REGULAR ARTICLE

Increased overall and bacterial infections following myeloablative allogeneic HCT for patients with AML in CR1

Celalettin Ustun,[1] Soyoung Kim,[2,3] Min Chen,[2] Amer M. Beitinjaneh,[4] Valerie I. Brown,[5] Parastoo B. Dahi,[6] Andrew Daly,[7] Miguel Angel Diaz,[8] Cesar O. Freytes,[9] Siddhartha Ganguly,[10] Shahrukh Hashmi,[11,12] Gerhard C. Hildebrandt,[13] Hillard M. Lazarus,[14] Taiga Nishihori,[15] Richard F. Olsson,[16,17] Kristin M. Page,[18] Genovefa Papanicolaou,[19] Ayman Saad,[20] Sachiko Seo,[21] Basem M. William,[20] John R. Wingard,[22] Baldeep Wirk,[23] Jean A. Yared,[24] Miguel-Angel Perales,[25] Jeffery J. Auletta,[26-28] Krishna V. Komanduri,[4] Caroline A. Lindemans,[29,30] and Marcie L. Riches[31]

[1]Division of Hematology/Oncology/Cell Therapy, Rush University, Chicago, IL; [2]Center for International Blood and Marrow Transplant Research, Department of Medicine, and [3]Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI; [4]Department of Hematology, University of Miami, Miami, FL; [5]Division of Pediatric Oncology/Hematology, Department of Pediatrics, Penn State Hershey Children's Hospital and College of Medicine, Hershey, PA; [6]Department of Medicine, Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY; [7]Tom Baker Cancer Center, Calgary, AB, Canada; [8]Department of Hematology/Oncology, Hospital Infantil Universitario Nino Jesus, Madrid, Spain; [9]Texas Transplant Institute, San Antonio, TX; [10]Division of Hematological Malignancy and Cellular Therapeutics, University of Kansas Health System, Kansas City, KS; [11]Department of Internal Medicine, Mayo Clinic, Rochester, MN; [12]Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; [13]Markey Cancer Center, University of Kentucky, Lexington, KY; [14]Stem Cell Transplant Program, Division of Hematology and Oncology, Department of Medicine, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, OH; [15]Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [16]Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden; [17]Centre for Clinical Research Sörmland, Uppsala University, Uppsala, Sweden; [18]Division of Pediatric Blood and Marrow Transplantation, Duke University Medical Center, Durham, NC; [19]Infectious Diseases Service, Memorial Sloan Kettering Cancer Center, New York, NY; [20]Division of Hematology, The Ohio State University, Columbus, OH; [21]Department of Haematology and Oncology, Dokkyo Medical University, Tochigi, Japan; [22]Division of Hematology & Oncology, Department of Medicine, University of Florida, Gainesville, FL; [23]Division of Bone Marrow Transplant, Seattle Cancer Care Alliance, Seattle, WA; [24]Blood & Marrow Transplantation Program, Division of Hematology/Oncology, Department of Medicine, Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, MD; [25]Adult Bone Marrow Transplant Services, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [26]Blood and Marrow Transplant Program and [27]Host Defense Program, Division of Hematology, Oncology, and Blood Marrow & Transplant, and [28]Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, OH; [29]Pediatric Blood and Marrow Transplantation Program, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [30]Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands; and [31]Division of Hematology/Oncology, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Key Points

- MAC leads to significantly increased infections per 100 days at risk (infection density) compared with RIC/NMA in the first 100 days.

- These higher infection rates were caused by a significantly higher bacterial infection density in the MAC group.

Presumably, reduced-intensity/nonmyeloablative conditioning (RIC/NMA) for allogeneic hematopoietic cell transplantation (alloHCT) results in reduced infections compared with myeloablative conditioning (MAC) regimens; however, published evidence is limited. In this Center for International Blood and Marrow Transplant Research study, 1755 patients (aged ≥40 years) with acute myeloid leukemia in first complete remission were evaluated for infections occurring within 100 days after T-cell replete alloHCT. Patients receiving RIC/NMA (n = 777) compared with those receiving MAC (n = 978) were older and underwent transplantation more recently; however, the groups were similar regarding Karnofsky performance score, HCT–comorbidity index, and cytogenetic risk. One or more infections occurred in 1045 (59.5%) patients (MAC, 595 [61%]; RIC/NMA, 450 [58%]; $P = .21$) by day 100. The median time to initial infection after MAC conditioning occurred earlier (MAC, 15 days [range, <1-99 days]; RIC/NMA, 21 days [range, <1-100 days]; $P < .001$). Patients receiving MAC were more likely to experience at least 1 bacterial infection by day 100 (MAC, 46% [95% confidence interval (CI), 43-49]; RIC/NMA, 37% [95% CI, 34-41]; $P = .0004$), whereas at least a single viral infection was more prevalent in the RIC/NMA cohort (MAC, 34% [95% CI, 31-37]; RIC/NMA, 39% [95% CI, 36-42]; $P = .046$). MAC remained a risk factor for bacterial infections in multivariable analysis (relative risk, 1.44; 95% CI, 1.23-1.67; $P < .0001$). Moreover, the rate of any infection per patient-days at risk in the first 100 days (infection density) after alloHCT was greater for the MAC cohort (1.21; 95% CI, 1.11-1.32; $P < .0001$). RIC/NMA was associated with reduced infections, especially bacterial infections, in the first 100 days after alloHCT.

Introduction

Allogeneic hematopoietic cell transplantation (alloHCT) is increasingly used for the treatment of hematologic malignancies. Due to the development of nonmyeloablative (NMA) or reduced-intensity conditioning regimens (RICs), older patients and patients with comorbidities are more frequently offered alloHCT.[1-4] Overall survival seems similar in patients with hematologic malignancies after either a myeloablative (MAC) or an RIC/NMA regimen. However, an increased relapse is offset by a reduced nonrelapse mortality (NRM) and affects relapse-free survival.[5-14] Bacterial infections early after alloHCT are associated with increased mortality.[15] Factors associated with decreased infections after alloHCT include less mucositis,[16-19] shorter duration and decreased severity of neutropenia/lymphopenia,[16] and faster immune recovery,[20] all of which are observed more frequently with RIC/NMA than with MAC.[21,22] The incidence of infections, a common and often severe complication of alloHCT, is expected to be lower after RIC/NMA compared with MAC and thus contribute to the decreased NRM.[23-25]

In this large Center for International Blood and Marrow Transplant Research (CIBMTR) retrospective study, we compared the incidence and outcomes of bacterial, viral, and fungal infections occurring in the first 100 days after alloHCT in adult patients with acute myeloid leukemia (AML) in first complete remission receiving RIC/NMA or MAC.

Methods

The CIBMTR is a working group of >400 transplantation centers worldwide that contribute detailed data on HCT patients to the statistical center at the Medical College of Wisconsin. Participating centers are required to report all consecutive transplantations and to follow up patients longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality.

The CIBMTR performs observational studies in compliance with all applicable federal regulations pertaining to the protection of human research participants. The CIBMTR collects data at 2 levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. TED data include disease type, age, sex, pretransplantation disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow–derived and/or blood-derived stem cells), conditioning regimen, posttransplantation disease progression and survival, development of a new malignancy, and cause of death. All CIBMTR centers contribute TED data. A subset of registered patients selected by weighted randomization has CRF data that include more detailed disease and pretransplantation and posttransplantation clinical information, including infection data. TED- and CRF-level data are collected pretransplantation, 100 days and 6 months post-HCT, and annually thereafter or until death. The current analysis includes only CIBMTR CRF data. All patients provided written informed consent.

The Institutional Review Boards of the National Marrow Donor Program and the Medical College of Wisconsin approved this study.

Patients

The study population consisted of: (1) patients aged ≥40 years (patients aged <40 years were excluded, given that younger patients with AML were expected to receive a MAC but actually received an RIC most likely indicates an existent comorbid condition and would have led to inherent biases); (2) patients who received alloHCT for AML in first complete remission (to decrease heterogeneity in previous chemotherapy and thus in previous infectious exposures); and (3) patients whose data were reported to the CIBMTR between 2006 and December 2013. All T-replete donor sources (ie, sibling, unrelated donors, umbilical cord blood [UCB]) except haploidentical donors and all graft sources (ie, peripheral blood, bone marrow, UCB) were included. HLA matching criteria were defined as previously reported.[26] Previous alloHCT, ex vivo T-cell depletion, HIV seropositivity, ex vivo manipulated UCB, and UCB accompanied by another source of stem cells were excluded. There was no exclusion regarding conditioning regimen (eg, antithymocyte globulin [ATG], total body irradiation). Centers without patients in both the MAC and RIC/NMA categories were excluded to minimize center bias.

Definitions

Infection data reported to the CIBMTR are captured as a microorganism, site(s) of infection, and date of onset of infection. No information on symptoms, diagnostic criteria, or therapy of infection is collected. Infections are determined by the center as significant for reporting based on educational information and center-specific diagnostic test results. Because patients can have multiple infections, recurrent infections require a period of negative cultures, which differ by microrganism.[27] Furthermore, multiple infections require assessment of infection density determined by the number of infections per potential days at risk during the first 100 days after transplantation.[28] Conditioning intensity was determined by using standard criteria.[29] Neutropenia is defined as the time from transplantation until the absolute neutrophil count was >0.5 × 10^9/L for the first of 3 days after the nadir.

End points

The primary end point was the comparison of the incidence of any infection within the first 100 days posttransplantation based on conditioning intensity (MAC vs RIC/NMA). Secondary end points specifically compared the incidence of bacterial, viral, and fungal infections between conditioning intensities as well as infection density for total infections and according to microbial category to account for multiple infections.

Statistical analysis

Patient-, disease-, and treatment-related factors were compared by using the χ^2 test if variables were categorical or the Mann-Whitney U test if variables were continuous. Cumulative incidence of infection examined the first event of infection (overall) or according to the type of infection (viral, fungal or bacterial) using death as a competing risk. Poisson regression examined infection density as a ratio of MAC to RIC/NMA to account for multiple infections for both overall infections and according to microbial category.

A cause-specific hazards model was conducted for multivariable analysis for infections to handle competing risks and was examined for the primary and secondary outcomes of infection.[30] Variables examined in each model included the main effect variable (MAC vs RIC/NMA). Presumed risk factors for infection, including age, Karnofsky performance score, cytogenetic risk group, time from

Table 1. Patient characteristics in MAC and RIC/NMA groups

Variable	MAC (n = 978)	RIC/NMA (n = 777)	P
Male sex, n (%)	489 (50)	448 (58)	.0
Age, median (range), y	52 (40-71)	61 (41-81)	<.001
40-49	404 (41)	87 (11)	<.001
50-59	451 (46)	237 (31)	
≥60	123 (13)	453 (58)	
Performance score, n (%)			.269
<90	300 (31)	258 (33)	
≥90	662 (68)	502 (65)	
Missing	16 (2)	17 (2)	
HCT–comorbidity index, n (%)			.173
0	268 (27)	190 (24)	
1-2	221 (23)	179 (23)	
≥3	263 (27)	236 (30)	
Not collected (before 2007)	216 (22)	159 (20)	
Missing	10 (1)	13 (2)	
Presence of previous MDS, yes, n (%)	155 (16)	173 (22)	.003
Cytogenetic risk, n (%)			.31
Favorable	26 (3)	20 (3)	
Intermediate	608 (62)	469 (60)	
Poor	285 (29)	232 (30)	
Not tested	22 (2)	12 (2)	
Missing	37 (4)	44 (6)	
Time from diagnosis to AlloHCT, median (range), mo	5 (2-12)	5 (<1-13)	<.001
Donor/recipient HLA match, n (%)			<.001
Cord blood	88 (9)	169 (22)	
Matched related donor	381 (39)	216 (28)	
Well-matched unrelated	391 (40)	299 (38)	
Partially matched unrelated	94 (10)	66 (8)	
Mismatched unrelated	4 (< 1)	3 (< 1)	
Unrelated (HLA match information missing)	20 (2)	24 (3)	
Graft type, n (%)			<.001
Bone marrow	136 (14)	55 (7)	
Peripheral blood	754 (77)	553 (71)	
Cord blood	88 (9)	169 (22)	
GVHD prophylaxis, n (%)			<.001
TAC/CsA + MTX ± others (not MMF)	657 (67)	290 (37)	
TAC/CsA + MMF ± others (not MTX)	202 (21)	378 (49)	
TAC/CsA ± others (not MMF/MTX)	96 (10)	70 (9)	
Other GVHD prophylaxis*	23 (2)	39 (5)	
ATG/alemtuzumab as conditioning or GVHD prophylaxis, n (%)			<.001
ATG alone	236 (24)	276 (36)	
Alemtuzumab alone	6 (<1)	29 (4)	
No ATG or alemtuzumab	736 (75)	472 (61)	
Donor-recipient sex match, n (%)			.01
Male-male	321 (33)	294 (38)	

CsA, cyclosporine; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-monocyte colony-stimulating factor; MMF, mycophenolate mofetil; MTX, methotrexate; Tac, tacrolimus.

*Other GVHD prophylaxis: MMF ± others (MAC = 2, RIC/NMA = 6), sirolimus ± others (MAC = 4, RIC/NMA = 9), others (MAC = 17, RIC/NMA = 24).

Table 1. (continued)

Variable	MAC (n = 978)	RIC/NMA (n = 777)	*P*
Male-female	295 (30)	181 (23)	
Female-male	168 (17)	154 (20)	
Female-female	193 (20)	148 (19)	
Missing	1 (< 1)	0	
Donor-recipient CMV status, n (%)			.44
+/+	272 (28)	189 (24)	
+/−	92 (9)	76 (10)	
−/+	332 (34)	300 (39)	
−/−	269 (28)	200 (26)	
Missing	13 (1)	12 (2)	
Total body irradiation, yes, n (%)	300 (31)	312 (40)	<.001
Planned G-CSF, GM-CSF use, yes, n (%)	363 (37)	293 (38)	.29
History of clinically significant fungal infection, yes, n (%)	115 (12)	102 (13)	.67
Year of transplant, n (%)			<.001
2006-2007	216 (22)	159 (20)	
2008-2009	336 (34)	259 (33)	
2010-2011	236 (24)	143 (18)	
2012-2013	190 (19)	216 (28)	

CsA, cyclosporine; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-monocyte colony-stimulating factor; MMF, mycophenolate mofetil; MTX, methotrexate; Tac, tacrolimus.

*Other GVHD prophylaxis: MMF ± others (MAC = 2, RIC/NMA = 6), sirolimus ± others (MAC = 4, RIC/NMA = 9), others (MAC = 17, RIC/NMA = 24).

diagnosis to transplantation, HCT–comorbidity index, donor/recipient HLA match, use of total body irradiation, use of ATG/alemtuzumab, history of pre-HCT fungal infection, occurrence of neutrophil recovery before infection, and occurrence of acute graft-versus-host disease (GVHD) before infection, were examined in each model. For each bacterial, viral, and fungal infection, the other 2 infections are added as time-dependent covariates examined as occurring before the infection of interest. The stepwise selection method was used to identify significant risk factors associated with the outcomes. Factors significantly associated with the outcome variable at a 5% level were retained in the final model. Neutrophil recovery and acute GVHD were then tested as time-dependent covariates. If at least 1 of either neutrophil recovery or acute GVHD was significant and at least 1 of the other 2 infections was significant, the interaction between them was examined. The proportional hazards assumption was examined. If violated, the variable was reported as a time-dependent covariate. The center effect was examined by using the score test of Commenges and Andersen.[31] Interactions between the main effect and significant covariates were examined. In particular, an interaction between the main effect and recipient age was checked for all outcomes. Models using propensity scoring were examined, with outcomes similar to results of cause-specific modeling; therefore, only cause-specific models are reported.

Results

Patient characteristics and general outcomes

Table 1 shows the characteristics of the patient cohort. All patients had AML in first remission, with 978 patients receiving MAC and 777 patients receiving RIC/NMA. Patients receiving RIC/NMA were older and underwent transplantation more recently. The groups were similar regarding Karnofsky performance score, HCT–comorbidity index, and cytogenetic risk; however, patients receiving RIC/NMA had more frequent previous myelodysplastic syndrome (MDS). As pertains to infection risks, the groups had a similar frequency of fungal infection before alloHCT and planned use of growth factors but those receiving RIC/NMA had more in vivo T-cell depletion with either ATG or alemtuzumab.

Although the median time from diagnosis to transplantation for both MAC and RIC/NMA transplant recipients was 5 months, the ranges differed (2-12 months for MAC recipients and <1-13 months for RIC/NMA recipients), with 73% of the MAC group receiving their transplant <6 months from diagnosis vs 65% in the RIC/NMA group (*P* < .001). The median time to engraftment and GVHD, as well as the cumulative incidence of acute (grade II-IV) and chronic GVHD, is presented in Table 2. The median follow-up of survivors was longer after MAC (MAC, 59 months [range, 3-102 months]; RIC/NMA, 48 months [range, 3-105 months]; *P* = .002). At 1 year posttransplant, relapse predominated as the primary cause of death (MAC, 47%; RIC/NMA, 54%) (Table 3). Infection as a primary or contributing cause of death was reported in 33% of MAC patients and 25% of RIC/NMA patients.

Effect of conditioning regimen on posttransplantation infections by day 100

Of 1755 patients, 1045 (59.5%) patients (MAC, 595 [61%]; RIC/NMA, 450 [58%]; *P* = .21) experienced at least 1 infection. The median time to infection for patients after MAC conditioning

Table 2. Comparisons the MAC and RIC/NMA groups regarding engraftment and GVHD

Variable	MAC (n = 978)	RIC/NMA (n = 777)	P
Neutrophil recovery, median (range), d			
Time from transplant to engraftment	14 (1-111)	15 (<1-96)	.497
Acute GVHD grades II-IV			
Cumulative incidence (95% CI), %	38 (35-41)	31 (27-34)	.0011
Time from transplantation to acute GVHD grades II-IV, median (range), d	28 (7-176)	33 (9-177)	<.001
Chronic GVHD			
Cumulative incidence (95% CI), %	30 (27-33)	23 (20-26)	.0018
Time from transplantation to chronic GVHD, median (range), mo	6 (2-72)	6 (2-67)	.801

occurred at 15 days (range, <1-99 days) and was 21 days (range, <1-100 days) for the RIC/NMA cohort (P < .001) (Figure 1). The cumulative incidence of infections is shown in Figure 2. Patients receiving MAC had a greater probability of developing at least 1 bacterial infection by day 100 (cumulative incidence: MAC, 46% [95% confidence interval (CI), 43-49]; RIC/NMA, 37% [95% CI, 34-41]; P = .0004), whereas patients in the RIC/NMA cohort were more likely to develop at least 1 viral infection (MAC, 34% [95% CI, 31-37]; RIC/NMA, 39% [95% CI, 36-42]; P = .046). In addition, the rate of any infection, accounting for multiple infections, per patient days at risk in the first 100 days (infection density) after HCT was greater for the MAC cohort. Infection densities for broad subsets of bacterial, viral, and fungal infections are shown in Figure 3. The increased bacterial infections after MAC were due to gram-positive bacteria, and the increased viral infections in RIC/NMA were due to cytomegalovirus (CMV). Setting the mean of RIC/NMA infection rate at 1, the mean ratio of any infection in the MAC group was significantly higher at 1.21 (95% CI, 1.11-1.32) infections per patient in the first 100 days (P < .0001) (Figure 4). These higher infection rates were caused by a significantly higher bacterial infection density in the MAC group at 1.36 (95% CI, 1.21-1.54) bacterial infections per patient in the first 100 days (P < .0001). Fungal and viral infection rates were similar between the MAC and the RIC/NMA groups.

Risk factors for infection

In multivariable analysis (Table 4), a center effect was observed and adjusted for when assessing the risk of developing any infection and viral infections by day 100 but was not observed for either bacterial or fungal infection. Patients receiving MAC conditioning, compared with those receiving RIC/NMA conditioning, had a significantly increased risk of any infection, bacterial, fungal, or viral (relative risk [RR], 1.28; 95% CI, 1.11-1.48; P < .001) and bacterial infections (RR, 1.44; 95% CI, 1.23-1.67; P < .0001) but not viral (RR, 1.00; 95% CI, 0.82-1.21; P = .9930) or fungal (RR, 0.99; 95% CI, 0.64-1.54; P = .969) infections.

Additional factors associated with an increased risk of any infection include UCB as the stem cell source (RR, 1.81; 95% CI, 1.40-2.34; P < .0001), use of ATG/alemtuzumab (RR, 1.33; 95% CI, 1.13-1.55; P = .0004), HCT–comorbidity index ≥3 (RR, 1.19; 95% CI, 1.02-1.38; P = .0008), and development of acute GVHD grades II to IV (RR, 1.53; 95% CI, 1.33-1.77; P < .0001). In addition to MAC, there was an increased risk of bacterial infections for patients receiving UCB (RR, 1.57; 95% CI, 1.27-1.95; P ≤ .0001), having a previous viral infection (RR, 1.82; 95% CI 1.46-2.26; P < .0001),

or experiencing a previous fungal infection (RR, 2.13; 95% CI, 1.38-3.30; P = .0007). As expected, neutrophil recovery (ie, resolution of neutropenia due to engraftment) decreased the risk of bacterial infection (RR, 0.60; 95% CI, 0.44-0.81; P = .0009). An increased risk of viral infections was observed in patients with an HCT–comorbidity index ≥3 (RR, 1.26; 95% CI, 1.03-1.55; P = .0270), UCB (RR, 2.63; 95% CI, 2.06-3.35; P < .0001), partially matched/mismatched unrelated donors (RR, 1.46; 95% CI, 1.10-1.93; P = .0078), previous acute GVHD (RR, 1.73; 95% CI, 1.46-2.06; P < .0001), and previous bacterial infection (RR, 1.40; 95% CI, 1.18-1.67; P = .0002). In addition, patients receiving ATG/alemtuzumab had an increased risk of viral infections during the first 39 days posttransplantation (RR, 2.48; 95% CI, 1.94-3.15; P < .0001); however, by day 40, this negative impact was lost. Moreover, there was no interaction between conditioning intensity and ATG/alemtuzumab. For fungal infections, the risk increased for recipients of UCB (RR, 2.65; 95% CI, 1.41-5.00; P = .0026), those with previous bacterial infections (RR, 1.81; 95% CI, 1.41-2.89; P = .0119), or those with previous viral infections (RR, 2.17; 95% CI,

Table 3. Cause of death (COD) by 1 year posttransplantation

| COD	MAC	RIC/NMA
No. of deaths	275	301
Recurrent/persistent disease, n (%)	120 (44)	169 (56)
Infection as contributing COD, n	17	21
Infection, n (%)	47 (17)	38 (13)
GVHD	38 (14)	30 (10)
Infection as contributing COD, n	12	7
Organ Failure	45 (16)	31 (10)
Infection as contributing COD, n	10	6
Interstitial pneumonitis	9 (3)	2 (< 1)
Infection as contributing COD, n	2	0
Graft rejection	4 (1)	10 (3)
Infection as contributing COD, n	2	2
Secondary malignancy	1 (<1)	6 (2)
Infection as contributing COD, n	1	0
Hemorrhage	2 (<1)	6 (2)
Infection as contributing COD, n	1	0
Other cause, n (%)	5 (2)	7 (2)
Unknown, n (%)	4 (1)	2 (<1)
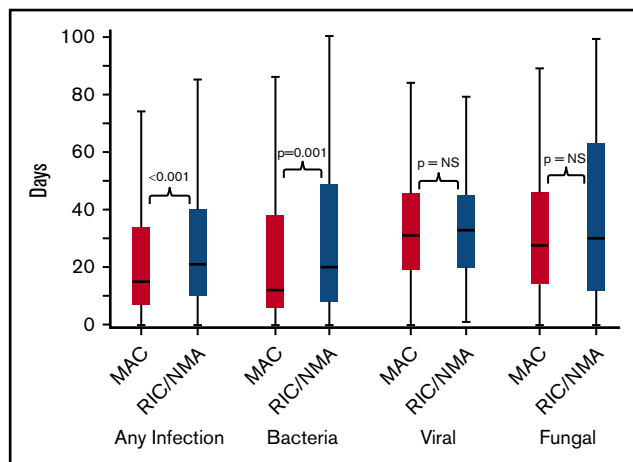
Figure 1. Time to infections. The median onset and interquartile range for development of infections (any, bacterial, viral, or fungal) comparing patients receiving MAC vs RIC/NMA conditioning. NS, not significant.

1.28-3.67; $P = .0038$) but was decreased with neutrophil recovery (RR, 0.37; 95% CI, 0.18-0.74; $P = .0053$). Total body irradiation was not associated with infections in multivariable analysis.

Discussion

Our data show that, for patients receiving alloHCT for AML in first remission, MAC was associated with greater infection events of any type (bacterial, fungal, or viral) in the first 100 days after transplantation. This effect was driven primarily by bacterial infections. Viral infections were slightly higher in patients receiving RIC/NMA conditioning, and fungal infections were similar regardless of conditioning intensity. Beyond conditioning intensity, additional risk factors for infection varied according to the infection examined, although receipt of a UCB graft and a previous infection of another type were consistent across the multivariable analyses.

A higher incidence of bacterial infections after MAC has been previously reported. Kim et al[32] reported that bacterial infections were higher during the entire follow-up period of ~700 days (14% vs 5%; $P = .012$) after MAC, whereas the incidence of fungal and viral infections was similar after MAC compared with RIC. That study reported that both bacterial infections preengraftment and from engraftment to day 100 were greater in the MAC group compared with the RIC group (8% vs 4% [$P = .269$] and 4% vs 0% [$P = .095$], respectively). Of note, cumulative incidence of infections was less common in the study of Kim et al than that of our study, perhaps due to a much younger population (median age, 35 years). Neutropenia is a known risk for bacterial infections. Although several studies have reported shortened time to
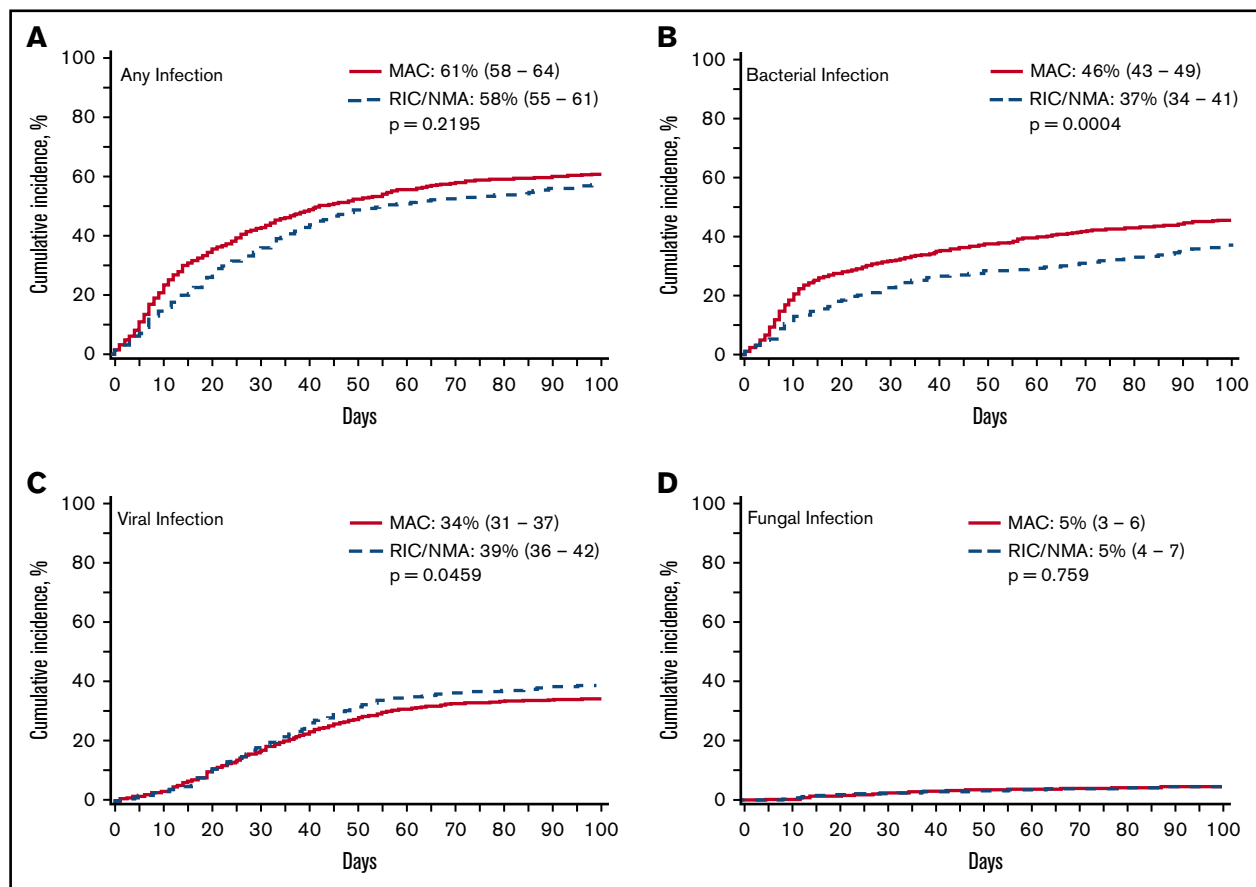

Figure 2. Incidence of infections. The cumulative incidence of any infection (A), bacterial infection (B), viral infection (C), and fungal infection (D) occurring by day 100 in patients receiving MAC or RIC/NMA conditioning.

Figure 3. Density of infections. Infection density for specific bacterial (A), viral (B), and fungal (C) infections according to conditioning intensity regimen. $**P \leq .001$. The remaining comparisons were not significant.
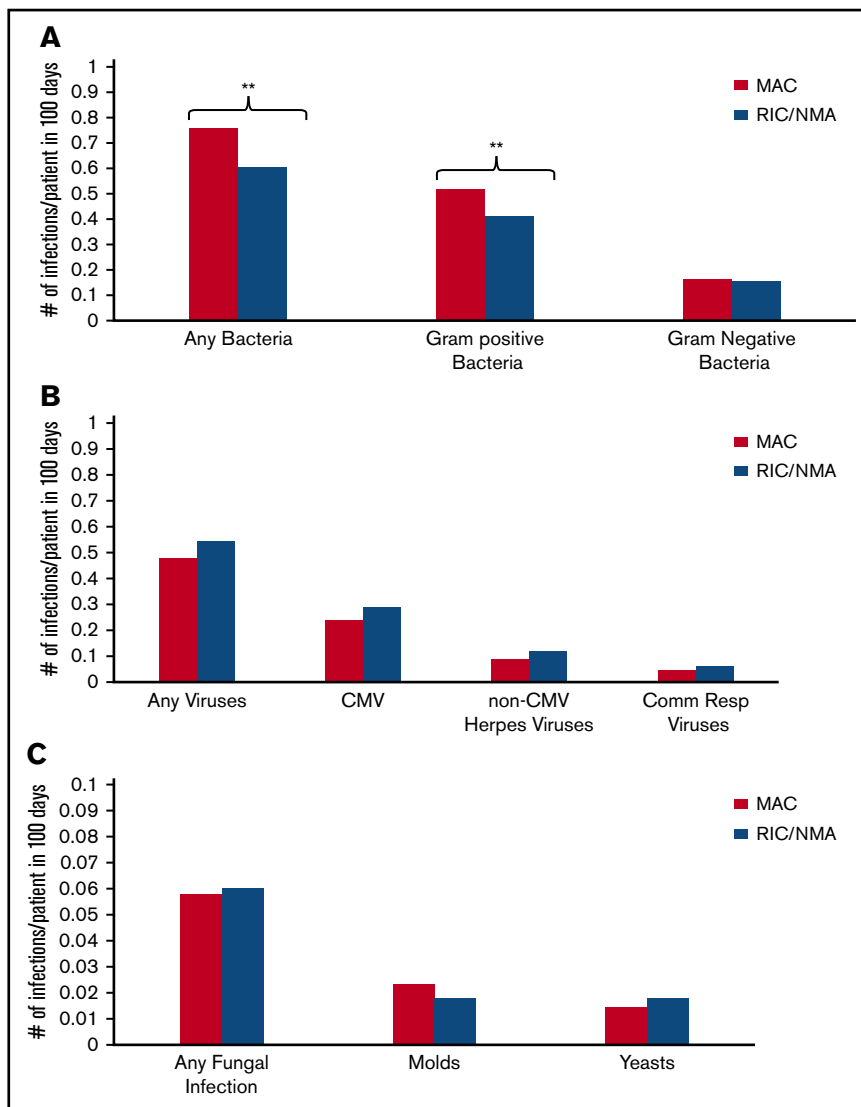
engraftment after RIC/NMA, our cohorts had a similar median time to neutrophil recovery.[6,33-36] However, the current data show that neutrophil recovery decreased the risk of bacterial infection by 40%. It is possible that bacterial infections are influenced not only by duration of neutropenia but also by the severity of neutropenia.[24,34] Unfortunately, the CIBMTR does not capture severity, only the time to neutrophil engraftment; severity was therefore not examined in this analysis. Interestingly, UCB, known to result in prolonged time to engraftment, was an independent risk factor for bacterial infections and corroborates a previously published CIBMTR analysis.[20,37] Another hypothesis for increased bacterial infections after MAC is that most early bacterial infections originate from gastrointestinal (GI) flora and that MAC causes increased mucosal damage in the GI tract.[36,38,39] Acute GVHD, reportedly more common with MAC compared with RIC,[5,7,8,40,41] might be another reason for more GI mucosal damage. Although our data showed an increased incidence of acute GVHD grades II to IV after MAC, the development of acute GVHD before an infection was associated with an increased risk of viral infections specifically, but it also increased the risk of any infection in the first 100 days. Our data indicate that these bacterial infections are driven by gram-positive organisms often associated with oropharyngeal flora rather than the gram-negative bacteria associated with lower GI tract damage. Consequently, the impact of mucosal damage from conditioning may be the driver for bacterial infection, whereas the increased immunosuppression associated with acute GVHD treatment may trigger the higher risk for viral infections.

We identified a slightly higher probability of developing a single viral infection by day 100 in the RIC/NMA group compared with the MAC group; however, the number of viral infections when accounting for multiple viral infections per patient per days at risk (infection density) was similar between the 2 groups. This result suggests that those patients receiving MAC and developing at least a single viral infection were either more likely to have multiple viral infections more frequently than the RIC/NMA group, that the days at risk in the RIC/NMA group were less because of early mortality, or a combination of both factors. The published data are conflicting regarding the effect of conditioning intensity on viral infections. Similar to our data, Satwani et al[42] reported that viral infections
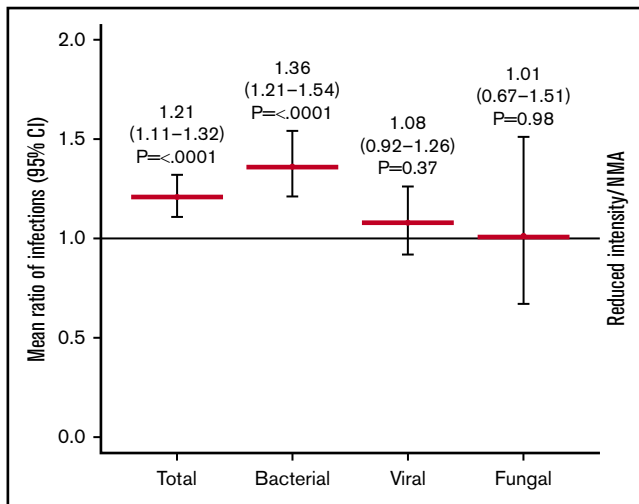
Figure 4. Relative ratio of density of infections. Infection density, defined as the number of infections according to type (overall, bacterial, viral, and fungal) based on the patient days at risk in the first 100 days. The Poisson regression normalizes the rate as a ratio with RIC/NMA at 1 and shows a higher risk of overall infections and bacterial infections in recipients of MAC in the first 100 days after alloHCT.

were not significantly affected by conditioning intensity in a pediatric cohort. However, when examining only CMV, a small, randomized prospective study reported that CMV infection was more common in patients receiving MAC (14 of 19) compared with RIC (6 of 18; $P = .02$).[19] Notably, a larger study found that CMV-seropositive recipients had less high-grade CMV viremia (CMV pp65 antigenemia >10/200 000 peripheral blood leukocytes or polymerase chain reaction [PCR] >1000 copies/mL) (hazard ratio, 0.7; 95% CI, 0.5-0.9; $P = .02$) after NMA than after MAC; however, there was no difference in overall CMV infection rates.[23] Although our study did not examine CMV alone, a comparison of the median infection density found similar rates of CMV infection after MAC and RIC/NMA conditioning. As expected, factors associated with increased immunosuppression were associated with viral infections by day 100. Interestingly, use of ATG or alemtuzumab as a component of conditioning or GVHD prophylaxis was nonproportional in the multivariable analysis and associated with early viral infections before 40 days; however, by 40 days after transplantation, the impact was lost. ATG use was reportedly associated with increased NRM in a previous CIBMTR study.[43] Furthermore, the development of acute GVHD preceding infection was associated with increased risk of viral infections, most likely due to the initiation or addition of immunosuppression to treat the episode of acute GVHD, as well as the innate immune dysfunction associated with GVHD precluding the patient from clearing a viral infection and/or preventing viral reactivation.

Fungal infections, fortunately, remain a rare event in the first 3 months after transplantation, with a similar occurrence regardless of conditioning intensity. In accordance with our data, other studies have not identified a difference in fungal infections or an increased risk of atypical mold infections based on conditioning intensity.[42,44] Notable factors that contributed include receipt of UCB and lack of neutrophil recovery by the time of infection. Furthermore, a previous bacterial infection and a previous viral infection both resulted in an increased risk of subsequent fungal infection. Congruent with our

data, Yong et al[45] previously reported that previous CMV reactivation is associated with risk of invasive fungal infection (IFI). This association may simply sow profound immune compromise, although it is notable that neither ATG or alemtuzumab use nor preceding acute GVHD was associated with an increased risk of fungal infection. However, this scenario may simply be a function of too few events. Preexisting IFIs are a known risk factor for posttransplantation IFI and increased mortality.[46] In the current study, the numbers of pre-HCT fungal infections were small and similar in each conditioning cohort, potentially accounting for the lack of significance in the multivariable analysis. However, in a CIBMTR study examining the impact of pretransplantation IFI, Maziarz et al[46] reported a greater likelihood of experiencing a posttransplantation IFI in patients with preexisting IFI compared with those with no history of IFI (RR, 1.35; 95% CI, 1.16-1.58; $P = .001$). Notably, conditioning intensity was not an independent risk factor for posttransplantation IFI in that the analysis enriched for patients with pretransplantation IFI.

Our study has limitations. One significant limitation is examination of infections occurring only in the first 100 days. However, the differences in infections mediated by conditioning intensity are expected to occur early, in the peri-transplantation period. Other studies have shown that very early (first 30 days) infections were less common after RIC/NMA compared with MAC but that this differences does not persist.[34,35,47] Junghanss et al[34] reported that NMA was associated with fewer episodes of bacteremia during the first 30 days (9% vs 27%; $P = .01$) and a trend to fewer episodes of bacteremia during the first 100 days posttransplantation (27% vs 41%; $P = .7$). Later infections from ongoing immunocompromise are likely similar, regardless of initial conditioning intensity. As patients leave the transplantation center, common infections such as bacterial pneumonia and viral upper respiratory tract infections are less likely to be reported back to the transplantation center and, consequently, to the CIBMTR, which therefore necessitated the truncation of infections by day 100 for this analysis. The current study did not examine the impact of these infections on survival specifically. This approach was chosen to focus on the frequency and likelihood of infections, in total and by broad category, after these 2 conditioning intensities. However, infection as the reported primary cause of death by 1 year after HCT was similar (MAC, 17%; RIC/NMA, 13%) in our cohorts. Finally, we do not have detailed information regarding antimicrobial prophylaxis, severity of infection, or treatment of infection. In addition, diagnostic criteria for infection or reactivation, such as PCR viral loads, are not available. The prophylaxis data, in particular, may alter frequency of infection. To account for these, our data set was limited to centers with patients in both the MAC and RIC/NMA cohorts because centers would be expected to have fairly uniform antimicrobial prophylaxis regimens, indications for treatment based on viral load PCRs, and antimicrobial management. Furthermore, we also assessed for a center effect to account for potential biases of these unavailable, but pertinent, data. Although patients in the RIC/NMA group had more previous MDS and we did not examine directly its effect, time to transplantation was not significant for any infection in the multivariable analysis.

In conclusion, RIC/NMA alloHCT is associated with a decreased risk of any infection and particularly early bacterial infections. The risk of viral and fungal infections per days at risk is similar. Furthermore, a preceding infection of one type (bacterial/fungal/viral) increases the likelihood of subsequent infection. Recipients of UCB have increased risk of all types of infection. In the future, efforts to modify conditioning regimens, perhaps with more targeted

Table 4. Multivariable analysis for risk factors for development of infections

Variable	n	RR of infection (95% CI)	P
Any infection (bacterial/viral/fungal)*			
Main effect variable			.0006
RIC/NMA	777	1.00	
MAC	978	1.28 (1.11-1.48)	
HCT−comorbidity index			<.0001
0	458	1.00	
1-2	400	1.14 (0.96-1.36)	.1318
≥3	499	1.19 (1.02-1.38)	.0261
NA (before 2007)	375	0.70 (0.57-0.86)	.0008
Missing	23	1.28 (0.77-2.14)	.3335
Donor/recipient HLA match			<.0001
HLA-identical related donor	597	1.00	
UCB	257	1.81 (1.40-2.34)	<.0001
Well-matched unrelated	690	0.97 (0.80-1.18)	.7708
Partially matched/mismatched unrelated	167	1.19 (0.95-1.49)	.187
Unrelated—match unknown	44	1.68 (1.20-2.35)	.0024
ATG/alemtuzumab peri-HCT			.0004
No	1208	1.00	
Yes	547	1.33 (1.13-1.55)	
Acute GVHD grades II-IV before infection			<.0001
No	1135	1.00	
Yes	620	1.53 (1.33-1.77)	
Bacterial infection			
Main effect variable			<.0001
RIC/NMA	777	1.00	
MAC	978	1.44 (1.23-1.67)	
Donor/recipient HLA match			<.0001
HLA-identical related donor	597	1.00	
UCB	257	1.57 (1.27-1.95)	<.0001
Well-matched unrelated	690	0.90 (0.76 −1.08)	.2531
Partially matched/mismatched unrelated	167	1.00 (0.76-1.30)	.9752
Unrelated—match unknown	44	0.70 (0.41-1.20)	.1937
Neutrophil engraftment before infection			.0009
No	396	1.00	
Yes	1359	0.60 (0.44-0.81)	
Viral infection before bacterial infection			<.0001
No	1323	1.00	
Yes	432	1.82 (1.46-2.26)	
Fungal infection before bacterial infection			.0007
No	1706	1.00	
Yes	49	2.13 (1.38-3.30)	
Viral infection*			
Main effect variable			.9930
RIC/NMA	777	1.00	
MAC	978	1.00 (0.82-1.21)	

Table 4. (continued)

Variable	n	RR of infection (95% CI)	P
HCT−comorbidity index			.0001
0	458	1.00	
1-2	400	1.09 (0.85-1.40)	.5118
≥3	499	1.26 (1.03-1.55)	.0270
NA (before 2007)	375	0.62 (0.45-0.86)	.0036
Missing	23	1.45 (0.88-2.38)	.1495
Donor/recipient HLA match			<.0001
HLA-identical related donor	597	1.00	
UCB	257	2.63 (2.06-3.35)	<.0001
Well-matched unrelated	690	1.19 (0.96-1.49)	.1152
Partially matched/mismatched unrelated	167	1.46 (1.10-1.93)	.0078
Unrelated—match unknown	44	2.50 (1.52-4.11)	.0003
ATG/alemtuzumab peri-HCT, ≤39 d			<.0001
No	1208	1.00	
Yes	547	2.48(1.94-3.15)	
ATG/alemtuzumab peri-HCT, >39 d			.8328
No	1417	1.00	
Yes	338	1.03 (0.77-1.38)	
Acute GVHD grades II-IV before infection			<.0001
No	1116	1.00	
Yes	639	1.73 (1.46-2.06)	
Bacterial infection before viral infection			.0002
No	1140	1.00	
Yes	615	1.40 (1.18-1.67)	
Fungal infection			
Main effect variable			.9696
RIC/NMA	777	1.00	
MAC	978	0.99 (0.64-1.54)	
Donor/recipient HLA match			.0226
HLA-identical related donor	597	1.00	
UCB	257	2.65 (1.41-5.00)	.0026
Well-matched unrelated	690	1.31 (0.72-2.38)	.3684
Partially matched/mismatched unrelated	167	1.49 (0.65-3.44)	.3467
Unrelated—match unknown	44	2.74 (0.92-8.15)	.0708
Neutrophil engraftment before infection			.0053
No	65	1.00	
Yes	1690	0.37 (0.18-0.74)	
Bacterial infection before viral infection			.0119
No	1037	1.00	
Yes	718	1.81 (1.14-2.89)	
Viral infection before bacterial infection			.0038
No	1135	1.00	
Yes	620	2.17 (1.28-3.67)	

*Center effect identified.

therapies with less toxicity, may decrease infections, especially bacterial infections. Moreover, antibiotic prophylaxis might be modified by conditioning intensity.

Authorship

Contribution: C.U., M.L.R., C.A.L., K.V.K., J.J.A., S.K., and M.C. conceived the study and its design; S.K. and M.C. performed the statistical analysis; C.U., M.L.R., C.A.L., K.V.K., J.J.A., S.K., and M.C. analyzed and interpreted the data; C.U., M.L.R., and C.A.L. drafted the manuscript; and all authors contributed patients to the CIBMTR for data acquisition, and all authors revised the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: C.U., 0000-0001-6896-6213; S.K., 0000-0003-1404-0575; C.O.F., 0000-0003-2880-6797; S.H., 0000-0002-8914-7927; G.C.H., 0000-0003-0478-3340; H.M.L., 0000-0002-1159-5607; T.N., 0000-0002-2621-7924; R.F.O., 0000-0001-5970-2128; A.S., 0000-0003-0003-0130; J.A.Y., 0000-0002-5346-6299; K.V.K., 0000-0003-3715-5236; M.L.R., 0000-0003-0257-0990.

Correspondence: Celalettin Ustun, Rush University, 1725 W Harrison St, Suite 834, Chicago, IL 60612; e-mail: celalettin_ustun@rush.edu.

References

1. Ustun C, Lazarus HM, Weisdorf D. To transplant or not: a dilemma for treatment of elderly AML patients in the twenty-first century. *Bone Marrow Transplant*. 2013;48(12):1497-1505.

2. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)–specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106(8):2912-2919.

3. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA*. 2011;306(17):1874-1883.

4. Sandhu KS, Brunstein C, DeFor T, et al. Umbilical cord blood transplantation outcomes in acute myelogenous leukemia/myelodysplastic syndrome patients aged ≥70 years. *Biol Blood Marrow Transplant*. 2016;22(2):390-393.

5. Luger SM, Ringdén O, Zhang MJ, et al. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. *Bone Marrow Transplant*. 2012;47(2):203-211.

6. Flynn CM, Hirsch B, Defor T, et al. Reduced intensity compared with high dose conditioning for allotransplantation in acute myeloid leukemia and myelodysplastic syndrome: a comparative clinical analysis. *Am J Hematol*. 2007;82(10):867-872.

7. Abdul Wahid SF, Ismail NA, Mohd-Idris MR, et al. Comparison of reduced-intensity and myeloablative conditioning regimens for allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia and acute lymphoblastic leukemia: a meta-analysis. *Stem Cells Dev*. 2014;23(21):2535-2552.

8. Aoudjhane M, Labopin M, Gorin NC, et al; Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). *Leukemia*. 2005;19(12):2304-2312.

9. Ustun C, Courville E, DeFor T, et al. Myeloablative, but not reduced-intensity, conditioning overcomes the negative effect of flow-cytometric evidence of leukemia in acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2016;22(4):669-675.

10. Diaconescu R, Flowers CR, Storer B, et al. Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. *Blood*. 2004;104(5):1550-1558.

11. Shimoni A, Hardan I, Shem-Tov N, et al. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. *Leukemia*. 2006;20(2):322-328.

12. Alyea EP, Kim HT, Ho V, et al. Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. *Blood*. 2005;105(4):1810-1814.

13. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35(11):1154-1161.

14. Ustun C, Wiseman AC, Defor TE, et al. Achieving stringent CR is essential before reduced-intensity conditioning allogeneic hematopoietic cell transplantation in AML [published correction appears in *Bone Marrow Transplant*. 2013;48(11): 1488]. *Bone Marrow Transplant*. 2013;48(11): 1415-1420.

15. Ustun C, Young JH, Papanicolaou GA, et al. Bacterial blood stream infections (BSIs), particularly post-engraftment BSIs, are associated with increased mortality after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2019;54(8):1254-1265.

16. Facchini L, Martino R, Ferrari A, et al. Degree of mucositis and duration of neutropenia are the major risk factors for early post-transplant febrile neutropenia and severe bacterial infections after reduced-intensity conditioning. *Eur J Haematol*. 2012;88(1):46-51.

17. Kashiwazaki H, Matsushita T, Sugita J, et al. A comparison of oral mucositis in allogeneic hematopoietic stem cell transplantation between conventional and reduced-intensity regimens. *Support Care Cancer*. 2012;20(5):933-939.

18. Takahashi K, Soga Y, Murayama Y, et al. Oral mucositis in patients receiving reduced-intensity regimens for allogeneic hematopoietic cell transplantation: comparison with conventional regimen. *Support Care Cancer*. 2010;18(1):115-119.

19. Ringdén O, Erkers T, Aschan J, et al. A prospective randomized toxicity study to compare reduced-intensity and myeloablative conditioning in patients with myeloid leukaemia undergoing allogeneic haematopoietic stem cell transplantation. *J Intern Med*. 2013;274(2):153-162.

20. Ballen K, Woo Ahn K, Chen M, et al. Infection rates among acute leukemia patients receiving alternative donor hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2016;22(9):1636-1645.

21. Larosa F, Marmier C, Robinet E, et al. Peripheral T-cell expansion and low infection rate after reduced-intensity conditioning and allogeneic blood stem cell transplantation. *Bone Marrow Transplant*. 2005;35(9):859-868.

22. Busemann C, Wilfert H, Neumann T, Kiefer T, Dölken G, Krüger WH. Mucositis after reduced intensity conditioning and allogeneic stem cell transplantation. *Onkologie*. 2011;34(10):518-524.

23. Nakamae H, Kirby KA, Sandmaier BM, et al. Effect of conditioning regimen intensity on CMV infection in allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2009;15(6):694-703.

24. Frère P, Baron F, Bonnet C, et al. Infections after allogeneic hematopoietic stem cell transplantation with a nonmyeloablative conditioning regimen. *Bone Marrow Transplant*. 2006;37(4):411-418.

25. Meijer E, Dekker AW, Lokhorst HM, Petersen EJ, Nieuwenhuis HK, Verdonck LF. Low incidence of infectious complications after nonmyeloablative compared with myeloablative allogeneic stem cell transplantation. *Transpl Infect Dis*. 2004;6(4):171-178.

26. Weisdorf D, Spellman S, Haagenson M, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. *Biol Blood Marrow Transplant*. 2008;14(7):748-758.

27. CIBMTR. Forms infection manual. The Medical College of Wisconsin, Inc. and the National Marrow Donor Program; 2015. https://www.cibmtr.org/manuals/fim/1/en/topic/f2100-q428-440. Accessed 4 April 2019.

28. Tomblyn M, Young JA, Haagenson MD, et al; CIBMTR Infection and Immune Reconstitution Working Committee. Decreased infections in recipients of unrelated donor hematopoietic cell transplantation from donors with an activating KIR genotype. *Biol Blood Marrow Transplant*. 2010;16(8):1155-1161.

29. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15(12): 1628-1633.

30. Dignam JJ, Zhang Q, Kocherginsky M. The use and interpretation of competing risks regression models. *Clin Cancer Res*. 2012;18(8):2301-2308.

31. Commenges D, Andersen PK. Score test of homogeneity for survival data. *Lifetime Data Anal*. 1995;1(2):145-156, NaN-159.

32. Kim SH, Kee SY, Lee DG, et al. Infectious complications following allogeneic stem cell transplantation: reduced-intensity vs. myeloablative conditioning regimens. *Transpl Infect Dis*. 2013;15(1):49-59.

33. Ringdén O, Labopin M, Ehninger G, et al. Reduced intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukemia. *J Clin Oncol*. 2009;27(27):4570-4577.

34. Junghanss C, Marr KA, Carter RA, et al. Incidence and outcome of bacterial and fungal infections following nonmyeloablative compared with myeloablative allogeneic hematopoietic stem cell transplantation: a matched control study. *Biol Blood Marrow Transplant*. 2002;8(9):512-520.

35. Bachanova V, Brunstein CG, Burns LJ, et al. Fewer infections and lower infection-related mortality following non-myeloablative versus myeloablative conditioning for allotransplantation of patients with lymphoma. *Bone Marrow Transplant*. 2009;43(3):237-244.

36. Khabori MA, El-Emary M, Xu W, et al. Impact of intensity of conditioning therapy in patients aged 40-60 years with AML/myelodysplastic syndrome undergoing allogeneic transplantation. *Bone Marrow Transplant*. 2011;46(4):516-522.

37. Brunstein CG, Gutman JA, Weisdorf DJ, et al. Allogeneic hematopoietic cell transplantation for hematologic malignancy: relative risks and benefits of double umbilical cord blood. *Blood*. 2010;116(22):4693-4699.

38. Johansson JE, Brune M, Ekman T. The gut mucosa barrier is preserved during allogeneic, haemopoietic stem cell transplantation with reduced intensity conditioning. *Bone Marrow Transplant*. 2001;28(8):737-742.

39. Shigematsu A, Yasumoto A, Yamamoto S, et al. Regimen-related mucosal injury of the gut increased the incidence of CMV disease after allogeneic bone marrow transplantation. *Biol Blood Marrow Transplant*. 2009;15(6):679-685.

40. Pérez-Simón JA, Díez-Campelo M, Martino R, et al. Influence of the intensity of the conditioning regimen on the characteristics of acute and chronic graft-versus-host disease after allogeneic transplantation. *Br J Haematol*. 2005;130(3):394-403.

41. Lazaryan A, Weisdorf DJ, DeFor T, et al. Risk factors for acute and chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation with umbilical cord blood and matched sibling donors. *Biol Blood Marrow Transplant*. 2016;22(1):134-140.

42. Satwani P, Baldinger L, Freedman J, et al. Incidence of viral and fungal infections following busulfan-based reduced-intensity versus myeloablative conditioning in pediatric allogeneic stem cell transplantation recipients. *Biol Blood Marrow Transplant*. 2009;15(12):1587-1595.

43. Soiffer RJ, Lerademacher J, Ho V, et al. Impact of immune modulation with anti-T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies. *Blood*. 2011;117(25):6963-6970.

44. Riches ML, Trifilio S, Chen M, et al. Risk factors and impact of non-Aspergillus mold infections following allogeneic HCT: a CIBMTR infection and immune reconstitution analysis [published correction appears in *Bone Marrow Transplant*. 2016;51(2): 322]. *Bone Marrow Transplant*. 2016;51(2):277-282.

45. Yong MK, Ananda-Rajah M, Cameron PU, et al. Cytomegalovirus reactivation is associated with increased risk of late-onset invasive fungal disease after allogeneic hematopoietic stem cell transplantation: a multicenter study in the current era of viral load monitoring. *Biol Blood Marrow Transplant*. 2017; 23(11):1961-1967.

46. Maziarz RT, Brazauskas R, Chen M, et al. Pre-existing invasive fungal infection is not a contraindication for allogeneic HSCT for patients with hematologic malignancies: a CIBMTR study. *Bone Marrow Transplant*. 2017;52(2):270-278.

47. Hori A, Kami M, Kim SW, et al. Development of early neutropenic fever, with or without bacterial infection, is still a significant complication after reduced-intensity stem cell transplantation. *Biol Blood Marrow Transplant*. 2004;10(1):65-72.