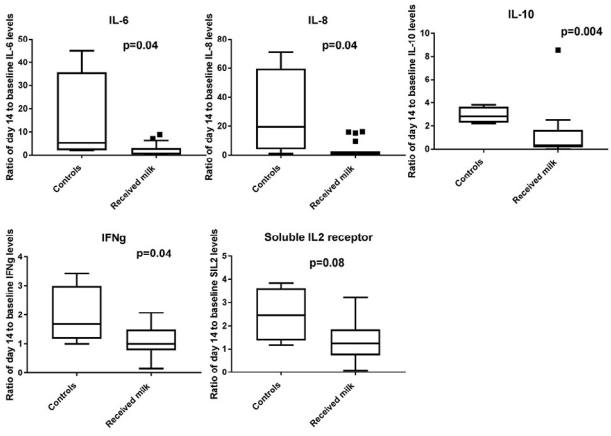

Figure 1. Ratio of day +14: baseline cytokines

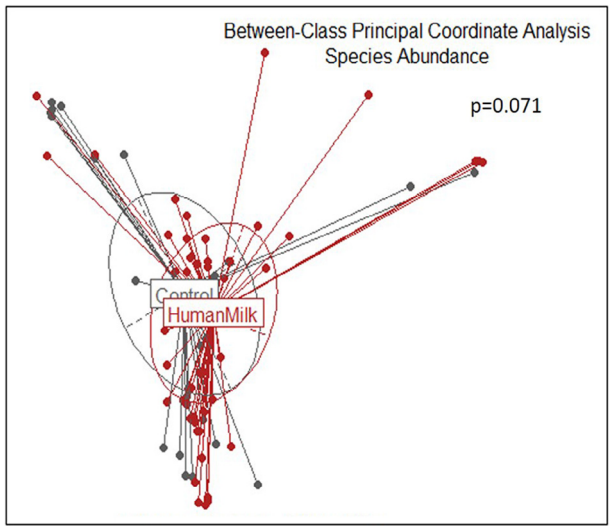

Figure 2. Beta Diversity

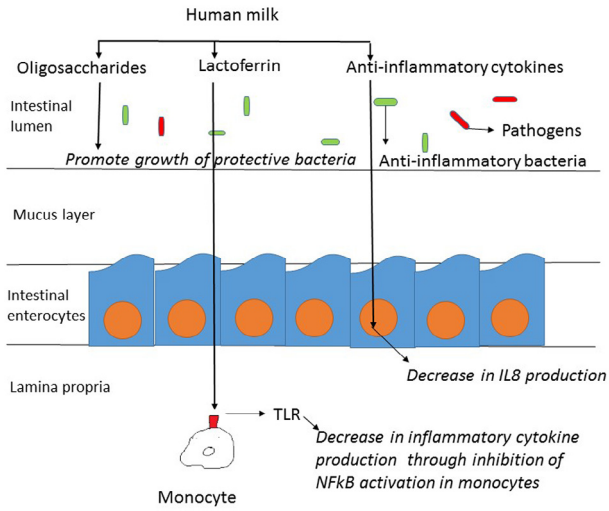

Figure 3. Proposed mechanism through which human milk maintains intestinal homeostasis

84

Long-Term Treatment Outcome in IPEX Syndrome Patients: An International Multicenter Retrospective Study

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Immunedysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) syndrome is a monogenic autoimmune disease caused by *FOXP3* mutations. It occurs in male newborns and can be rapidly fatal. In addition to the traditional clinical presentation (i.e. severe enteropathy, type 1 diabetes, and eczema), sporadic cases with uncommon clinical manifestations have been reported. Because it is a rare disease, the natural history and response to treatments, including allogeneic hematopoietic stem cell transplantation (HSCT) and immunosuppression (IS), have not been thoroughly examined. One of the objective of this international multicenter retrospective study was to evaluate long-term outcome of the two main treatments in long-term IPEX survivors. The clinical histories of 96 patients with IPEX syndrome and their respective treatment outcomes were collected from different institutions worldwide, within the European and American PID networks (EBMT-IEWP and PIDTC), and retrospectively analyzed. Results show that HSCT patients (n = 58) had a median follow-up of 2.7 years with the longest of 15 years. The overall survival (OS) after HSCT was 73.2% (95% confidence interval [CI], 59.4 to 83.0). Patients receiving chronic IS (n = 34) had a median follow-up of 4 years, with the longest at 25 years. After IS was 65.1% (95% CI, 62.8 to 95.8). To investigate possible factors suitable to predict the outcome, a scoring system was developed. The pre-treatment organ involvement (OI) was the only significant predictor of OS after transplant ($P = .035$), regardless of age, donor source, conditioning regimen.
In conclusion, IPEX patients receiving chronic IS were hampered by disease recurrence or complications, impacting long-term disease-free survival. HSCT resulted in disease resolution with better quality of life only when performed early in IPEX patients with a low OI score.
On behalf of PIDTC and IEWP of EBMT

85

BK Viremia is Common in Children after Allogeneic Hematopoietic Cell Transplant

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We prospectively enrolled children >2 years old undergoing a first allogeneic hematopoietic cell transplant (HCT) at a single center to test associations between BK viremia (BKV), short-term (hemorrhagic cystitis, HC), and longer-term (death, chronic kidney disease, CKD) outcomes. Plasma samples were collected monthly during the first 3 months after HCT for later BKV testing. HC (gross hematuria) was confirmed by monthly patient/caregiver interview and CKD defined as the patient's latest creatinine-estimated glomerular filtration rate (GFR) < 90 ml/min/1.73 m^2. 39 children (median age 12.4 years, interquartile range (IQR) 7.6-16.2 years) received HCT (72% malignancy, 13% bone marrow failure, 10% immune deficiency, 5% genetic/other) with myeloablative conditioning in 33/39 (85%) of whom 16/33 (49%) received antithymocyte globulin; 32/39 (82%) received cyclophosphamide. Ex vivo partial T-cell depletion was used in the 24/39 (62%) with unrelated donor peripheral HCT. Median follow-up time was 2.2 years (IQR 1-3 years). Acute (any grade) and chronic GVHD were diagnosed in 22/39 (56%) and 8/39 (21%) patients, respectively. 21/39 (54%) had detectable BKV (>0 copies/mL) in at least one monthly plasma sample in the first 3 months after HCT. A total of 9/39 (23%) patients had a peak BKV >10, 000 copies/mL and 3/39 (7.7%) had a peak BKV >100, 000 copies/mL. HC was diagnosed in 16/39 (41%) at a median of 36 days after HCT (IQR 33-49 days). 81% of patients with HC had detectable BKV at some point during the first 3 months and 36% of those who did not have HC had detectable BKV ($P < .01$). By logistic regression, the odds ratio for HC associated with detectable BKV at 1 month was 5.5 (95% confidence interval (CI) 1.3-23.7; $P = .02$) and was not attenuated by adjustment for any grade acute or chronic GVHD, other viremias (CMV, EBV, adenovirus, HHV6), or cyclophosphamide. To improve the evidence for a temporal association where BKV precedes HC, we excluded 5 patients diagnosed with HC before their first monthly sample was obtained and observed that BKV significantly predicted subsequent HC (HR 7.6, 95% CI 1.4-42.0; $P = .02$) in a time-to-event Cox model, independent of any grade acute GVHD and cyclophosphamide exposure. Examining longer-term outcomes, 10/39 (26%) patients developed CKD and 11/39 (28%) died of any cause, 4 of whom had a decreased GFR at the time of death.
By Cox regression, peak BKV >100, 000 copies/mL was associated with death (HR 9.9, 95% CI 1.9-52.0; $P < .01$); all 3 patients with peak BKV >100, 000 copies/mL died. HC was also independently associated with death (HR 4.6, 95% CI 1.2-17.4; $P = .02$).
In conclusion, BKV was very common in children after HCT and higher copy numbers and HC were associated with mortality. Early post-HCT, BKV significantly predicted subsequent HC, potentially supporting more frequent plasma monitoring to offer a window for trial of prophylactic cellular or pharmaceutical interventions.

86

Short Chain Fatty Acids are Reduced after Hematopoietic Stem Cell Transplant in Humans and are Associated with Modifications of the Gut Microbiome

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