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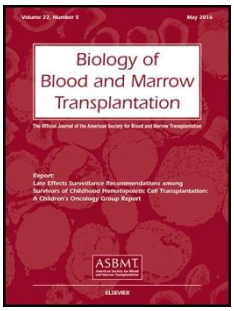

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Short Title: NiCord Decreases Infection and Hospitalization

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Highlights

- Neutrophil engraftment is faster with ex vivo expanded NiCord than standard UCB
- NiCord transplant is associated with decreased infection in the first 100 days
- NiCord transplant is also associated with decreased early hospitalization

Abstract:

Delayed hematopoietic recovery contributes to increased infection risk following umbilical cord blood (UCB) transplantation. In a Phase 1 study, adult recipients of UCB stem cells cultured ex vivo for 3 weeks with nicotinamide (NiCord) had earlier median neutrophil recovery compared to historical controls. To evaluate the impact of faster neutrophil recovery on clinically relevant early outcomes, we reviewed infection episodes and hospitalization during the first 100 days in an enlarged cohort of 18 NiCord recipients compared to 86 standard UCB recipients at our institution. Median time to neutrophil engraftment was shorter in NiCord than in standard UCB recipients (12.5 days vs. 26 days, $p<0.001$). Compared to standard UCB transplantation, NiCord recipients had significantly reduced risk for total infection (RR 0.69, $p=0.01$), grade 2-3 (moderate to severe) infection (RR 0.36, $p<0.001$), bacterial infection (RR 0.39, $p=0.003$), and grade 2-3 bacterial infection (RR 0.21, $p=0.003$) by Poisson regression analysis; this effect persisted after adjustment for age, disease stage, and grade II-IV acute GVHD. NiCord recipients also had significantly more time out of the hospital in the first 100 days compared to standard UCB recipients after adjustment for age and KPS (69.9 days vs. 49.7 days, $p=0.005$). Overall, transplantation of NiCord was associated with faster neutrophil engraftment, reduced total and bacterial infections, and shorter hospitalization in the first 100 days compared to standard UCB transplantation.

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In conclusion, rapid hematopoietic recovery from an ex vivo expanded UCB transplantation approach is associated with early clinical benefit.

Keywords: umbilical cord blood transplantation, stem cell expansion, infections, hospitalization

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Introduction:

Umbilical cord blood (UCB) extends the curative potential of stem cell transplantation to adult patients without an HLA compatible donor.[1] After UCB transplantation, overall survival is comparable to matched related or unrelated donor transplantation, but treatment related mortality is significantly higher.[2, 3] UCB grafts are limited by low total and stem cell doses that are associated with delayed hematopoietic and immunologic recovery. Delayed neutrophil engraftment likely contributes to increased risk of life-threatening infection and longer hospitalization in the early post-UCB transplantation period.[4, 5]

In order to overcome the limitation of low UCB cell dose, several techniques have been developed to expand cord blood-derived hematopoietic stem and progenitor cells ex vivo prior to transplantation.[6, 7] While each technique employs a different mechanism for ex vivo expansion, all have shown promise in reducing the time to neutrophil and platelet engraftment.[8-11] NiCord is an UCB-derived cell product that uses a small molecule, nicotinamide, to inhibit differentiation and enhance functionality of hematopoietic stem and progenitor cells (HSPC) expanded in ex vivo culture.[12] The NiCord graft consists of two fractions from the UCB unit. The CD133 positive fraction containing HSPCs is expanded for 21 days in the presence of hematopoietic stem cell active cytokines plus nicotinamide. The CD133 negative fraction containing lymphoid cells is retained, cryopreserved and ultimately co-infused with the expanded CD133 positive cell fraction on the day of transplantation. Results from a phase I trial of transplantation with NiCord along with a second unmanipulated UCB unit showed

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earlier median neutrophil recovery compared to historical controls, and long term engraftment with the NiCord unit was also observed in the majority of patients.[10] Rapid neutrophil recovery has also been observed in a subsequent ongoing phase II trial exploring the use of NiCord as a single unit graft.[13]

Since use of the NiCord ex vivo expanded UCB graft resulted in rapid hematopoietic recovery, we hypothesized that NiCord transplantation would improve clinically relevant early outcomes by decreasing risk of infection and length of hospitalization. Therefore, we analyzed infection episodes and hospitalization during the first 100 days after transplantation in an enlarged cohort of patients undergoing NiCord transplantation compared to a historical control of consecutive adult patients undergoing standard UCB transplantation at our institution.

Methods:

Patients and Transplantation Approach:

Two cohorts of adult patients ≥ 18 years old with hematologic malignancies who underwent umbilical cord blood transplantation at Duke University were compared in this study. Cohort 1 included 18 consecutive adults transplanted with expanded NiCord grafts as part of two Phase I and II clinical trials from January 2010 to March 2015.[10, 13] Cohort 2 included 86 consecutive adults transplanted with unmanipulated standard single or double umbilical cord blood grafts from January 2005 to March 2015. All patients received a myeloablative total body irradiation 1350 cGy (TBI) and fludarabine 160 mg/m^2 (Flu)-based conditioning regimen. No patient received in vivo T cell depletion. Cord blood units were matched to the recipient at 4 or more HLA loci (intermediate-resolution for A and B, high-resolution for DRB1). In Cohort 1, 11 of 18

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patients received double UCB transplantation with one NiCord expanded cord blood unit of minimum 1.5 x 10^7 TNC/kg and one unmanipulated cord blood unit of minimum 2.5 x 10^7 total nucleated cells per kilogram recipient body weight (TNC/kg) as previously described.[10] The other seven patients in cohort 1 were transplanted at Duke Medical Center with a single NiCord expanded cord blood unit of minimum 1.8 x 10^7 TNC/kg prior to expansion as part of a multicenter Phase II trial.[13] In Cohort 2, patients received either a single cord blood unit with minimum cryopreserved cell dose of 3 x 10^7 TNC/kg or two cord blood units each containing a minimum cryopreserved cell dose of 1.5 x 10^7 TNC/kg. Graft versus host disease (GVHD) prophylaxis consisted of tacrolimus (target level 10-15 ng/mL) for at least 6 months and mycophenolate mofetil for at least 60 days after transplantation. Unless contraindicated, patients from both cohorts received antimicrobial prophylaxis with acyclovir 800 mg twice daily to day +365, ciprofloxacin 500 mg twice daily to day +180, voriconazole 200 mg twice daily to at least day +100, and trimethoprim-sulfamethoxazole 400/80 mg once daily to at least day +180 following transplantation. Supportive care measures including evaluation and management of febrile neutropenia, weekly PCR surveillance for cytomegalovirus (CMV; for the entire study period) and human herpesvirus (HHV)-6 viremia (starting in 2010), and infection control practices were conducted per institutional protocol in both cohorts. G-CSF (5 μg/kg) was administered daily starting on day 1 after transplantation until the absolute neutrophil count (ANC) exceeded 1,000 cells per μL blood. Patients were eligible for discharge from the hospital when the ANC exceeded 500 cells per μL blood.

Definitions:

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The time to neutrophil engraftment was defined as the first of three consecutive days with an absolute neutrophil count of 0.5 x 10^9 per liter or higher. Disease status at the time of transplantation was categorized as "early" for patients with acute leukemia in first complete remission (CR), myelodysplastic syndrome (MDS) untreated or in first CR, chronic myelogenous leukemia in first chronic phase, or non-Hodgkin's lymphoma (NHL) or multiple myeloma in first CR; all other patients were considered "non-early".[14] Acute graft versus host disease (GVHD) was defined and graded according to standard criteria.[15]

Infection Data:

Early infection episodes through day 100 after transplantation were retrospectively identified and categorized by organism type and severity per BMT CTN Technical MOP Version 3.0, Appendix 4-A (supplemental Table 1). Recurrence interval definitions in Appendix 4-A were also utilized to determine whether a given infection was part of a prior episode or new. Each new infection episode was first classified by type as bacterial, fungal, viral, parasitic, or non-microbiologically defined, then further characterized by severity as grade 1 (mild), grade 2 (moderate), or grade 3 (severe/life-threatening). Patients were considered at risk of early infection through day 100 after transplantation, day of relapse, day of second transplant, or day of death, whichever happened first.

Hospitalization Data:

Hospitalization was defined as "days alive and out of the hospital in the first 100 days" in order to account for the incongruous association of earlier mortality with shorter

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hospitalization, as previously reported by Ballen and colleagues.[5] For patients who survived to day 100, "days alive and out of the hospital in the first 100 days" was calculated by subtracting the total number of days in the hospital during the initial admission and any readmissions from 100. For patients who died before day 100, "days alive and out of the hospital in the first 100 days" was calculated by subtracting the total number of days in the hospital during the initial admission and any readmissions from the day of transplantation to the day of death. In this way, if a patient's death occurred during the initial hospitalization, then there were no days alive and out of the hospital.

Statistical Analysis:

Patient baseline and transplant characteristics were compared using the Fisher's exact test and t-test for categorical and continuous variables, respectively. The cumulative incidence of neutrophil recovery was compared between study groups with death, relapse, or subsequent transplant as competing risks, and the hazard ratio (HR) and 95% confidence interval (CI) for study group was estimated from a proportional hazards model that also accounted for competing risks. Infection rates were calculated as the number of patients who experienced each infection at least one time during their observation period, and Fisher's exact tests were used to test for differences between groups. To account for multiple infections in an individual patient as well as differing periods of risk, infection densities were calculated as the total number of infections per patient per days at risk. Individual patient infection densities were then averaged over all patients in a group to calculate the mean number of infections experienced per 100 patient days, and Wilcoxon rank-sum tests were used to test for differences between

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groups. Poisson regression was used to estimate the effect of NiCord versus standard UCB transplantation on the rates of total infection, grade 2-3 infection, bacterial infection, grade 2-3 bacterial infection, and grade 2-3 non-viral infection, both univariately and after adjustment for covariates known to affect the risk of infection including age, disease status, and acute GVHD.[16] An offset was included in the model to account for the observation time for each patient. Risk ratios (RR) and 95% CI were estimated from the Poisson model. Analysis of variance (ANOVA) was used to univariately examine the association of time alive and out of the hospital during the first 100 days post-transplant with study group, and analysis of covariance (ANCOVA) was used to examine the association after adjustment for known covariates including age and Karnofsky performance status (KPS). To determine if the standard UCB patients transplanted from 2010-2015 (n=50) were different than the full group of control patients, a sensitivity analysis comparing these two groups was conducted. A second sensitivity analysis was performed by comparing the NiCord cohort to the contemporaneous cohort of standard UCB patients transplanted from 2010-2015. All statistical analyses were conducted with SAS version 9.4 (Cary, NC). This retrospective analysis was approved by the Duke University Medical Center Institutional Review Board.

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Results:

Patients:

A total of 104 patients were included in this study; 18 underwent NiCord transplantation and 86 underwent standard UCB transplantation. Patient baseline and transplant characteristics are summarized in Table 1. NiCord recipients were older (median age

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45.5, IQR 42-57 years) than standard UCB recipients (median age 37.5, IQR 28-51 years; p=0.007). Patient sex, pre-transplant weight, CMV serostatus, and KPS were similar between groups. The underlying malignant disease (acute leukemia/MDS 89%, lymphoid 11%) and disease status at transplant in each group were also similar. All patients received a myeloablative total body irradiation (TBI) and fludarabine-based conditioning regimen, and no patients received *in vivo* T cell depletion. In the NiCord group, 11 patients received NiCord with a second unmanipulated unit and 7 patients (39%) received NiCord as a single UCB graft, while only 4 patients (5%, p<0.001) in the standard UCB group underwent single UCB transplantation. There was a range of recipient to UCB unit HLA matching in both groups and cryopreserved total nucleated cell dose was similar. No significant differences between the groups were observed in grade II-IV acute GVHD, second transplant, disease relapse, or death in the first 100 days after transplantation.

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Neutrophil Engraftment:

Median time to neutrophil engraftment in NiCord patients was 12.5 days (95% CI 10-18), significantly faster than 26 days (95% CI 22-28) in standard UCB patients (HR 3.68, 95% CI 1.74-7.77; p<0.001)(Figure 1). In the NiCord group, one patient (6%) had engraftment failure after double UCB transplantation. In the standard UCB group, 10 of 86 patients (12%; p=0.68) had engraftment failure with 2 patients after single and 8 patients after double UCB transplantation.

Total Infections:

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A total of 343 infection episodes were identified in the study population with 58 in the NiCord group and 285 in the standard UCB transplantation group. The distribution of total infections by type was 107 bacterial, 157 viral, 10 fungal and 69 non-microbiologically defined infections (Table 2). By severity, 208 infections were grade 1, 99 infections were grade 2, and 36 infections were grade 3. All 18 NiCord and 86 standard UCB patients had at least one infection of any severity. Ten of 18 (56%) NiCord and 63 of 86 (73%) standard UCB patients had at least one grade 2-3 (moderate to severe) infection (p=0.16). Pathogen-specific comparison of grade 2-3 infection in NiCord versus standard UCB recipients showed significantly lower frequency of at least one bacterial infection, 22% vs. 57% (p=0.009) respectively, but no difference in frequency of at least one grade 2-3 viral (44% vs. 36%, p=0.59) or fungal (0% vs. 5%, p=1.0) infection. There was a strong trend toward reduction in non-microbiologically defined grade 2-3 infections (0% vs. 19%, p=0.07), however this did not reach significance, likely due to the small sample size.

Infection Density:

The mean number of total infections during the first 100 days following transplantation was 3.7 per patient in the NiCord group and 4.9 per patient in the standard UCB transplantation group (p=0.09, Figure 2a). Grade 2-3 infection was decreased in the NiCord group at 0.9/patient versus 2.5/patient in the standard UCB group (p=0.01). On further pathogen-specific analysis of this difference, grade 2-3 bacterial infection was significantly lower in the NiCord group at 0.3/patient versus 1.5/patient in the standard UCB group (p=0.007, Figure 2b), while there was no difference in grade 2-3 viral infection at 0.6/patient in both groups (p=0.7, Figure 2c).

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There were a low number of grade 2-3 fungal (0.1/patient) and non-microbiologically defined (0.4/patient) infections observed in the standard UCB group but none in the NiCord group. Total bacterial infection was also decreased in the NiCord group at 0.7/patient compared to 2.0/patient in the standard UCB group (p=0.01), largely due to the decrease in grade 2-3 bacterial infection (Figure 2b).

By Poisson regression analysis, recipients of NiCord versus standard UCB transplantation had significantly reduced risk for total infection (0.69, 95% CI 0.52-0.91; p=0.01), grade 2-3 infection (0.36, 95% CI 0.19-0.62; p<0.001), bacterial infection (0.39, 95% CI 0.2-0.69; p=0.003), and grade 2-3 bacterial infection (0.21, 95% CI 0.06-0.51; p=0.003)(Table 3). This effect was largely unchanged after multivariate adjustment for age, disease stage, and grade II-IV acute GVHD (Figure 3).

Unexpectedly, grade II-IV acute GVHD was also associated with a decreased risk of infection in the multivariate models. Further analysis of this observation revealed that a significantly higher proportion of patients without grade II-IV acute GVHD required second transplant (19% vs. 0%; p=0.001), increasing risk of infection in this group compared to patients with acute grade II-IV GVHD.

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Hospitalization:

NiCord recipients spent an unadjusted mean of 72.4 days (95% CI 61.6-83.2) out of the hospital in the first 100 days, significantly longer than 48.6 days (95% CI 42.3-54.9) in the standard UCB transplantation group (p=0.001; Figure 4). After adjustment for age and KPS, recipients of NiCord had on average 20.2 (95% CI 6.0-34.3) more days out of the hospital compared to standard UCB recipients (p=0.005; Table 4), resulting in an

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adjusted mean of 69.9 days (95% CI 57.1-82.7) out of the hospital in the NiCord group versus 49.7 days (95% CI 44.0-55.5) in the standard UCB transplantation group. KPS was independently associated with more time out of the hospital in the first 100 days, on average 6.0 more days per 10 point increase in KPS (95% CI 0.2-11.9; p=0.04). However, after adjustment, increasing age had no impact on length of hospitalization.

Discussion:

Delayed hematopoietic recovery remains a major limitation of umbilical cord blood transplantation. Several methods for ex vivo expansion of UCB units before transplantation have resulted in improved time to neutrophil engraftment, but the impact on clinically relevant early outcomes has not been evaluated. As previously reported in the Phase 1 trial of NiCord transplantation, we found that transplantation of the ex vivo expanded NiCord graft in an enlarged cohort was associated with rapid hematopoietic recovery compared to a historical cohort of patients undergoing standard UCB transplantation. In this study, we show that early hematopoietic recovery in NiCord recipients translates into a decreased burden of infectious complications and hospitalization in the first 100 days after transplantation.

A recent analysis of infectious complications from the randomized BMT CTN 0201 study comparing bone marrow to peripheral blood stem cells from unrelated donors showed a higher cumulative incidence of infection before engraftment and bacterial bloodstream infection during the first 100 days in the bone marrow group, which also had a 5 day longer median time to neutrophil engraftment.[17, 18] Several prior studies have reported a higher incidence of bacterial and fungal infections during the

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post-transplantation period in UCB transplantation recipients compared to other unrelated donor sources.[4, 19-21] A large registry analysis of UCB transplantation identified an association between early bacterial infection and increased risk of overall mortality, although another analysis comparing overall infection related mortality between UCB and other unrelated donor sources did not identify a significant difference.[4, 22] Regardless, decreasing morbidity and resource utilization associated with early infectious complications is a clinically relevant outcome.

In the current study, we identified an early bacterial infection rate of 2.0 per patient during the first 100 days in the standard UCB group, which is similar to the previously reported rate of 2.1 bacterial infections per patient in the first 100 days after UCB transplantation by Parody and colleagues, recognizing that there are some subtle differences in the method of categorizing infections.[4] By contrast, in the NiCord transplantation group, the rate of early bacterial infection was significantly decreased to 0.68 infections per patient, and this effect remained unchanged after adjusting for age, disease stage, and acute GVHD. Similarly, clinically significant grade 2-3 total and bacterial infection rates were also lower in the NiCord group compared to the standard UCB group in our analysis. The difference in moderate to severe bacterial infection was largely due to a decrease in bloodstream infection in the NiCord group, which may be a function of earlier neutrophil recovery. Bloodstream infection is the most common infection after allogeneic transplantation and has been associated with increased mortality.[23] In addition, antibiotic use that accompanies these infections may have a negative impact on intestinal bacterial flora. Recent studies have shown that broad spectrum antibiotic therapy can alter the intestinal microbiome, and low microbial

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diversity has been associated with increased acute GVHD and mortality after transplantation[24-26]. Therefore, the benefits of early engraftment may extend beyond reduction in the morbidity and mortality associated with bloodstream infections.

Conversely, there was no difference between the NiCord and standard UCB group in the rate of viral infection, which would not necessarily be expected with earlier hematologic recovery. The paradoxical protective effect of grade II-IV acute GVHD in our multivariate model was likely related to the significantly higher proportion of patients without acute grade II-IV GVHD who experienced primary graft failure and subsequently requiring a second rescue transplant. This resulted in an increased risk of infectious complications due to prolonged neutropenia.

A recent registry analysis comparing hospitalization between unrelated donor graft sources showed that double UCB recipients had a median of 55 days alive and out of the hospital in the first 100 days after transplantation, significantly shorter than median 75 days for peripheral blood stem cell graft recipients.[5] In our study, NiCord recipients had an adjusted mean of 69.9 days alive and out of the hospital in the first 100 days, significantly longer than 49.7 days in the standard UCB transplantation group. It is tempting to speculate that faster neutrophil engraftment and decreased infectious complications may be contributing to the improvement in time out of the hospital in the NiCord group.

Limitations of this study include the small sample size in the NiCord group and the inherent inability to control for all potential confounding factors in a retrospective analysis. However, since all the included patients were treated at a single institution,

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there is a lower risk of unaccounted differences in supportive care. In order to evaluate the potential impact of changes in supportive care over time, we performed a sensitivity analysis comparing NiCord patients to a contemporaneous cohort of standard UCB patients transplanted from 2010-2015, which did not differ from the primary analysis of infection density or hospitalization. The current analysis included detailed infection data that is generally not available in a larger registry based study. Larger studies will be required to determine if improved early clinical outcomes after NiCord transplantation compared to standard UCB recipients will translate into improved overall patient outcomes.

In conclusion, transplantation of NiCord was associated with faster neutrophil engraftment, reduced total and bacterial infections, and shorter hospitalization in the first 100 days after transplantation compared to standard UCB transplantation. Our results confirm that rapid hematopoietic recovery from an ex vivo expanded UCB transplantation approach is associated with early clinical benefit.

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Authorship Contributions:

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Conception and design: MH, SA, ST, TH
Collection and assembly of data: SA, MH
Data analysis and interpretation: SA, MH, ST
Manuscript writing: SA, MH, ST
Final approval of manuscript: MH, SA, ST, TH

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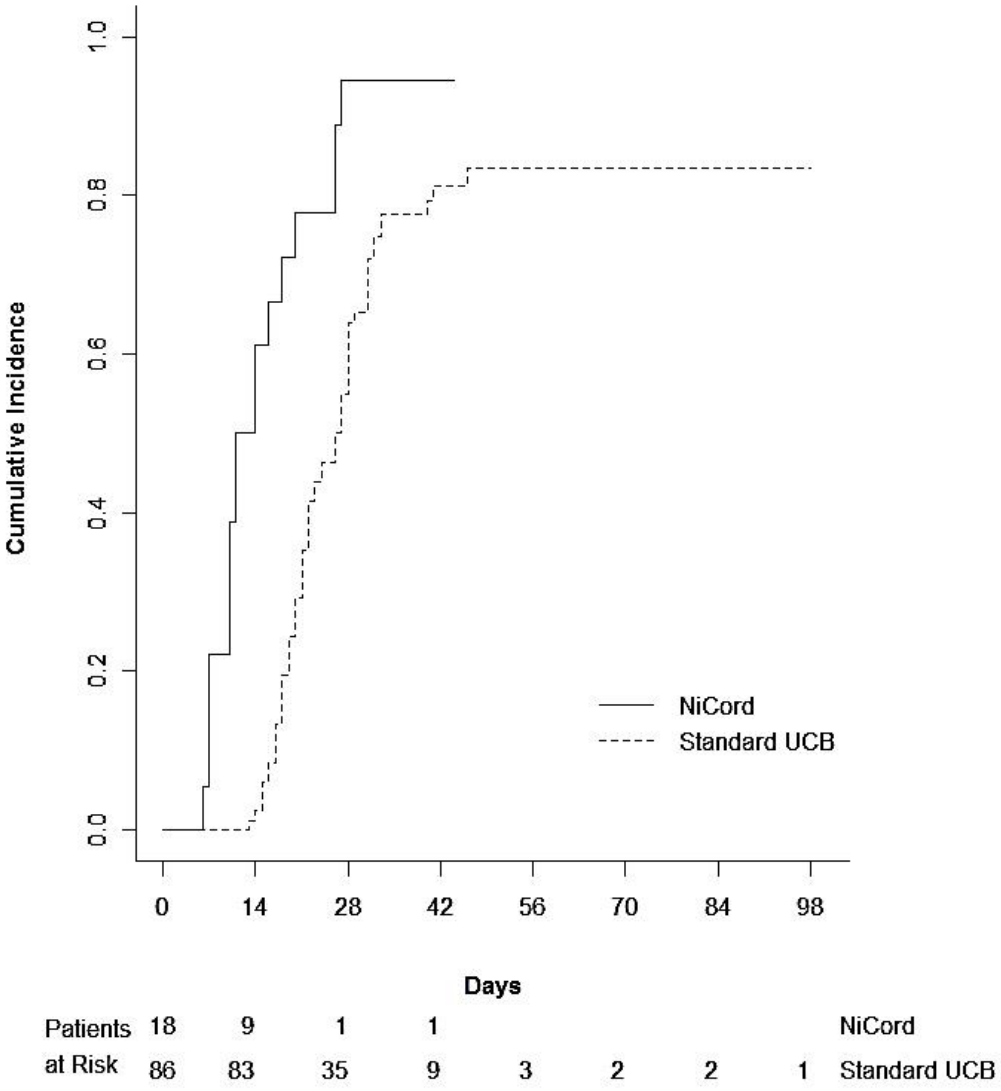

Figure 1: Cumulative incidence of time to ANC engraftment by study group (N=104).

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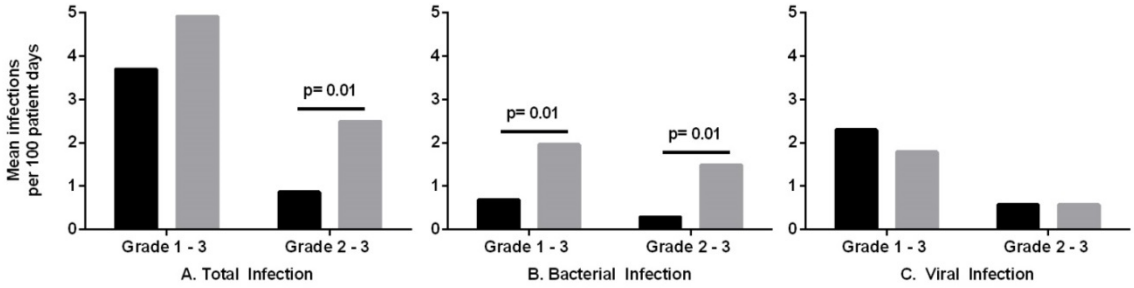

Figure 2: Infection density for total (A), bacterial (B), and viral (C) infections in NiCord (black) and standard UCB (gray) groups by infection grade.

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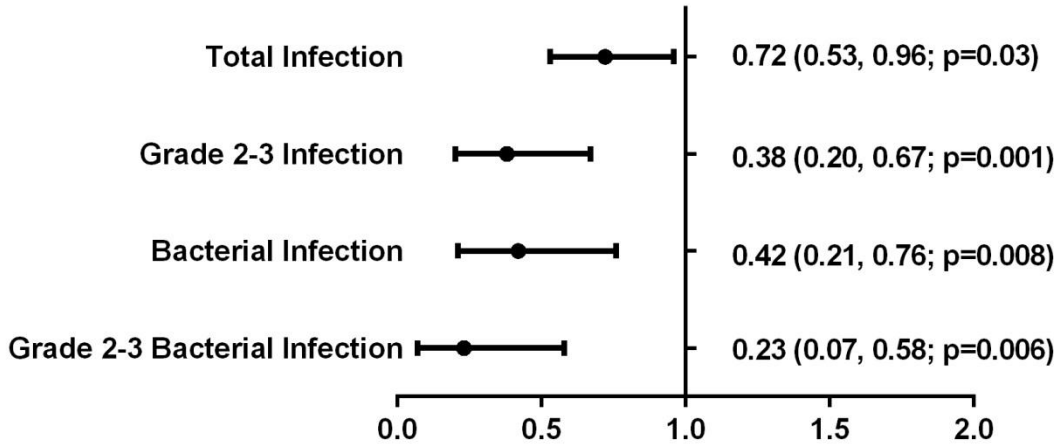

Figure 3: Adjusted risk ratio for infection in NiCord versus standard UCB (95% CI). Estimates are adjusted for age at transplant, disease status, and acute grade II-IV GVHD by Poisson regression analysis (N=104).

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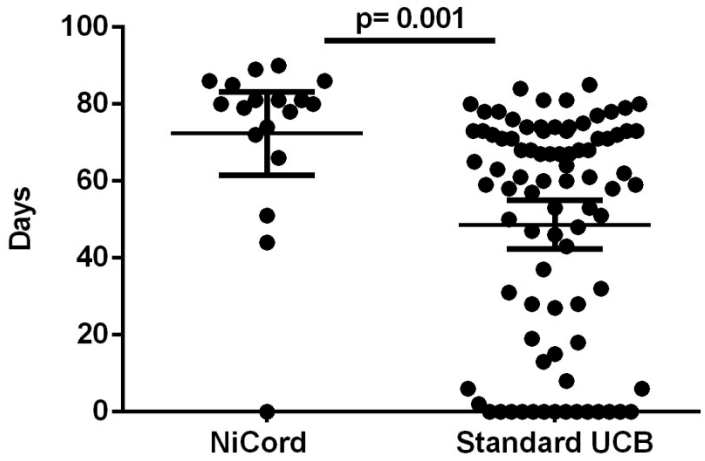

Figure 4: Days alive and out of the hospital in the first 100 days by study group (unadjusted mean; 95% CI). Each data point represents the number of days spent out of the hospital by an individual patient in the first 100 days. A value of zero indicates hospitalization during the entire 100 days or death during the initial hospital stay.

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Table 1: Patient Characteristics

	NiCord (N=18)	Standard UCB (N=86)	P
	N (%)	N (%)	
Age – Median (IQR)	45.5 (42 - 57)	37.5 (28 - 51)	0.007
Pre-Transplant Weight – Median (IQR)	91.15 (78 - 98.1)	77.628 (65.6 - 91.5)	0.42
Male Sex	8 (44.4%)	47 (54.7%)	0.45
CMV +	14 (77.8%)	47 (54.7%)	0.11
KPS – Median (IQR)	90 (80 - 90)	90 (80 - 90)	0.89
Transplant Diagnosis			1.00
Acute Leukemia/MDS	16 (88.9%)	77 (89.5%)	
Lymphoid Malignancy	2 (11.1%)	9 (10.5%)	
Non-Early Disease Status	10 (55.6%)	57 (66.3%)	0.42
UCB Type			<0.001
Single UCB	7 (38.9%)	4 (4.7%)	
Double UCB	11 (61.1%)	82 (95.3%)	
Conditioning			0.01
TBI+fludarabine	11 (61.1%)	46 (53.5%)	
TBI+fludarabine+cyclophosphamide	7 (38.9%)	17 (19.8%)	
TBI+fludarabine+thiotepa	0 (0%)	23 (26.7%)	
HLA Match			-
4/6	6 (33.3%)	4 (4.7%)	
4/6+4/6	5 (27.8%)	40 (46.5%)	
4/6+5/6	3 (16.7%)	15 (17.4%)	
4/6+6/6	1 (5.6%)	0 (0%)	
5/6+5/6	1 (5.6%)	19 (22.1%)	
5/6+6/6	1 (5.6%)	5 (5.8%)	
6/6	1 (5.6%)	0 (0%)	
6/6+6/6	0 (0%)	3 (3.5%)	
Cryo TNC ($x10^7$/kg) – Median (IQR)	5.1 (2.6 - 5.5)	4.7 (4.0 - 5.7)	0.17
Grade II-IV Acute GVHD	10 (55.6%)	36 (41.9%)	0.31
Second Transplant	1 (5.6%)	10 (11.6%)	0.68
Relapse	0 (0%)	6 (7%)	0.59
Death	1 (5.6%)	14 (16.3%)	0.46

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Table 2: Total Infection Episodes

Infections	NiCord (n=18)	Standard UCB (n=86)
Total episodes	58	285
Bacterial infection	11	96
Gram positive bacteremia	1	43
Coagulase negative Staphylococcus	1	13
Enterococcus species including VRE	0	8
MRSA	0	2
Viridans group Streptococcus	0	15
Other gram positive organisms	0	5
Gram negative bacteremia	2	11
Escherichia coli	0	3
Klebsiella species	0	2
Pseudomonas species	0	3
Stenotrophomonas maltophilia	1	2
Other gram negative organisms	1	1
Polymicrobial bacteremia	0	15
Clostridium difficile colitis	1	5
Other	7	22
Viral infection	37	120
CMV viremia[1]	11	32
CMV disease	1	4
HHV-6 viremia[2]	15	46
Other	10	38
Fungal infection	1	9
Invasive fungal infection	0	1
Fungemia	0	2
Other	1	6
Non-microbiologically defined infection	9	60
Uncomplicated fever with negative cultures	9	43
Pneumonia without an identified organism	0	17

[1] weekly PCR surveillance for CMV viremia during entire study period
[2] weekly PCR surveillance for HHV-6 viremia starting in 2010

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Table 3: Infection Density by Poisson Regression Analysis

Variable	Univariate Risk Ratio (95% CI)	P	Multivariate Risk Ratio (95% CI)	P
Total Infection Rate				
Study Group: NiCord vs. Standard UCB	0.69 (0.52, 0.91)	0.01	0.72 (0.53, 0.96)	0.03
Age at Transplant (Years)	0.99 (0.98, 1.00)	0.05	0.99 (0.99, 1.00)	0.26
Disease Status: Early vs. Non-Early	1.16 (0.93, 1.45)	0.19	0.93 (0.74, 1.17)	0.56
Grade II-IV Acute GVHD	0.71 (0.57, 0.88)	0.001	0.71 (0.57, 0.88)	0.002
Grade 2-3 Infection Rate				
Study Group: NiCord vs. Standard UCB	0.36 (0.19, 0.62)	<0.001	0.38 (0.20, 0.67)	0.001
Age at Transplant (Years)	0.98 (0.97, 1.00)	0.03	0.99 (0.98, 1.01)	0.34
Disease Status: Early vs. Non-Early	1.26 (0.89, 1.81)	0.20	0.88 (0.61, 1.27)	0.52
Grade II-IV Acute GVHD	0.54 (0.38, 0.75)	<0.001	0.54 (0.38, 0.75)	<0.001
Bacterial Infection Rate				
Study Group: NiCord vs. Standard UCB	0.39 (0.20, 0.69)	0.003	0.42 (0.21, 0.76)	0.008
Age at Transplant (Years)	0.99 (0.97, 1.00)	0.07	0.99 (0.97, 1.01)	0.31
Disease Status: Early vs. Non-Early	1.04 (0.71, 1.55)	0.84	1.08 (0.72, 1.61)	0.71
Grade II-IV Acute GVHD	0.57 (0.39, 0.83)	0.004	0.57 (0.39, 0.83)	0.004
Grade 2-3 Bacterial Infection Rate				
Study Group: NiCord vs. Standard UCB	0.21 (0.06, 0.51)	0.003	0.23 (0.07, 0.58)	0.006
Age at Transplant (Years)	0.98 (0.96, 1.00)	0.06	0.99 (0.97, 1.01)	0.32
Disease Status: Early vs. Non-Early	1.02 (0.63, 1.68)	0.93	1.11 (0.66, 1.85)	0.68
Grade II-IV Acute GVHD	0.50 (0.30, 0.81)	0.005	0.50 (0.30, 0.81)	0.005

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Table 4: Time Alive and Out of the Hospital in the First 100 Days by ANOVA/ANCOVA

	Change in Days Alive and Out of Hospital (95% CI)			
Variable	**Univariate Estimate**	**P**	**Multivariate Estimate**	**P**
Study Group: NiCord vs. Standard UCB	23.76 (9.55, 37.97)	0.001	20.17 (6.04, 34.31)	0.005
Age at Transplant (Years)	*0.55 (0.10, 1.00)	0.02	*0.34 (-0.10, 0.78)	0.13
Karnofsky Performance Status (KPS)	#6.02 (0.16, 11.87)	0.04	#5.88 (0.37, 11.39)	0.04

*change for every 1 year increase in age
#change for every 10 point increase in KPS

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