Original Article

Chlorhexidine Gluconate Bathing in Children With Cancer or Those Undergoing Hematopoietic Stem Cell Transplantation: A Double-Blinded Randomized Controlled Trial From the Children's Oncology Group

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BACKGROUND: To the authors' knowledge, information regarding whether daily bathing with chlorhexidine gluconate (CHG) reduces central line–associated bloodstream infection (CLABSI) in pediatric oncology patients and those undergoing hematopoietic stem cell transplantation (HCT) is limited. **METHODS:** In the current multicenter, randomized, double-blind, placebo-controlled trial, patients aged ≥2 months and <22 years with cancer or those undergoing allogeneic HCT were randomized 1:1 to once-daily bathing with 2% CHG-impregnated cloths or control cloths for 90 days. The primary outcome was CLABSI. Secondary endpoints included total positive blood cultures, acquisition of resistant organisms, and acquisition of cutaneous staphylococcal isolates with an elevated CHG mean inhibitory concentration. **RESULTS:** The study was stopped early because of poor accrual. Among the 177 enrolled patients, 174 were considered as evaluable (88 were randomized to the CHG group and 86 were randomized to the control group). The rate of CLABSI per 1000 central line days in the CHG group was 5.44 versus 3.10 in the control group (risk difference, 2.37; 95% confidence interval, 0.05-4.69 [$P = .049$]). Post hoc conditional power analysis demonstrated a 0.2% chance that the results would have favored CHG had the study fully enrolled. The rate of total positive blood cultures did not differ between groups (risk difference, 2.37; 95% confidence interval, −0.41 to 5.14 [$P = .078$]). The number of patients demonstrating the new acquisition of resistant organisms did not differ between groups ($P = .54$). Patients in the CHG group were found to be more likely to acquire cutaneous staphylococcal isolates with an elevated CHG mean inhibitory concentration ($P = .032$). **CONCLUSIONS:** The data from the current study do not support the use of routine CHG bathing in children with cancer or those undergoing allogeneic HCT. ***Cancer* 2021;127:56-66**.

KEYWORDS: bacteremia, central line–associated bloodstream infection (CLABSI), chlorhexidine gluconate (CHG), Multi-drug resistant organisms (MDRO).

INTRODUCTION

Central line–associated bloodstream infections (CLABSIs) and infections due to resistant organisms are prevalent and serious health care–associated infections experienced by patients with cancer.[1-3] Daily bathing with chlorhexidine gluconate (CHG) has been identified as a strategy with which to reduce CLABSI and the acquisition of resistant organisms and is recommended in the Center for Disease Control and Prevention (CDC)'s guidelines for the prevention of intravascular catheter–related infections.[4] To the best of our knowledge, the majority of studies regarding CHG bathing focus on critically ill patients with temporary, nontunneled central venous catheters (CVCs). It is important to study CHG in patients with cancer and hematopoietic stem cell transplantation (HCT) recipients because they

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often have tunneled CVCs and are likely to experience infections resulting from the translocation of bacteria across mucosal barriers due to graft-versus-host disease, neutropenia, or mucositis. Collectively, these are situations in which topical antisepsis may not impact infection risk. The few studies of CHG bathing performed in patients with cancer did not demonstrate a benefit, but they were retrospective and underpowered.[5,6]

The primary objective of the current study was to determine whether CHG bathing reduces the rate of CLABSI in children with cancer or those undergoing allogeneic HCT. Secondary objectives were to determine whether CHG bathing reduced the acquisition of resistant organisms in this population and whether CHG bathing was associated with the acquisition of cutaneous staphylococcal isolates with elevated CHG minimum inhibitory concentrations (MICs).

MATERIALS AND METHODS

The current study was a randomized, double-blind, placebo-controlled trial conducted by the Children's Oncology Group (COG) at 36 centers in the United States and Canada, enrolling patients at high risk of CLABSI. Eligible patients were aged ≥2 months and <22 years, were receiving treatment for an oncology diagnosis or were undergoing allogeneic HCT, and had an eligible CVC that was intended to remain in place for ≥3 months. Oncology patients were required to have a plan to receive chemotherapy for ≥3 months and could undergo autologous or allogeneic HCT during the 3-month period. Eligible CVCs included external tunneled CVCs; for patients with acute myeloid leukemia or recurrent acute lymphoblastic leukemia or those undergoing allogeneic HCT, nontunneled, percutaneously inserted CVCs also were allowed.

Exclusion criteria were receipt of treatment for a central line infection within the last 14 days, an allergy or hypersensitivity to CHG, severe generalized skin breakdown, a plan to receive prophylactic broad-spectrum antibiotics or prophylactic antimicrobial central line locks, a plan to receive sorafenib, or being pregnant or breastfeeding.

The study was approved by the National Cancer Institute's pediatric Central Institutional Review Board (IRB) and the IRBs at participating institutions. Participants or their guardians provided written informed consent and assent (if appropriate).

Due to unexpectedly slow accrual, several strategies and protocol modifications aimed at improving recruitment were used (see Supporting Information for details).

Randomization and Masking

Patients were randomized 1:1 to daily bathing with CHG or control bathing using the computerized COG study management system. Due to expected differences in CLABSI rates, randomization was stratified by myeloablative or reduced-intensity allogeneic HCT, nonmyeloablative allogeneic HCT, and an oncology diagnosis with receipt of chemotherapy with or without a subsequent HCT.

CHG and control products were manufactured by Sage Products LLC (Cary, Illinois) using identical packaging, wipe material, and secondary ingredients. Only the Investigational Drug Service at the coordinating center (Seattle Children's Hospital) knew what product was assigned to each patient.

Procedures

Patients underwent once-daily bathing for 90 days with either 2% CHG-impregnated cloths or cloths impregnated with mild cleansers (Comfort Bath; Sage Products LLC) regardless of inpatient or outpatient status (see Supporting Information for further details and modifications).

In August 2016, Sage Products LLC initiated a nationwide recall of a barrier cream cloth (not used in the current study) because of *Burkholderia cepacia* complex contamination. Other washcloth products manufactured in the same facility also were recalled, including some lots of the study product. All patients and IRBs were notified of the recall, study bathing was stopped (9 patients in the CHG group and 11 patients in the control group), and further enrollment was paused. Enrollment resumed 3 months later with the supply of new study product.

Adherence was monitored by counting the study cloths remaining approximately halfway through the study (day 45±7) and at the end of the study period (day 90±7). For patients who discontinued protocol therapy before the end of the study period, adherence data were obtained at the time they discontinued protocol therapy. Daily diaries were used to collect information regarding soap-and-water bathing, nonprotocol CHG bathing, and type(s) of lotion used.

To assess ease of use and overall satisfaction, patients (or caregivers) were asked to complete a survey at the end of protocol therapy (when the subject completed planned therapy at day 90 or at the time of withdrawal from protocol therapy).

Skin swabs of the neck and axilla were collected at baseline, at day 45 (±7 days), and at day 90 (±7 days) to assess the MIC in skin staphylococcal isolates (see Supporting Information for additional detail). CHG MIC was determined as previously described.[7]

Blood cultures were evaluated for CLABSI using the January 2015 criteria from the CDC.[8] Study sites submitted clinical and microbiology laboratory reports to a central database. Two blinded investigators (D.M.Z. and A.M.M.) independently used these data and CDC criteria to categorize blood cultures as CLABSI–mucosal barrier injury (MBI), CLABSI–non-MBI, non-CLABSI contaminant, and non-CLABSI secondary bloodstream infection (BSI). The CDC definition for repeat infection time frame was used to determine whether a new positive blood culture was considered a new infection. In addition, an event was categorized as a repeat infection if it occurred outside of the CDC repeat infection time frame but with the same organism(s), within 4 weeks of the previous infection, and in association with the same CVC (there was 1 event that was classified as a repeat infection). Discordant decisions were resolved by consensus.

To assess resistant organisms, study sites submitted microbiology laboratory reports for all cultures (both sterile and nonsterile) that were positive for a targeted organism during the study period, and in the year prior to enrollment. Resistant organisms were defined as *Staphylococcus aureus* resistant to oxacillin; *Enterococcus* spp. resistant to vancomycin; *Klebsiella pneumoniae* or *Escherichia coli* nonsusceptible (intermediate or resistant) to ceftriaxone, ceftazidime, cefepime, or any carbapenem; and *Pseudomonas aeruginosa* or *Acinetobacter baumannii* resistant to any carbapenem or ceftazidime, and either an aminoglycoside or fluoroquinolone. *Clostridium difficile* infection (CDI) also was included as a resistant organism[9] and was defined as a positive laboratory test for *C. difficile* and ≥3 unformed stools in <24 hours.[10]

Bacterial identification and antibiotic susceptibility were determined using the standard methods used by the clinical microbiology laboratory at each study site.

Outcomes

The primary outcome was CLABSI and included both CLABSI–non-MBI and CLABSI-MBI. Secondary outcomes were the total number of positive blood cultures, the acquisition of resistant organisms (resistant organisms identified during the study period that were not identified in the year prior to enrollment), and the acquisition of cutaneous *Staphylococcus* with elevated CHG MICs (cutaneous *Staphylococcus* isolated from a follow-up swab with a CHG MIC ≥4 ug/mL in a patient without a resistant *Staphylococcus* isolated from a baseline swab).

All patients were evaluated for cutaneous adverse events by site staff using version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events.

Statistical Analysis

The study design assumed a constant rate of CLABSI of 5 per 1000 central line days in the control group and that patients would be observed for 90 days for the outcome. Under these assumptions, simulation determined that 400 evaluable patients (200 patients per group) would be required to detect a CLABSI rate difference of 2 per 1000 central line days with 85% power and a 2-sided alpha of .05 using a Poisson regression model. The maximum sample size was increased to 450 patients to account for ineligible patients and the loss of at-risk days in some patients because of days without a CVC. Given the lower than expected accrual, another power analysis was performed assuming 174 patients (87 patients in each group), a constant rate of CLABSI of 5 per 1000 central line days in the control group, and that patients were observed for an average of 74 days for CLABSI.

All primary analyses were modified intention-to-treat analyses in that all evaluable patients were included regardless of compliance with the assigned therapy. Participants who discontinued protocol therapy prior to day 90 continued to be observed for primary and secondary outcomes unless consent was withdrawn or the patient died. Patients could contribute multiple events and rates were calculated per 1000 at-risk days (days on study with a CVC). Patients whose CVC was discontinued early did not contribute their days without a CVC as "at-risk days." Primary analysis compared the rate of CLABSI between the 2 groups using Poisson regression adjusting for the stratification factor using the duration of days on study with CVC as an offset. Secondary analysis of the primary outcome compared time to first CLABSI using the Kaplan-Meier method and log-rank test. Time to event was defined as time from the initiation of protocol bathing to first CLABSI, last patient contact, or day 90 on study, whichever occurred first.

Total blood cultures were compared between groups using Poisson regression, similar to the primary analysis. Acquisition of resistant organisms and the acquisition of cutaneous staphylococci with elevated CHG MICs both were compared between groups using a stratified Cochran Mantel-Haenszel chi-square test. A post hoc analysis using the chi-square test was performed to compare elevated CHG MICs between groups within each HCT and oncology cohort separately. Only those patients who contributed a baseline swab and at least 1 follow-up swab (day 45 and/or day 90) were included in the elevated CHG MIC analysis. For skin isolates, descriptive statistics were reported for the total number of isolates, total number of isolates per patient, and CHG MIC.

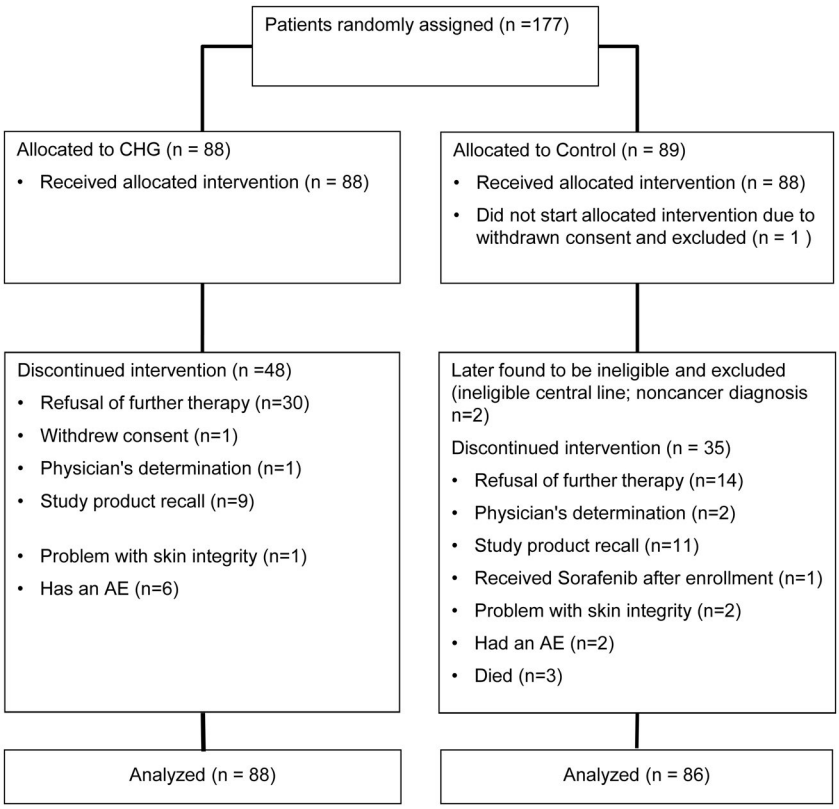

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. CHG indicates chlorhexidine gluconate; AE, adverse event.

Given the early study closure, we conducted a post hoc analysis estimating the probability of favoring CHG assuming the design alternative hypothesis for the remaining unenrolled patients had the study fully enrolled the planned 400 evaluable patients (see Supporting Information). Additional post hoc analyses included the effect of CHG on rates of CLABSI-MBI, CLABSI–non-MBI, non-CLABSI contaminant, and non-CLABSI secondary BSI separately. An additional Poisson regression of the primary outcome adjusted for the underlying oncology diagnosis (due to potential imbalance) was performed. In addition, given the number of patients who discontinued protocol therapy early and the variations in compliance, we performed a per-protocol analysis including only those patients who had a >80% adherence rate at day 45 and day 90 (or when removed from protocol therapy). This analysis considered events and days at risk that occurred up to the last date protocol therapy was used. Product count data were available for 165 patients (94%) (82 patients in the CHG group and 83 patients in the control group), and 111 patients met the adherence rate criteria to be included in this analysis. Limitations of per-protocol analyses are acknowledged in the Supporting Information.

Analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina) or R statistical software (version 3.4.2; R Core Team, Vienna, Austria) and a 2-sided P value <.05 was considered to be statistically significant. Due to multiple comparisons regarding elevated CHG MIC outcome, the significance level for these analyses was adjusted using the Bonferroni method so that $P < .017$ was considered to be statistically significant.

RESULTS

Between November 4, 2013, and April 21, 2017, a total of 177 patients were randomized. Enrollment was stopped early due to slow accrual, following the recommendation of the COG Data and Safety Monitoring Board. After excluding 1 unevaluable patient (patient withdrew consent immediately after randomization) and 2 ineligible patients, a total of 174 evaluable patients were included in the analyses (Fig. 1). Baseline characteristics appeared balanced between groups except possibly for

TABLE 1. Patient Baseline Characteristics by Group

Characteristics	Chlorhexidine Group N = 88	Control Group N = 87
Patient demographics		
Median age (IQR), y	5.5 (2-12)	4 (1-8)
Male sex, no.	53 (60.2%)	51 (58.6%)
Race, no.		
White	51 (58.0%)	53 (61.0%)
Black/African American	14 (15.9%)	9 (10.3%)
Asian	6 (6.8%)	5 (5.7%)
Native Hawaiian or Pacific Islander	2 (2.3%)	0 (0.0%)
Not reported	15 (17.0%)	20 (23.0%)
Ethnicity		
Hispanic or Latino	16 (18.2%)	20 (23.0%)
Not Hispanic or Latino	69 (78.4%)	61 (70.1%)
Not reported	3 (3.4%)	6 (6.9%)
Type of central line[a]		
External tunneled line	83 (94.3%)	85 (97.7%)
Peripherally inserted central catheter	5 (5.7%)	1 (1.1%)
Underlying diagnosis		
Allogeneic transplantation myeloablative stratum, no.[b]		
Malignant diagnoses[c]	11 (12.5%)	9 (10.3%)
Nonmalignant diagnoses	6 (6.8%)	8 (9.2%)
Allogeneic transplantation nonmyeloablative stratum, no.		
Malignant diagnoses	0	0
Nonmalignant diagnoses	3 (3.4%)	3 (3.4%)
Oncology stratum, no.		
Acute lymphoblastic leukemia	6 (6.8%)	10 (11.5%)
Acute myeloid leukemia/myelodysplastic syndrome	32 (36.4%)	22 (25.3%)
Other hematological malignancy	1 (1.1%)	2 (2.3%)
Lymphoma (Hodgkin or non-Hodgkin)	6 (6.8%)	7 (8.0%)
Brain tumor and retinoblastoma	10 (11.4%)	8 (9.2%)
Other solid tumor	13 (14.8%)	18 (20.7%)

Abbreviation: IQR, interquartile range.
[a]One unevaluable patient had data missing regarding the central line.
[b]There were no patients who received reduced-intensity condition regimens.
[c]A total of 3 patients in each group had acute myeloid leukemia or myelodysplastic syndrome.

underlying diagnosis in the oncology stratum (Table 1) (see Supporting Information Table 1).

For the primary outcome, the estimated adjusted rate of CLABSI per 1000 central line days was 5.44 in the CHG group compared with 3.1 in the control group (adjusted incidence rate ratio, 1.76 [95% confidence interval (95% CI), 1.00-3.08; $P = .049$]; risk difference, 2.37 [95% CI, 0.05-4.67]) (Table 2). On the basis of the sample size included in the analysis and the observed average of 74 days at risk per patient, there was 44% power to detect the original proposed difference of 2 CLABSIs per 1000 central line days. The results did not change after adjusting for the underlying diagnosis. The estimated 90-day cumulative incidence of CLABSI was 34.6% (95% CI, 25.1%-46.4%) in the CHG group and 24.1% (95% CI, 16.1%-35.3%) in the control group ($P = .091$ using the log-rank test) (Fig. 2). The post hoc conditional power analysis showed a 0.2% chance that CHG would have demonstrated a statistically significant reduction in the CLABSI rate compared with the control group if the study had fully enrolled. A post hoc per-protocol analysis of the primary outcome demonstrated trends similar to those of the intention-to-treat analysis and the result was not statistically significant (see Supporting Table 2)

There were no significant differences noted between groups for the secondary outcome of total positive blood cultures or the post hoc analysis of each blood culture category separately (Table 2). The organisms isolated from the blood are reported in Figure 3.

The number of patients demonstrating the new acquisition of resistant organisms was 13 of 88 patients in the CHG group (15%) and 10 of 86 patients in the control group (12%) (risk difference, 3.10%; 95% CI, −6.9% to 13.2% [$P = .540$]). Nearly all patients who experienced events had CDI events (12 patients in the CHG group and 10 patients in the control group) and few patients had events that were due to other organisms (2 patients in the CHG group and 2 patients in the control group); both CDI-resistant and non–CDI-resistant infections occurred in 3 patients (1 patient in the CHG group and 2 patients in the control group).

TABLE 2. CLABSI and Positive Blood Culture Outcomes by Group

	Chlorhexidine		Control			
	N = 88,6191 At-Risk Days		N = 86,6702 At-Risk Days			
	Total Events	Adjusted Rate (95% CI)	Total Events	Adjusted Rate (95% CI)	Adjusted IRR (95% CI)[a]	Unadjusted Rate Difference (95% CI)
Primary outcome[b,c]						
CLABSI primary analysis	35	5.44 (3.62 to 8.18)	22	3.1 (1.82 to 5.28)	1.76 (1.0 to 3.08); $P = .049$	2.37 (0.05 to 4.69)
CLABSI post hoc analysis adjusting for diagnosis	35	6.44 (4.30 to 9.63)	22	3.96 (2.27 to 6.90)	1.63 (0.93 to 2.85)	2.37 (0.05 to 4.69)
Secondary outcome[b]						
All positive blood cultures	47	7.24 (5.5 to 9.53)	35	4.93 (3.51 to 6.93)	1.47 (0.96 to 2.25); $P = .078$	2.37 (–0.41 to 5.14)
Post hoc outcomes[b]						
CLABSI-MBI	20	2.76 (1.66 to 4.59)	12	1.49 (0.74 to 3.03)	1.85 (0.86 to 3.97)	1.44 (–0.3 to 3.18)
CLABSI-non-MBI	15	2.28 (1.31 to 3.96)	10	1.39 (0.71 to 2.71)	1.64 (0.76 to 3.56)	0.93 (–0.61 to 2.47)
Non-CLABSI contaminant	10	1.71 (0.95 to 3.09)	11	1.76 (0.95 to 3.28)	0.97 (0.42 to 2.23)	–0.03 (–1.42 to 1.37)
Non-CLABSI secondary BSI	2	0.35 (0.08 to 1.55)	1	0.17 (0.03 to 1.04)	2.11 (0.21 to 21.52)	0.17 (–0.36 to 0.71)

Abbreviations: 95% CI, 95% confidence interval; BSI, bloodstream infection; CLABSI, central line–associated bloodstream infection; IRR, incident rate ratio; MBI, mucosal barrier injury.

[a]*P* values were calculated using Poisson regression and presented only for primary analysis of the primary and secondary outcomes.

[b]The primary and secondary outcome analyses were adjusted for the stratification factor consisting of 3 groups (myeloablative allogeneic transplantation vs nonmyeloablative allogeneic transplantation vs oncology diagnosis). Analyses of post hoc outcomes were adjusted for the stratification factor consisting of 2 groups because of sparse data (allogeneic transplantation vs oncology diagnosis). The post hoc analysis of the primary outcomes also was adjusted for diagnosis (acute myeloid leukemia/myelodysplastic syndrome vs all others).

[c]CLABSI included both CLABSI-MBI and CLABSI–non-MBI.

For the secondary outcome of the acquisition of cutaneous staphylococcal isolates with elevated CHG MICs, a total of 135 participants contributed a baseline and at least 1 follow-up swab and were included in this analysis (62 in the CHG group vs 73 in the control group). The vast majority of study isolates were coagulase-negative *Staphylococcus*, with *S. aureus* accounting for only 3% of the isolates. The number of isolates were 485 isolates and 558 isolates, respectively, for the CHG and control groups. The median of number of isolates per patient in the CHG group was 5 (range, 1-22 isolates) and that in the control group was 5 (range, 1-17 isolates). The median CHG MIC (MIC50) was 1 (range, 0.25-4) for the CHG group and 1 (range, 0.13-4) for the control group. Patients in the CHG group were more likely to acquire cutaneous staphylococcal isolates with elevated CHG MICs than those in the control group ($P = .032$) (Table 3).

Cutaneous adverse events were reported in more patients in the CHG group compared with the control group (24% vs 15%). When limited to events adjudicated to be at least possibly related to the intervention, the frequency of events was lower (10% vs 6%) (Fig. 4) (Table 4).

Product count data were available for 164 patients (94%) (82 patients in each group). The median adherence in the CHG group was 93.5% (interquartile range, 66.4%-99.3%) compared with 95.6% in the control group (interquartile range, 83.3%-100%). Approved soap and lotion use did not differ between groups (data not shown).

Responses from the satisfaction survey demonstrated that the majority of subjects in both the CHG group and the control group were satisfied with the cloths and nearly all participants believed they were easy to use (see Supporting Information).

The use of CHG for line care was similar between the groups (41% in the CHG group vs 50% in the control group). During the study period, only 9 patients received CHG bathing while in the pediatric intensive care unit (5 in the CHG group vs 4 in the control group).

DISCUSSION

In the current study, CHG bathing did not reduce the risk of CLABSI, total blood cultures, or the acquisition of resistant organisms in children with cancer and pediatric HCT recipients with an external CVC. Although the study was closed early due to slow accrual, conditional power analysis of the primary outcome (CLABSI) demonstrated

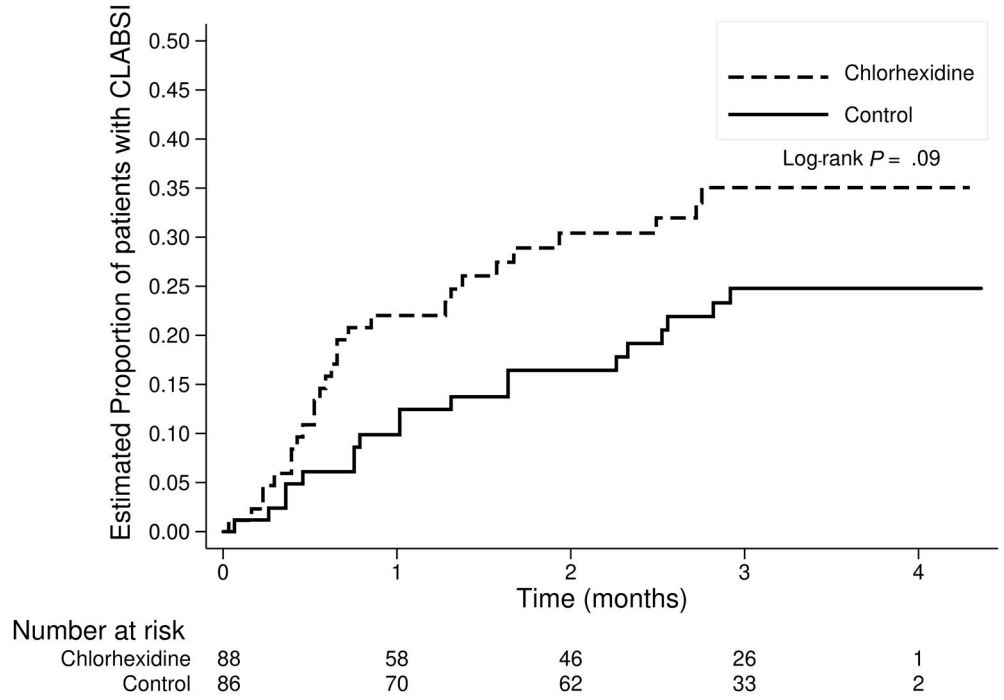

Figure 2. Cumulative incidence of time to first central line–associated bloodstream infection (CLABSI).

a 0.2% chance that the results would have favored CHG had the study been fully enrolled. In addition, post hoc per-protocol analysis demonstrated a trend similar to that of the intention-to-treat analysis. Finally, patients randomized to CHG were at a higher risk of acquiring cutaneous staphylococcal isolates with elevated CHG MICs.

Results from the primary CLABSI analysis favored the control group, although the level of significance was marginal. There are 2 potential explanations. First, as with any statistical test, by design there is a 5% chance of committing a type I error (false-positive or the null hypothesis is falsely rejected). In the case that the null hypothesis is true, the result should equally favor the intervention or control group. The second possibility is that there is something about the intervention that directly or indirectly increased the risk of CLABSI; however, we were unable to conceive of a hypothesis that would explain such an effect.

The finding that CHG failed to reduce CLABSI in patients with cancer and HCT recipients is consistent with what to the best of our knowledge are the 2 existing studies conducted in patients with cancer.[5,6] Reasons for the differential effect of CHG in critically ill patients compared with oncology and HCT patients may be related to the pathogenesis of BSIs, with translocation of bacteria across mucosal surfaces being more significant in those receiving cancer therapies. However, this hypothesis is not directly supported by the post hoc analysis, in which the effect of CHG against CLABSI-MBI and CLABSI–non-MBI appeared similar. It also is possible that CVCs tend to be temporary in critically ill patients whereas CVCs in patients with cancer and HCT recipients often are tunneled with a cuff and in place for prolonged periods, possibly modifying the potential benefits of CHG.

In contrast to the findings of the current study, several trials performed in critically ill adults have demonstrated a reduction in BSI with the use of CHG,[11-18] although results have varied among the 4 randomized controlled trials conducted in this population.[11,13,19,20] Two studies demonstrated a benefit of CHG in reducing BSI[13,11] whereas 2 studies did not.[19,20] Moreover, a recent cluster randomized trial in non–critically ill hospitalized adults did not find a benefit to CHG in their primary analysis, but did find a benefit among patients with medical devices in post hoc analyses.[21] To the best of our knowledge, there exists 1 randomized trial of CHG bathing performed in critically ill children.[22] This was a 5-center, cluster randomized, controlled trial that demonstrated a nonsignificant reduction in BSI associated with CHG bathing in the intention-to-treat analysis, but a statistically significantly lower incidence of BSI associated with CHG bathing in the per-protocol analysis.

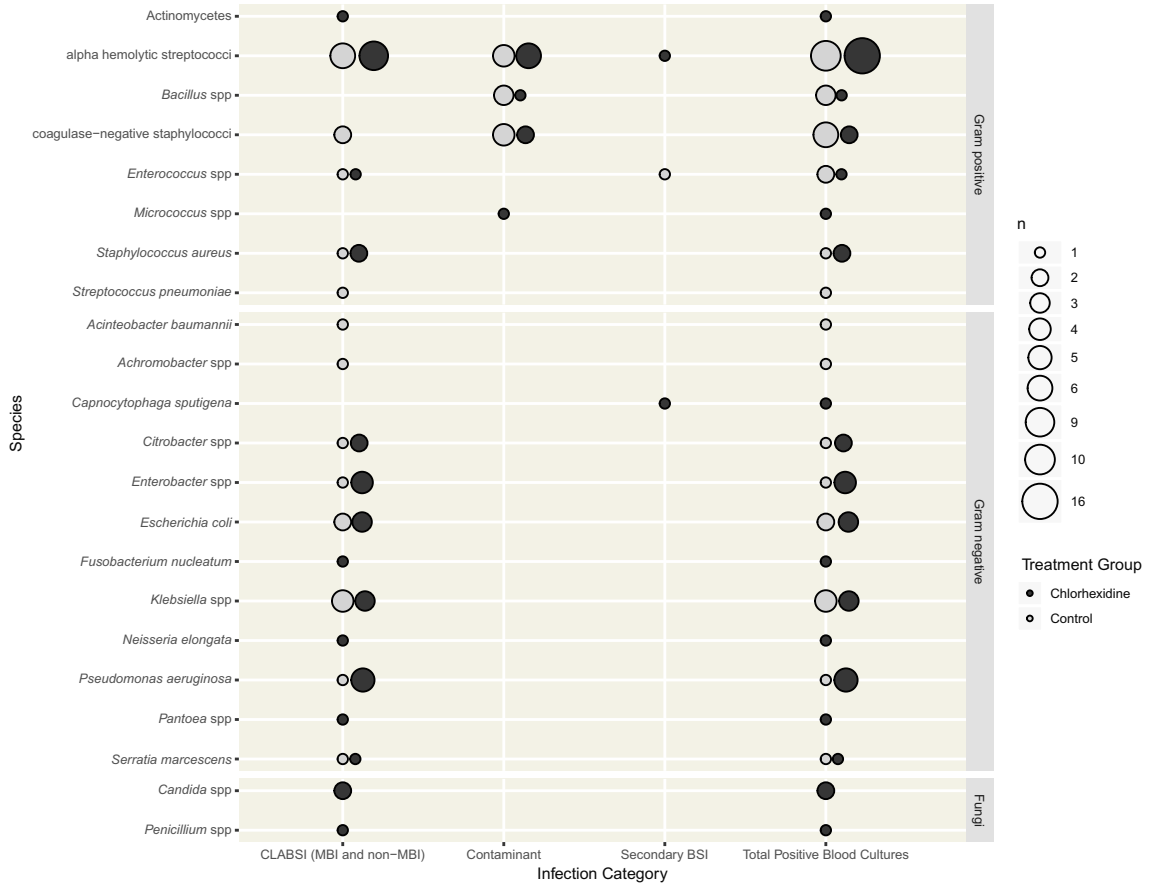

Figure 3. Organisms identified from positive blood cultures by infection category and treatment group. The size of the circles represents the number of events. BSI indicates bloodstream infection; CLABSI, central line–associated bloodstream infection; MBI, mucosal barrier injury.

TABLE 3. Patients With Acquisition of Cutaneous Staphylococci Isolates With Elevated CHG MIC

Cutaneous Staphylococci Isolates	CHG	Control	*P*
Elevated CHG MIC overall	11/62 (17.7%)	4/73 (5.5%)	.032[a]
Elevated CHG MIC by strata			.004[b]
HCT	7/16 (43.8%)	0/15 (0%)	.73
Oncology	4/46 (8.7%)	4/58 (6.9%)	

Abbreviations: CHG, chlorhexidine gluconate; HCT, hematopoietic stem cell transplantation; MIC, minimum inhibitory concentration.

[a]The *P* value was calculated using the Cochran Mantel-Haenszel chi-square test and adjusted for the stratification factor (allogeneic transplantation vs oncology diagnosis). Due to multiple comparisons, the significance level was adjusted using the Bonferroni method so that $P < .017$ was considered to be statistically significant.

[b]The *P* value was calculated using the chi-square test. Due to multiple comparisons, the significance level was adjusted using the Bonferroni method so that $P < .017$ was considered to be statistically significant.

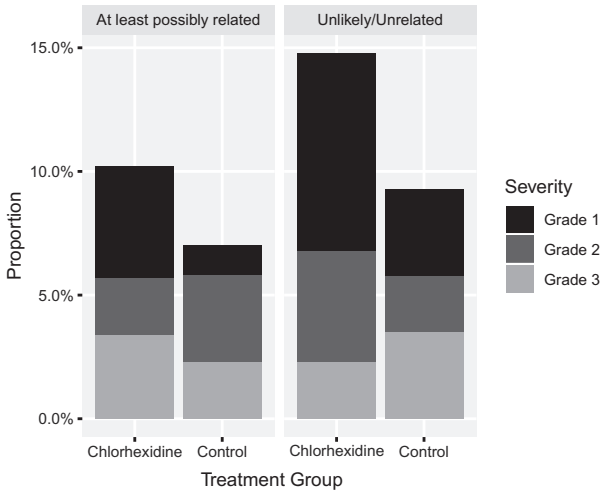

Figure 4. Cutaneous adverse events and their attribution by treatment group.

TABLE 4. Adverse Events in the Chlorhexidine Group Versus the Control Group

	Chlorhexidine		Control	
	22		14	
Overall no. of cutaneous events	At Least Possibly Related	Unlikely/Unrelated	At Least Possibly Related	Unlikely/Unrelated
By attribution	9[a]	13	6[b]	8
By grade and attribution[c]				
Grade 1	4	7	1	3
Grade 2	2	4	3	2
Grade 3	3	2	2	3

[a]Maculopapular rash in 9 patients.
[b]Maculopapular rash (4 patients), urticaria (1 patient), and dry and/or itchy skin (1 patient).
[c]Grading of cutaneous adverse events was performed by site staff using version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events.

We did not demonstrate an association between the use of CHG and reduced acquisition of resistant organisms, in contrast to some studies conducted in critically ill adults.[13,15,23,24] When evaluating only randomized controlled trials, one cluster randomized, controlled crossover trial demonstrated a reduction in the acquisition of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci (VRE) with the use of CHG (5.10 cases vs 6.60 cases per 1000 patient days; $P = .028$),[13] whereas 2 other randomized controlled trials failed to demonstrate a significant decrease in the acquisition of resistant organisms among those who used CHG.[11,19] The retrospective study by Bass et al regarding CHG bathing in adult oncology patients and HCT recipients demonstrated a nonsignificant reduction in VRE acquisition with CHG (relative risk, 0.48; 95% CI, 0.21-1.09).[6] We may have failed to demonstrate a benefit of CHG due to the small number of resistant organisms detected, particularly because the majority were CDI. Alternatively, CHG may not reduce the acquisition of resistant organisms in this population.

We also found that CHG exposure was associated with the acquisition of cutaneous staphylococci isolates with CHG MICs ≥4 ug/mL. To our knowledge, what constitutes clinically meaningful resistance to CHG and its associated implications remains largely undefined. We chose ≥4 a priori because this was a cut point used in other studies.[25,26] In another study of these staphylococci isolates, we found that the presence of a CHG MIC ≥4 was associated with a newly described variant of the *qacA* gene, which has the capacity to efflux CHG.[7] This new variant also was found to be associated with resistance to commonly used antimicrobials. The what to our knowledge are the few controlled trials of CHG bathing that have assessed CHG resistance in critically ill adults have reported variable results.[11,24] In one study, the median CHG MIC was slightly higher for bloodstream isolates identified in the CHG arm compared with those identified in the soap-and-water arm.[11] However, this appeared to result from the recovery of a few highly CHG-susceptible, gram-positive bacteria in the CHG arm rather than an increase in the absolute number or rate of isolates with elevated CHG MICs. In another study, the median CHG MICs for VRE were similar across the 3 arms (soap-and-water arm, CHG-impregnated cloths, and cloths without CHG).[24] Although the clinical implications of this finding are unclear, it raises a potential downside associated with the intervention.

To the best of our knowledge, few controlled trials of CHG bathing have performed systematic assessments for adverse events. Among critically ill adults, Climo et al reported skin reactions in approximately 1.9% of patients in the CHG group versus 3.4% in the controls.[13] Among critically ill children, Milstone et al[22] reported rashes in 3% of the CHG group compared with 1% of controls; however, only 1.2% of patients had a rash attributed to CHG. Cutaneous adverse events were not reported in the 2 previous oncology studies.[5,6] We found that cutaneous adverse events occurred in approximately 24% of patients in the CHG groups versus 15% of the control group. Although the frequencies of adverse events at least possibly attributable to the intervention were much lower (10% and 7%, respectively), the rates of cutaneous adverse events were higher than documented in other studies. This may reflect the sensitivity of the skin in pediatric patients receiving chemotherapy or merely indicate a difference in outcome ascertainment.

The strengths of the current study included the multicenter, double-blind, randomized design and the

blinded central adjudication of the primary outcome. In addition, the inclusion of an outcome that considered cutaneous staphylococcal isolates with elevated CHG MICs provided a balancing measure of potential risk. Its major limitations were the large number of patients who discontinued the study early and the early closure due to poor accrual, resulting in a small sample size and low power to detect hypothesized differences between the treatment and control groups. One reason for the poor accrual was the adoption of CHG bathing as the standard of care at many COG institutions. Although we conducted a post hoc conditional power analysis, it is important to emphasize that the findings may not have reflected the result that would have been observed had the trial been completed as planned. Nonetheless, considering the results of this sensitivity analysis, the likelihood that patients in the CHG group fared better than those in the control group appears to be very small. Other limitations included the fact that we did not have standardized approaches for CLABSI prevention or for bacterial identification and antibiotic susceptibility.

Although the current study had limitations, the results suggested that CHG bathing did not reduce rates of CLABSI, total blood cultures, or the acquisition of resistant organisms in children with cancer or those undergoing allogeneic HCT. CHG exposure was associated with the acquisition of cutaneous staphylococcal isolates with elevated CHG MICs. Ideally, data from fully enrolled randomized controlled trials would be used to guide practice change; however, at this time, there is no evidence that CHG bathing offers a benefit to children with cancer or those undergoing allogeneic HCT. Developers of clinical practice guidelines for the prevention of CLABSI will need to incorporate the results of this trial into their analysis of the aggregated evidence to determine whether the widely adopted practice of using CHG wipes in pediatric oncology and HCT patients should continue, and hospitals must carefully consider whether the potential benefit of using CHG in patients with cancer outweighs the potential harm.

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CONFLICT OF INTEREST DISCLOSURES

Danielle M. Zerr has received grants from the National Institutes of Health for work performed as part of the current study. Aaron M. Milstone has received grants from Sage Products LLC and personal fees from Becton Dickinson for work performed outside of the current study. Amanda L. Adler has received grants from the National Institutes of Health for work performed as part of the current study. Lu Chen was supported by a Statistics and Data Center Grant from the National Cancer Institute for the Children's Oncology Group (COG) for work performed as part of the current study. Brian T. Fisher has received grants from Pfizer and Merck and has received personal fees from Astellas for serving on a Data Safety Monitoring Board for work performed outside of the current study. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Danielle M. Zerr conceived the study and obtained grant funding with **Aaron M. Milstone** and **Lillian Sung**, and together with **Aaron M. Milstone**, **Christopher C. Dvorak**, **Amanda L. Adler**, **Xuan Qin**, and **Lillian Sung** designed the study. **Amanda L. Adler**, **Lolie C. Yu**, **Mary Conway Keller**, **Adam J. Esbenshade**, and **Keith J. August** obtained data and provided supervision for the study. **Amin Addetia** performed and **Xuan Qin** oversaw the laboratory studies on the cutaneous staphylococci isolates. **Lu Chen** designed the statistical analysis plan and **Doojduen Villaluna** and **Ha Dang** performed the analyses. **Doojduen Villaluna** and **Ha Dang** together with **Danielle M. Zerr**, **Aaron M. Milstone**, **Christopher C. Dvorak**, **Amanda L. Adler**, **Xuan Qin**, **Amin Addetia**, **Brian T. Fisher**, and **Lillian Sung** interpreted the data. **Danielle M. Zerr** drafted the article and all authors critically revised it.

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