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the ND and non-ND groups with regards to age, sex, diagnosis and conditioning regimen, or the number of days to resolution of neutropenia. There were no significant differences in the number of positive cultures between the groups during the neutropenic period. However, after the resolution of neutropenia, there was a significantly higher number of non-enteric gram-positive coccal infections in the ND group compared to non-ND. There was also a trend towards a higher incidence of *C. difficile*, and a significantly higher incidence of new positive surveillance cultures of VRE on rectal swabs in the ND group.

Our findings show that there is no apparent benefit associated with ND. However, more surprising is the finding that some infections were more common with ND. It could be speculated that the microbial content of the non-ND is higher and, in the setting of broad-spectrum antimicrobial prophylaxis and therapy, such a diet could contribute to reduced colonization with virulent microorganisms. These findings suggest that additional studies are needed to investigate the role of dietary restrictions. If our findings are confirmed, a major change in an established but non-evidence-based practice will be needed. An added benefit of the more liberal diet would be greater palatability - which may contribute to reduction in the use of TPN and better nutrition.

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### SEVERE HEPATOCELLULAR INJURY AFTER HEMATOPOIETIC CELL TRANSPLANTATION: INCIDENCE, ETIOLOGY, AND OUTCOME

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Hepatic complications of transplant are a common cause of mortality. While mild elevations of serum aminotransferase enzymes (AST, ALT) do not carry an adverse prognosis, this is not the case with severe hepatocellular injury.

**Methods:** We reviewed 6,225 consecutive patients transplanted from 1992–2007 to determine the incidence, causes, and outcomes of severe hepatocellular injury (defined as serum AST >1,500 U/L during the time from day 0 to day 100).

**Results:** Severe hepatocellular injury occurred in 88 patients (1.4%). Causes were Sinusoidal Obstruction Syndrome (SOS) (n = 46), hypoxic hepatitis (n = 33), Varicella Zoster Virus (VZV) hepatitis (n = 4), drug-induced liver injury (N = 2), and Unknown (n = 3). The incidence declined from 1.9% in the 1990s to 1.1% recently (due to a 5-fold decline in SOS as a cause and disappearance of VZV hepatitis). VZV hepatitis was seen in 4 patients, all before 1999 and none since. Severe drug injury was attributed to liposomal amphotericin and to carboplatin/etoposide/melphalan, respectively. In hypoxic hepatitis, peak serum AST was 3,545 U/L (range 1,380–25,246) within days of shock or prolonged hypoxemia; the case fatality rate was 88%. In SOS, AST increases occurred 2–6 weeks after diagnosis; peak AST was 2,252 U/L (range 1,437–8,281) and the case fatality rate was 76%, with only total serum bilirubin able to distinguish survivors from those who died (2.7 mg/dL vs. 11.3 mg/dL, respectively, p = 0.0009).

**Conclusions:** Hepatic circulatory insults (sinusoidal injury from the conditioning regimen, hypotension, hypoxemia) and not infection are the most common cause of severe hepatocellular injury. Although the frequency of severe hepatocellular injury has declined sharply because of a falling incidence of SOS and VZV hepatitis, the case fatality rate remains high.

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### GENERATION OF HLA-RESTRICTED T-LYMPHOCYTE RESPONSES AGAINST RECOMBINANT INFLUENZAVIRUS HEMAGGLUTININ A/NEW CALEDONIA BY AN IN VITRO UMBILICAL CORD BLOOD MODEL OF DENDRITIC CELL VACCINATION

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**Introduction:** Influenza infection following treatment with chemotherapy and/or concomitant radiation therapy remains a

significant cause of morbidity among immunocompromised patients in the hospital setting. Further, such patients tend to seroconvert inefficiently and with suboptimal titers following prophylactic vaccination with either the standard or recombinant influenza vaccines. Toward the goal of addressing this issue, we have developed an *in vitro* model of dendritic cell (DC) immunotherapy utilizing DCs generated from umbilical cord blood (UCB).

**Methods:** UCB monocytes were harvested by adherence, and UCB DCs were generated by incubation in GM-CSF and IL-4. Immature DCs were loaded with purified rHA protein [A/New Caledonia (H1N1)], matured with an inflammatory cytokine cocktail, and used to stimulate autologous T-lymphocytes. T-lymphocyte priming and development were supported by supplementation with IL-12, IL-2, IL-7, and IL-15. DC and T-cells were analyzed by flow cytometry. Antigen specific responses were documented by IFN- $\gamma$  ELISpot, <sup>51</sup>Cr lysis, and tetramer staining. Recombinant hemagglutinin HLA-restricted peptides were synthesized by Sigma-Genosys (The Woodlands, Texas). MHC class II DR15-restricted tetramer was synthesized by Beckman-Coulter (Fullerton, CA).

**Results:** DCs were primarily of myeloid Langerhans phenotype (CD11c<sup>+</sup>, CD14<sup>+</sup>) and expressed high levels of CD209, HLA-DR and costimulatory molecules CD80, CD86, and CD83. Primed and expanded T-cells were predominantly CD62L<sup>+</sup>CCR7<sup>+</sup>, indicative of effector status; however, there were also small but distinct populations CD127<sup>+</sup> and CCR7<sup>+</sup> memory cells. Upon recall with HA-loaded autologous DC, a 4 to 10-fold increase in the number of IFN- $\gamma$  producing T-lymphocytes was observed in comparison to T-cells stimulated with autologous unloaded DCs or allogeneic DCs loaded with irrelevant antigens. Antigen-specific T-cell functionality was determined by <sup>51</sup>Cr lysis assay. Using a peptide library of predicted HA binding epitopes, we mapped an HA-specific, DR15-restricted CD4<sup>+</sup> T-cell epitope (GNLIAPWYAFALSRG) and documented tetramer-positive CD4<sup>+</sup> cells in a DR15<sup>+</sup> background.

**Conclusions:** The model demonstrates that HA-specific, HLA-restricted immune responses may be generated from UCB lymphocytes and suggests that dendritic cell immunotherapy for the prevention of influenza might be feasible.

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### HUMAN CORONAVIRUS (HCoV) AND RHINOVIRUS (HRhV) INFECTION AMONG HEMATOPOIETIC STEM CELL TRANSPLANTATION (HCT) RECIPIENTS

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**Background:** Little is known about clinical and virologic manifestations of HCoV and HRhV infections after HCT. HCoV and HRhV are not usually associated with severe illness but have been reported to cause pneumonia in immunocompromised patients.

**Methods:** From Dec. 2005-June 2008, prospective surveillance was performed on 215 allogeneic HCT recipients for 100 days post-HCT. Weekly symptom surveys, nasal washes and throat swabs were collected and samples were tested by RT-PCR. We tested for 4 different types of HCoV (OC43, 229E, HKU1 and NL63).

**Results:** Among 215 patients, the cumulative incidence estimate for HCoV infection at day 100 was 11.6 (95% CI, 7.3–15.9) and for HRhV was 20.9 (95% CI, 15.5–26.4); median time of first detection was 54 days (range 2–93) and 38 days (0–93), respectively. Incident virus infections occurred mostly in winter months for HCoV whereas HRhV infections occurred year-round. Prolonged viral shedding for  $\geq 3$  months was observed in 6 (13%) patients with HRhV and in 4 (16%) with HCoV. Twelve of the 25 (48%) subjects with HCoV and 4 of 45 (9%) with HRhV detections were asymptomatic during every week of virus detection. An additional 3 patients with >10 samples positive for HRhV reported symptoms only once during the duration of positivity. Frequently reported symptoms associated with HRhV detection included rhinorrhea (52%), cough (32%), shortness of breath (32%), and wheezing (22%); symptoms reported with HCoV detections were similar to those when no virus was detected. Of the 45 cases of HRhV infection, 43 had upper respiratory infection only (URI) and 2 developed URI plus lower respiratory infection (LRI). None of the 25 cases of

HCoV infection developed LRI. BAL was performed in 38 (18%) patients, 6 of whom had HRhV detection in upper respiratory samples. Two of these BALs tested positive for HRhV.

**Conclusion:** This prospective study is the first to describe the natural history of HCoV and HRhV infections during the first 100 days after HCT. HRhV and HCoV infections were common and prolonged shedding may occur. While HRhV frequently caused symptomatic URI and occasionally LRI, there was no apparent association with either URI or LRI in patients infected with HCoV in this study group. However, this study does not exclude the possibility that HCoV is a rare cause of lower tract disease. Studies are on-going to further investigate this.

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### TACROLIMUS AND SIROLIMUS AS GVHD PROPHYLAXIS FOR SIBLING DONOR HEMATOPOIETIC STEM CELL TRANSPLANT (HCT) USING THREE CONDITIONING REGIMENS; FLUDARABINE-MELPHALAN, FTBI-VP16, AND BUSULFAN-CYCLOPHOSPHAMIDE

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Based on encouraging phase II data, we prospectively tested the combination of tacrolimus and sirolimus (tacro/siro) as GVHD prophylaxis in patients undergoing HLA-matched sibling donor HCT. Eighty-five patients were stratified according to conditioning regimen as follows: fludarabine-melphalan (FluMel: n = 46); FTBI-VP16 (TBI: n = 28), and busulfan-cyclophosphamide (BuCy: n = 11). The median age was 47 years (range: 10–67). The patient diagnoses were AML (33), ALL (18), NHL/HD (11/3), MDS (6), CML (5), myeloma (3), MPD (3), and CLL (1). A majority of patients received a PBSC graft except for five who received a BM graft with the overall median CD34+ cell dose of  $5.1 \times 10^6/\text{kg}$  (range: 1.7–10.5). All patients engrafted (median neutrophil engraftment: 15 days). Fifty five of 85 patients are alive after a median follow up of 26 months (range: 14–37). Twenty-two patients died of relapse while eight were due to non-relapse causes including acute/chronic GVHD (3), multi-organ failure (1), mucormycosis (1), leukoencephalopathy (1), and respiratory failure (1). The probabilities of overall survival (OS), disease-free survival (DFS), and relapse at 2 years were 66% (CI: 59–72), 58% (CI: 52–64), and 34% (CI: 28–42), respectively. The day 100 and 2 year transplant-related mortality (TRM) was 3.6% (CI: 2–12) and 10.2% (CI: 7–20), respectively. Conditioning regimen was not significantly associated with OS, DFS, relapse, or TRM. The cumulative incidence of acute GVHD grade II-IV and III-IV was 40% (CI: 37–50) and 16% (CI: 12–27), respectively. Fourteen of 21 patients with grade II GVHD had upper GI involvement only. There was a trend for higher probability of acute GVHD in patients conditioned with BuCy compared with TBI and FluMel (64%, 49% and 34%, respectively) ( $p = 0.12$ ). The probability of chronic GVHD was 45% (limited: 14%, extensive: 31%). Thrombotic microangiopathy (TMA) was a major complication which developed in 19% of patients, significantly associated with BuCy (55%) compared with TBI (25%) and FluMel (6.5%) ( $p = 0.005$ ). TMA was reversible in all cases, managed by holding tacro and/or siro except for two who required plasma exchange/hemodialysis. In summary, the combination of tacro/siro is associated with a low TRM rate over 2 years. The encouraging results on acute GVHD in our study support the ongoing phase III trial comparing tacro/siro versus tacro/MTX (CTN 0402). However, TMA was frequently observed and the risk was significantly greater with BuCy conditioning.

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### PREDICTION OF VOD USING BIOMARKERS OF ENDOTHELIAL INJURY

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Clinical risk factors for VOD are well known, however, predicting the occurrence of VOD in individuals remains challenging. Since the primary mechanism of injury in VOD is conditioning-related damage to hepatic sinusoidal endothelial cells and hepatocytes, we measured soluble biomarkers of endothelial injury in the peri-stem cell transplant (SCT) period to determine if they correlated with the occurrence of VOD.

**Methods:** 59 patients who underwent HLA-matched donor SCT received conditioning with cyclophosphamide ( $1800 \text{ mg/m}^2 \times 2$ ) and TBI (14 Gy) and tacrolimus with sirolimus or methotrexate as GVHD prophylaxis are included in this analysis. They are stratified based on the occurrence of VOD (VOD+ n = 18, VOD- n = 41), diagnosed by clinical, radiologic and pathologic criteria. Banked samples collected after conditioning but prior to SCT (day -1) and weekly after SCT (day 7, 14, 21) were thawed and analyzed using commercial ELISA kits and quantified using a VersaMax plate reader. Von Willebrand Factor (vWF) and thrombomodulin (TM) were assayed in plasma; E-selectin and soluble intercellular adhesion molecule-1 (ICAM) were assayed in serum. Assays were performed in duplicate and the mean of two assays were analyzed. Not all patients had every time point analyzed due to missing specimens. The within-sample results were compared using the 2-sided Wilcoxon rank-sum test using the Bonferroni method to adjust for multiple comparisons.

**Results:** Among patients who received sirolimus, levels of vWF, TM and ICAM were significantly different between VOD+ and VOD- groups on day -1 ( $p \leq 0.04$ ), day+7 ( $p \leq 0.0001$ ) and day+14 ( $p \leq 0.004$ ). E-selectin was only predictive on day+7 ( $p = 0.009$ ). Using pre-defined thresholds, vWF ( $>1400 \text{ IU/ml}$ ) and TM ( $>100 \text{ ng/ml}$ ) levels on day +7 were 100% sensitive and 100% specific in predicting the occurrence of VOD. Biomarkers could not reliably predict VOD among patients not treated with sirolimus. There were no differences in biomarkers among VOD- patients, suggesting that in the absence of VOD, markers of endothelial injury are not elevated, even when sirolimus is used.

**Conclusions:** Plasma vWF and TM and serum ICAM elevations before and early after SCT can be used to predict the occurrence of VOD in patients receiving sirolimus. This analysis demonstrates the contribution of sirolimus to endothelial injury and VOD after SCT, and may help select patients in whom prophylactic or pre-emptive strategies against endothelial damage and VOD may be useful.

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### CYTOMEGALOVIRUS (CMV) REACTIVATION IN RECIPIENTS OF UMBILICAL CORD BLOOD (UCB): RISK FACTORS AND OUTCOMES

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Pre-transplant CMV serostatus has been shown to be an adverse risk factor in allo-HCT recipients. The consequences of CMV reactivation after transplantation have not been extensively described in the UCB setting. We analyzed the impact of pre-transplant CMV seropositivity and CMV reactivation on UCBT outcomes. Between 1994 and 2007, 332 patients with malignancies underwent UCBT at the University of Minnesota and 54% were CMV seropositive. All UCB units were considered seronegative. While there was a trend to greater day 100 TRM ( $p = 0.07$ ), CMV seropositivity was not associated with survival ( $p = 0.55$ ) or relapse ( $p = 0.78$ ). For the 180 CMV seropositive patients, the median age at UCBT was 51 years (range 6–68). Myeloablative conditioning consisting of cyclophosphamide (CY) and TBI 13.2 Gy, with ATG (n = 31, 25%) or fludarabine (FLU, n = 91, 75%). Myeloablative conditioning was followed by single (n = 56, 46%) or double (n = 66, 54%) UCBT. Reduced intensity conditioning (RIC) consisted of CY, FLU and TBI 2 Gy and was followed by double UCBT in all 58 patients. GVHD prophylaxis consisted of cyclosporine/methylprednisone (17%) or cyclosporine/mycophenolate mofetil (83%). All patients had weekly screening for CMV reactivation (by pp65 antigenemia or PCR) and received acyclovir prophylaxis until day 100. The incidence of CMV reactivation was 51% (92/180) with no difference in recipients of a myeloablative vs. RIC ( $p = 0.33$ ). Among recipients of myeloablative conditioning, CMV reactivation was similar regardless of GVHD prophylaxis regimen ( $p = 0.8$ ). In univariate analysis, the only variables associated with CMV reactivation were older age