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Effectiveness of Bath Wipes After Hematopoietic Cell Transplantation: A Randomized Trial

Margie Kjellin, MSN[1], Amr Qudeimat, MD[1], Emily Browne, DNP[1], Dinesh Keerthi, MS[1], Anusha Sunkara, MS[1], Guolian Kang, PhD[1], Alicia Winfield, CRRP[1], Mary Anne Giannini, MT[1], Gabriela Maron, MD[1], Randall Hayden, MD[1], Wing Leung, MD, PhD[1,2], Brandon Triplett, MD[1,2], and Ashok Srinivasan, MD[1,2]

Abstract

Objective: Bacteremia is a leading cause of morbidity and mortality in children undergoing hematopoietic cell transplantation (HCT). Infections of vancomycin-resistant enterococci (VRE) and multidrug resistant (MDR) gram-negative rods (GNRs) are common in this population. Our objective was to assess whether experimental bath wipes containing silver were more effective than standard bath wipes containing soap at reducing skin colonization by VRE and MDR GNRs, and nonmucosal barrier injury bacteremia. **Study Design:** Patients undergoing autologous or allogeneic HCT in a tertiary referral center were randomized to receive experimental or standard bath wipes for 60 days post-HCT. Skin swabs were collected at baseline, discharge, and day +60 post-HCT. The rate of VRE colonization was chosen as the marker for efficacy. **Results:** Experimental bath wipes were well tolerated. Before the study, the rate of colonization with VRE in HCT recipients was 25%. In an interim analysis of 127 children, one (2%) patient in the experimental arm and two (3%) in the standard arm were colonized with VRE. Two (3%) patients had nonmucosal barrier injury bacteremia in the standard arm, with none in the experimental arm. MDR GNRs were not isolated. The trial was halted because the interim analyses indicated equivalent efficacy of the two methods. **Conclusions:** Skin cleansing with silver-containing or standard bath wipes resulted in very low and equivalent rates of bacteremia and colonization with VRE and MDR GNRs in children post-HCT. Future studies in other high-risk populations are needed to confirm these results.

Keywords

hematopoietic stem cell transplantation (HSCT), infection, pediatric, safety

Introduction

Health care–associated infections have substantial morbidity, mortality, and cost burden in children undergoing hematopoietic cell transplantation (HCT; Dandoy et al., 2016; Srinivasan et al., 2013; Wilson et al., 2014). The incidence of colonization with vancomycin-resistant enterococci (VRE), and multidrug resistant (MDR) gram-negative rods (GNRs) in HCT recipients is rapidly increasing (Ford et al., 2017; Girmenia et al., 2015). Colonization with VRE and MDR GNRs increases the risk of bacteremia and nonrelapse mortality and decreases overall survival (Bilinski et al., 2016; Ford et al., 2017; Girmenia et al., 2015; Poutsiaka et al., 2007).

Nonmucosal barrier injury (non-MBI) bacteremia is often caused by the patient's own skin flora. Hence, skin decontamination is expected to decrease the risk of infection. Daily bathing with chlorhexidine gluconate compared with standard bathing practices reduced bacteremia in critically ill children (Milstone et al., 2013). However, chlorhexidine is not tolerated by patients with skin graft-versus-host disease (GVHD), which is common after HCT. Increased bacterial resistance to chlorhexidine has been reported (Wand et al., 2017). Strategies to limit pathogen transmission have focused on improving the adherence of health care workers to

[1]St. Jude Children's Research Hospital, Memphis, TN, USA
[2]University of Tennessee Health Science Center, Memphis, TN, USA

Corresponding Author:
Margie Kjellin, Department of Nursing, St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS 1540, Memphis, TN 38105-3678, USA.
Email: margie.kjellin@stjude.org

recommended infection control practices. However, these measures require scrupulous adherence by numerous personnel and can be difficult to sustain (Siegel et al., 2007). Levofloxacin prophylaxis has not been effective in reducing bacteremia in children undergoing HCT (Alexander et al., 2018).

The emergence and persistence of MDR GNRs have led to renewed interest in the antimicrobial properties of silver. Silver-coated dressings suppress microbial infection in burn wounds (Yabanoglu et al., 2013). Resistance to silver is uncommon, and these dressings are well tolerated (Klasen, 2000). Therefore, we hypothesized that experimental bath wipes containing silver would be safe and reduce colonization by VRE and MDR GNRs and non-MBI bacteremia in children undergoing HCT.

Method

Study Design

Patients ≤21 years of age on the date of enrollment who were scheduled to undergo an autologous or allogeneic HCT were eligible to participate in a randomized controlled trial (RCT) at St. Jude Children's Research Hospital (St. Jude), Memphis, Tennessee, from October 2014 to September 2017 (both inclusive), which compared experimental and standard bath wipes for skin cleansing. The study excluded females who were pregnant or lactating as well as participants (or parents) who did not provide written informed consent. The study was approved by the St. Jude Institutional Review Board.

The primary objectives were to assess the safety of experimental bath wipes in the first 12 patients enrolled, and skin colonization with VRE and MDR GNRs, and rates of non-MBI bacteremia in all patients. Other objectives included comparing the incidence of acute skin GVHD, and parent and patient satisfaction with experimental and standard bath wipes. Acute skin GVHD was assessed by using consensus criteria (Przepiorka et al., 1995).

The trial was registered under *ClinicalTrials.gov* NCT02241005. Patients were randomized to receive either experimental or standard bath wipes at a 1:1 ratio from the Division of Nursing Research. Investigators, physicians, nurse practitioners, and clinical research staff were blinded to the randomization. Both types of wipes were packaged in a similar manner but differed in texture. Bath wipes were started on the day of admission to the inpatient unit and were used once daily for 60 days post-HCT. They were used on all parts of the body, including areas with abrasions and skin rashes. A single bath wipe was used for a region of the body. Bath wipes were not used on days of thiotepa administration or during radiation therapy. Experimental bath wipes (Theraworx, Avadim Technologies, Inc., Asheville, North Carolina) contained allantoin, colloidal silver, preservatives, vitamin E, aloe, and lauryl glucoside. Standard bath wipes (Comfort bath PBS Wipe Solution, Sage Products, Inc., Cary, Illinois) contained rinse-free soap and lotion. No other method of bathing was used for participants. Wipes were placed in occlusive bags after warming, by a third party to protect blinding. Comfort bath wipes were called "standard" bath wipes to differentiate them from the experimental wipes. Standard of care for nonstudy patients remained bathing with soap and water.

Baseline skin swabs were collected from the axilla and groin before initiating the conditioning regimen. Skin swabs from these two sites were repeated when the patient was discharged from the inpatient unit, and day +60 post-HCT when the patient was taken off study. Patients for whom skin swabs were not collected by the 7-day window period at discharge were considered unevaluable. Skin swabs were collected using a single e-swab (Covance, Nashville, Tennessee). Rectal surveillance cultures were obtained from all patients before admission and weekly until discharge. Blood cultures were obtained for patients with fever with or without neutropenia according to our standard operating procedures. Positive blood cultures from admission until time of discharge were evaluated. Conventional bacteriologic culture media was used. Susceptibility testing was done by the E-test and the automated MIC method.

Satisfaction Survey

A satisfaction survey was administered to the patient and/or legal guardian at the end of the study. Patients and parents documented their compliance with the bath regimen daily by using a diary, which was reviewed daily while inpatient, and weekly while outpatient by nursing staff. Nursing staff received education about the study through a web-based learning module. Competency in the use of bath wipes was validated by a nurse educator. Patients and parent competency in the use of bath wipes was confirmed by direct nursing observation.

Statistical Analysis

The statistical design was an RCT stratified by the type of HCT (autologous vs. allogeneic), and conditioning with total body irradiation versus no total body irradiation. Block randomization with block sizes varying randomly between two and four was used in each stratum. Randomization was performed by the Division of Nursing Research, using the randomization software program developed by the Department of Biostatistics. All randomized and evaluable patients were included in the analyses, consistent with an intention-to-treat principle.

The null hypothesis for efficacy (H_0) was that rates of VRE colonization in HCT patients using the experimental (p_A) and standard bath wipes (p_C) are equal, and the alternative hypothesis (H_1) was that rates of VRE colonization with experimental bath wipes are less than those with standard bath wipes, represented by the formula H_0: $p_A = p_C \leftrightarrow H_1$: $p_A < p_C$. The rate of colonization with VRE in HCT recipients from the date of admission to initial discharge at St. Jude, over a 12-month period, from January 2013 to December 2013 (both months inclusive), was 25% (unpublished data). The standard for cleansing was with soap and water. Using design parameters at a significance level set at $\alpha = .05$ power of 90%, and $p_A = 10\%$, 250 evaluable patients (125 for each group) were required by the one-sided two-sample test for difference of proportions (Cytel, n.d.), assuming one interim analysis to assess efficacy and futility after enrolling 125 patients. The trial was designed to be halted in favor of H_1 if the p value was less than .006, and in favor of H_0 if the p value was greater than .47. If the p value for testing H_0 after study completion was less than .05, the rate of VRE colonization was expected to decrease by at least 15%.

The rate of VRE colonization was chosen as a marker of efficacy since its prevalence was high and colonization is a predictor of bacteremia. Besides monitoring the primary endpoint of VRE colonization, the trial was designed to be stopped if the central line–associated blood stream infection (CLABSI) rate between the two arms was significantly different by the Fischer's exact test.

Descriptive statistics for patients in the experimental and standard arms were reported and compared by the Fischer's exact test. The number and proportion of patients with VRE, MDR GNRs, and non-MBI CLABSI from admission until discharge from the inpatient unit were provided. Colonization was defined as a swab testing positive for VRE or MDR GNRs, with a negative baseline swab. Fischer's exact test was used to test for the null hypothesis. Although the wipes were used for a period of 60 days, VRE colonization and CLABSI rates from admission until discharge were used for statistical analysis. Patients came off study on day +60. If a patient was discharged beyond day +60, day +60 was used as cutoff.

Non-MBI bacteremia was classified according to the Centers for Disease Control and Prevention National Health Safety Network 2019 guidelines (Centers for Disease Control and Prevention, 2019). MBI bacteremia was noted but not analyzed, as it was unlikely to be affected by a skin-cleansing regimen. The use of prophylactic antibiotics and management of fever and neutropenia in both arms from admission until discharge was according to standard operating procedures. The number of patients with acute skin GVHD in the two arms was compared by the Fischer's exact test. For patient and parent satisfaction, measurements were scored on a nominal scale and compared by Fischer's exact or chi-square test, respectively, between the two groups. The p values were two-sided except as noted and were considered significant if $<.05$.

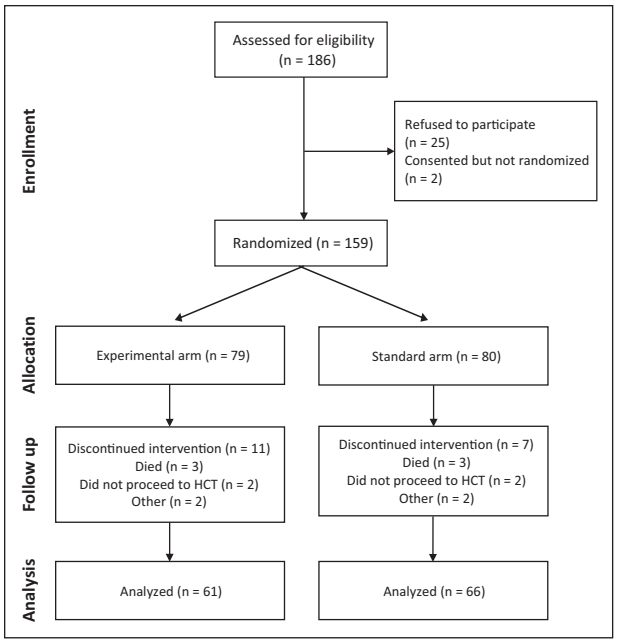

Figure 1. Participant flow diagram.

Results

Patient Characteristics

A total of 186 eligible patients were approached for consent. Of them, 25 declined to participate in the study. These patients used standard bath wipes and/or soap and water for bathing. Two patients gave consent but were not randomized. Of the 159 patients who were randomized, 32 dropped out of the study due to dissatisfaction with the wipes ($n = 18$), death ($n = 6$), not proceeding to HCT ($n = 4$), or other reasons ($n = 4$). The patients who dropped out due to dissatisfaction with the wipes were equally distributed between the two arms ($p = .33$; Figure 1). These patients preferred soap and water for bathing. No patients were lost to follow-up. Thus, a total of 127 patients were analyzed: 61 in the experimental arm and 66 in the standard arm.

Table 1 gives demographic, disease, and treatment characteristics of 127 patients in the experimental and standard arms. Age, ethnicity, gender, diagnosis, remission status, donor and product type, and receipt of multiple HCT were comparable between the two arms. Prophylactic antibiotics (Srinivasan et al., 2013; Srinivasan et al., 2014) and management of febrile episodes in the period between admission and initial discharge did not differ between the two arms. For eight quarters prior to the study, the daily bathing compliance

Table 1. Transplant Characteristics of Patients on Experimental and Standard Study Arm.

Variable	Experimental study arm ($n = 61$)	Standard study arm ($n = 66$)	p value
Age			.20
Mean age at HCT	9.68[a] (6.24)	8.29 (6.18)	
Median	10.01	6.08	
Range	.26-20.95	.43-21.12	
Race			.39
White	41 (67)	42 (64)	
African American	6 (10)	12 (18)	
Other	14 (23)	12 (18)	
Male	27 (44)	37 (56)	.22
Diagnosis			.92
Heme malignancy	38 (62)	45 (68)	
Solid tumor	15 (24)	13 (20)	
Hematologic	4 (7)	4 (6)	
Immunologic	4 (7)	4 (6)	
Remission before HCT	31 (51)	41 (62)	.21
Product			.85
HPC, A	37 (61)	43 (65)	
HPC, M	23 (38)	22 (34)	
HPC, C	1 (1)	1 (1)	
Donor			.57
Haploidentical	20 (33)	28 (43)	
Matched	23 (38)	18 (27)	
Mismatched unrelated	1 (1)	2 (3)	
Autologous	17 (28)	18 (27)	
Myeloablation	32 (52)	29 (44)	.38
Multiple HCT	7 (11)	9 (14)	.79

Note. Data are number of patients (%), unless otherwise indicated. HCT = hematopoietic cell transplantation; HPC = human progenitor cells; A = apheresis; M = marrow; C = cord.
[a]Mean with standard deviation.

was an average of 60%. All patients on study were compliant with use of the wipes in the inpatient unit. For all 127 patients, skin swabs were collected at discharge within the window period; for 103 (81%) patients, skin swabs were collected on day +60.

Safety

Safety was determined by Grade IV skin toxicity (National Cancer Institute Common Terminology Criteria version 3.0) as a result of using wipes that occurred until the time of discharge in the first 12 patients enrolled in the experimental arm. Experimental bath wipes were well tolerated. No patient in either study arm had a skin rash or Grade I skin toxicity attributable to wipes.

Clinical Outcomes

Table 2 summarizes the results of the interim analysis. One (2%) patient in the experimental arm was colonized with VRE. In the standard arm, two (3%) patients were colonized with VRE ($p = 1.0$). There were no patients with non-MBI bacteremia in the experimental arm, and two (3%) with non-MBI bacteremia in the standard arm ($p = .50$). MDR GNRs were not isolated from patients in either arm. The RCT was halted because the interim analyses indicated equivalent efficacy of the two methods. The p value of testing the differences in rates of VRE colonization between the two arms was 1.

Table 2. VRE, MDRO Colonization and Non-MBI Bacteremia in Patients on Experimental and Standard Arms.

	Study arm			
Variable	Experimental ($n = 61$)	Standard ($n = 66$)	p value*	Overall ($n = 127$)
VRE	1 (2)	2 (3)	1	3 (2)
MDRO	0 (0)	0 (0)	NA	0 (0)
Non-MBI CLABSI	0 (0)	2 (3)	.50	2 (2)

Note. VRE = vancomycin-resistant enterococcus; MDRO = multidrug resistant organisms; MBI = mucosal barrier injury; CLABSI = central-line associated blood stream infection.
*p value compares characteristics of patients on experimental and standard study arms.

The two patients with non-MBI bacteremia in the standard arm included a 14-year-old male patient with *Staphylococcus epidermidis* bacteremia on day +9 after a second haploidentical HCT for lymphoma, and an infant with *Pseudomonas aeuroginosa* bacteremia on Day 0 after a haploidentical HCT for relapsed acute lymphoblastic leukemia. Both patients recovered from the bacteremia.

There were eight patients with acute skin GVHD in the experimental arm and nine patients in the standard arm ($p = 1.00$), all Grades I to II in severity. GVHD was manifested as palmar and/or plantar erythema.

Patient and Parent Satisfaction

Patient and parent surveys showed no significant differences in the degree of skin irritation after using wipes, frequency of use of wipes as outpatients, and ease and satisfaction with use of wipes (Table 3). No patient withdrew because of skin irritation related to the use of bath wipes.

There were 24 protocol deviations: discharge swab was missed at the time of discharge but collected within the window period in 10 patients. Two patients consented to the study but were not randomized. The day +60 swab was not collected in another 12 patients who withdrew from the study due to dissatisfaction with the wipes. These patients preferred soap and water for bathing.

Table 3. Survey Data.

Variable	Overall ($n = 127$)	Experimental ($n = 61$)	Standard ($n = 66$)	p value
Patients completing survey	78 (61)	42 (69)	36 (55)	.11
Did your child experience skin irritation as a result of using the wipes?				.85
Moderate	1 (1)	1 (1)	0 (0)	
Minimal	9 (7)	4 (7)	5 (8)	
None	68 (53)	37 (61)	31 (47)	
How easy were the bath wipes to use?				.15
Neither easy nor difficult	1 (1)	1 (1)	0 (0)	
Easy	19 (15)	13 (22)	6 (9)	
Very easy	58 (45)	28 (46)	30 (46)	
How often did you use the bath wipes?				.84
Some days	8 (6)	5 (8)	3 (5)	
Most days	25 (20)	14 (23)	11 (17)	
Every day	45 (35)	23 (38)	22 (33)	
How satisfied were you with the feel of the wipes on your child's skin?				.65
Very dissatisfied	1 (1)	0 (0)	1 (1)	
Neither satisfied nor dissatisfied	11 (8)	5 (8)	6 (9)	
Satisfied	31 (24)	16 (26)	15 (23)	
Very satisfied	35 (28)	21 (35)	14 (22)	
How well do you think the wipes cleaned your child's skin?				.21
Poorly	3 (2)	0 (0)	3 (5)	
Moderately well	8 (6)	6 (10)	2 (3)	
Well	28 (22)	15 (25)	13 (20)	
Very well	39 (31)	21 (34)	18 (27)	

Note. Data are number of patients (%), unless otherwise indicated.

Discussion

Experimental bath wipes constitute a self-drying cleansing agent that combines specialized surfactant and skin-healthy ingredients such as aloe, allantoin, and vitamin E to moisturize and nourish the skin, as well as silver, which has broad-spectrum antimicrobial activity (Yabanoglu et al., 2013). The colloidal silver-based skin cleanser was not inferior to 4% chlorhexidine, as confirmed by log of the number of colony-forming units of viable organisms recovered in the inguinal region of healthy adults (Paulson et al., 2018). Clinical use of experimental bath wipes in children has not been previously reported.

Our RCT showed that the experimental bath wipes were well tolerated in children, and no patient experienced Grade I toxicity. There was no difference in skin colonization with VRE and MDR GNRs, rates of non-MBI bacteremia or the incidence of acute skin GVHD between patients in the two arms. More than half of the patients/parents surveyed expressed satisfaction with the use of the wipes.

The rate of VRE colonization was chosen as a marker of efficacy since its prevalence was high comparable with other studies (Bilinski et al., 2016; Ford et al., 2017). Colonization with vancomycin-resistant enterococci is a significant predictor of bacteremia after HCT (Kamboj et al., 2010; Vydra et al., 2012). Patients with VRE bacteremia have poor 1-year survival (Vydra et al., 2012).

VRE colonization was substantially lower than the 25% incidence noted in the prestudy period in patients using soap and water for bathing. CLABSI rates were also substantially lower compared with previously published St. Jude reports of an 8% risk of CLABSI in the first 28 days after allogeneic and autologous HCT, predominantly due to non-MBI bacteremia in patients using soap and water for bathing (Srinivasan et al., 2013; Srinivasan et al., 2014).

We investigated potential sources of bias. The CLABSI bundle (O'Grady et al., 2011) was implemented in January 2013, 20 months before initiating this study. There were no major changes in infection control practices and antimicrobial stewardship between the prestudy (2013) and the study period (2014-2017). Metronidazole was used for GVHD prophylaxis in all HCT patients and discontinued in April 2016, midway through the study. Rectal surveillance cultures were obtained on all HCT patients before admission and weekly until discharge, both in the prestudy and study period. Additional swabs were obtained on

study patients. Patients who declined to participate in the study used a combination of standard wipes and/or soap and water for bathing, and compliance was poor. Hence, a comparison was not made with patients on study.

It has been shown that VRE colonizes the patients' skin, contaminates environmental surfaces and the hands of health care workers, resulting in dissemination to other patients (Duckro et al., 2005; Sundermann et al., 2019). A prospective single-arm clinical trial reported that cleansing patients with chlorhexidine-saturated cloths was a simple and effective strategy to reduce VRE contamination of patients' skin, leading to a reduction in the incidence of acquiring VRE. There was also lower VRE contamination of environmental surfaces and health care workers' hands than when soap and water baths were used (Vernon et al., 2006). This was confirmed in a multicenter study, where daily bathing with chlorhexidine in intensive care units decreased the rate of acquiring VRE by 50%, with significant reduction in VRE bacteremia (Climo et al., 2009). However, chlorhexidine wipes cannot be used in patients with skin GVHD, which occurred in 13% of our patients. Vernon et al. (2006) demonstrated that chlorhexidine-medicated wipes resulted in significantly fewer patients developing skin breakdown compared with bathing with soap and water. It is possible that skin abrasions with soap and water baths may increase the risk for colonization.

Compliance with the use of bath wipes and parent/patient education in the period between admission and discharge most likely contributed to the effectiveness of the wipes (Page et al., 2016). For eight quarters prior to the study, the daily bathing compliance was an average of only 60%, which increased to 100% for patients on study in the inpatient unit. This nurse-led initiative highlights the impact of improvements to nursing practice (i.e., bath compliance) on nursing-sensitive indicators (i.e., prevention of hospital-acquired infections). The study had the support of nursing leadership, quality of delivery was assessed by conducting direct observations and performing audits, nursing staff underwent sessions in patient education, and feedback was provided.

The strengths of this study include an RCT design with complete follow-up of all patients. Patient-centered outcomes were assessed. The study was blinded to investigators and clinicians in a high-risk population that largely comprised patients with refractory hematologic malignancies and solid tumors, half of whom were not in remission before transplantation, and with 10% to 14% of patients undergoing a second allogeneic HCT. In a recent prospective multicenter study on a similar high-risk population, the overall cumulative incidence of gram-negative bacteremia was 17% at 30 days after allogeneic HCT, and 9% at 20 days after autologous HCT (Girmenia et al., 2017).

A major limitation of this study is the lack of a control arm with soap and water baths, which was the standard for cleansing prior to the trial. However, this would have been beyond the scope of a single institutional study and interfered with blinding. The wipes differed in texture; hence, the study was not completely blinded to the patients and parents. Only 60% of patients and/or parents completed the satisfaction survey.

Conclusion

Experimental bath wipes were well tolerated. No difference was noted in the extremely low rates of skin colonization with VRE and MDR GNRs and rates of non-MBI bacteremia in patients using experimental and standard wipes. Future studies in other high-risk populations are required to confirm these results. Mortality from MDR GNRs and VRE bacteremia is high and may be lowered by implementing the use of wipes instead of soap and water baths if confirmed by other studies, in combination with nursing and family education, pre- and post-HCT rectal and skin surveillance for MDR GNRs, isolation precautions for patients at risk, and use of the CLABSI bundle.

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ORCID iDs

Margie Kjellin https://orcid.org/0000-0002-6138-4920
Emily Browne https://orcid.org/0000-0003-2098-365X

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Author Biographies

Margie Kjellin, MSN, is director of inpatient nursing at St. Jude Children's Research Hospital in Memphis, Tennessee.

Amr Qudeimat, MD, is an assistant member of Bone Marrow Transplant & Cellular Therapy at St. Jude Children's Research Hospital in Memphis, Tennessee.

Emily Browne, DNP, is director of the Transition Oncology Program at St. Jude Children's Research Hospital in Memphis, Tennessee.

Dinesh Keerthi, MS, is a project manager in Bone Marrow Transplant & Cellular Therapy at St. Jude Children's Research Hospital in Memphis, Tennessee.

Anusha Sunkara, MS, worked in biostatistics at St. Jude Children's Research Hospital in Memphis, Tennessee.

Guolian Kang, PhD, is an associate member of biostatistics at St. Jude Children's Research Hospital in Memphis, Tennessee.

Alicia Winfield, CRRP, was a clinical research assistant at St. Jude Children's Research Hospital in Memphis, Tennessee.

Mary Anne Giannini, MT, is a supervisor in Infection Prevention & Control at St. Jude Children's Research Hospital in Memphis, Tennessee.

Gabriela Maron, MD, is an associate member of infectious diseases at St. Jude Children's Research Hospital in Memphis, Tennessee.

Randall Hayden, MD, is a member of pathology at St. Jude Children's Research Hospital in Memphis, Tennessee.

Wing Leung, MD, PhD, was the chair of Bone Marrow Transplant & Cellular Therapy at St. Jude Children's Research Hospital in Memphis, Tennessee.

Brandon Triplett, MD, is an associate member of Bone Marrow Transplant & Cellular Therapy at St. Jude Children's Research Hospital in Memphis, Tennessee.

Ashok Srinivasan, MD, is an associate member of Bone Marrow Transplant & Cellular Therapy at St. Jude Children's Research Hospital in Memphis, Tennessee.