EDITORIAL

Daily Chlorhexidine Bathing for Critically Ill Patients
A Note of Caution

Didier Pittet, MD, MS; Derek C. Angus, MD, MPH

With increasing concern about health care–associated infections and transmission of multidrug-resistant organisms (MDROs), there has been substantial support for universal decolonization strategies, especially for high-risk patients, such as those in the intensive care unit (ICU). One such strategy that is being adopted widely is the use of daily chlorhexidine bathing. However, the findings of Noto and colleagues[1] in this issue of *JAMA* challenge this approach.

This single-center, pragmatic, multiple crossover, cluster randomized clinical trial (RCT) involved 9340 patients admitted to 5 ICUs at a tertiary care medical center (Vanderbilt University). Because decolonization strategies, such as daily chlorhexidine bathing, are population-based interventions affecting the microbial ecology of the entire ICU population, the investigators appropriately assigned ICUs—not individual patients—to either intervention or control, using a cluster design. The ICUs were randomized to perform once-daily bathing of all patients with disposable cloths impregnated with 2% chlorhexidine or washing with nonantimicrobial cloths as the control measure. To increase the robustness of the research design to compensate for the small number of clusters, each ICU was crossed over 3 times between intervention and control bathing treatments. The bathing treatments were performed for a 10-week period followed by a 2-week period during which patients were bathed with nonantimicrobial disposable cloths before crossover to the alternative bathing treatment for 10 weeks. These sequential assignments facilitated better balance of patient case-mix between the control and intervention and helped control for other potential confounders.

Related article

The authors found that daily chlorhexidine bathing did not reduce the primary end point, the composite rate of central line-associated bloodstream infection (CLABSI), ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CAUTI), or *Clostridium difficile* infection. The primary outcome rate was 2.86 infectious episodes per 1000 patient-days during chlorhexidine bathing and 2.90 per 1000 patient-days during the control bathing period (rate difference, −0.04; 95% CI, −1.10 to 1.01; $P = .95$). Chlorhexidine bathing also did not reduce secondary outcomes, including health care–acquired bloodstream infection, blood culture contamination, or clinical cultures yielding MDRO.

This study has several limitations. First, the ICU staff could not be blinded to the bathing regimen, adherence to care practices was not monitored, and neither intracluster correlation nor the sequence of randomization to the bathing regimen was considered in the analysis. Second, the use of the chosen composite end point of CLABSI, VAP, CAUTI, and *C difficile* infection could be challenged because the evidence for the effect of daily chlorhexidine bathing on the latter 3 infection outcomes is relatively weak. Third, the overall health care–acquired infection rates were relatively low, and whether these results are applicable to other ICUs is unclear. Fourth, active surveillance was not performed to detect eventual cross-transmission of MDROs, although doing so is logistically challenging. Fifth, the study was not prospectively registered at a clinical trial registration site. The authors addressed this issue in the methods section of the article. During the editorial process, the authors provided extensive documentation, reassuring the *JAMA* editors that the study was conducted and analyzed in a manner faithful to the initial study protocol and analytic plan. Although investigators planning and conducting quality improvement projects may perceive that these studies do not need to be registered at clinical trial registration sites, all clinical trials, including those that focus on quality improvement, should be registered prospectively.

The findings of this study by Noto et al contrast with 2 notable prior studies by Climo et al[2] and by Huang et al.[3] Climo et al conducted a similar crossover, nonblinded cluster RCT involving 7727 patients in 6 ICUs or bone marrow transplant units to evaluate the effect of daily chlorhexidine bathing on the acquisition of MDROs and the incidence of health care–acquired bloodstream infection.[2] In this study, which reported a high MDRO prevalence in the control periods, the intervention significantly reduced the acquisition of vancomycin-resistant enterococci (VRE) (relative reduction, 25%) and the rate of health care–acquired bloodstream infection, including CLABSI (relative reduction, 28%). However, much of the reduction was explained by a lower frequency of positive blood cultures due to skin commensal organisms, and there was no significant effect on methicillin-resistant *Staphylococcus aureus* (MRSA) acquisition. Thus, chlorhexidine bathing could be considered to have reduced blood culture contamination rather than actual infection rates. In addition, the authors did not account for clustering effects and competing outcomes, resulting in a potential overestimate of the intervention effects.

The study by Huang et al did not assess chlorhexidine bathing directly.[3] Rather, the investigators sought to determine whether the rate of MRSA clinical isolates could be reduced among 74 256 patients in 74 ICUs using a multicomponent decolonization strategy (of which daily chlorhexidine bathing was a part) for all patients (universal decolonization) vs a strategy targeting only select high-risk patients. Universal decoloniza-

tion significantly reduced MRSA-positive clinical cultures (relative reduction, 37%) and health care–acquired bloodstream infection (relative reduction, 44%). However, adherence to key infection control measures, such as hand hygiene, was not monitored, and the individual benefit of daily chlorhexidine bathing could not be ascertained.

Universal decolonization strategies, such as daily chlorhexidine bathing, could accelerate resistance. Reduced susceptibility to antiseptic agents or disinfectants like chlorhexidine has received far less attention than the threat of antibiotic resistance. To date, there is no systematic method for measuring the clinical effect of reduced susceptibility to antiseptics and disinfectants. However, both cross-resistance and coresistance between antibiotics and antiseptics exist.[4] Indeed, widespread use of biocidal antiseptics into the environment might constitute a biological hazard via increased but selective pressure on microbial populations, potentially allowing more pathogenic organisms to flourish or facilitating resistance gene transfer.

Chlorhexidine bathing is considered a horizontal strategy,[5] applied universally, at population-based levels. Another horizontal strategy is application of nasal mupirocin ointment to suppress MRSA carriage. Different mechanisms of mupirocin resistance have been reported in parallel to its increasing use, associated with decolonization failure.[6] Chlorhexidine resistance is associated with plasmid-mediated *qacA/B* genes that code for multidrug efflux pumps in *S aureus*,[7] resulting in reduced bactericidal effects. Combined low-level mupirocin and genotypic chlorhexidine resistance significantly increased the risk of persistent MRSA carriage after decolonization therapy.[8] Of additional concern are reports of MDROs, in particular carbapenemase-producing *Klebsiella pneumoniae*, associated with chlorhexidine resistance. The use of low-dose chlorhexidine as a skin decolonization, device-coating antiseptic or environmental disinfectant agent may promote the selection and survival of strains with reduced susceptibility.[4] Thus, universal decolonization strategies are not without risk. At a minimum, any widespread use of mupirocin or chlorhexidine should be monitored for resistance and loss of effectiveness.[8] It would have been helpful to have had more complete data on resistance from all 3 of these studies.

Another helpful feature in future trials would be to monitor and report what is potentially the most useful horizontal strategy for reducing health care–acquired infections: improved hand hygiene.[9] Derde et al[10] recently assessed the association of different interventions with colonization and transmission of MDROs in 13 European ICUs. Improved hand hygiene combined with chlorhexidine bathing was associated with reduced acquisition of MDROs, especially MRSA (relative reduction, 57%). Importantly, the decrease in MDRO acquisition was principally related to increasing hand hygiene adherence.

Widespread treatment of patients with antimicrobials—whether antibiotics, antivirals, antifungals, or biocides—has never been a good idea. Issues around chlorhexidine use include allergy, costs, resistance, and even safety.[12] Although chlorhexidine bathing was found previously to reduce health care–acquired infection, the largest benefit appears to be in settings where the baseline prevalence of MDROs is high. In these settings, the same benefits potentially could be gained through other approaches, such as improved hand hygiene, which may be safer and less likely to affect the ecology of bacterial resistance in the ICU. The current study by Noto et al suggests that widespread adoption of daily chlorhexidine bathing is not indicated at this point, a position also articulated in the 2014 Society for Healthcare Epidemiology of America guidelines.[11] Rather, for institutions with infection rates similar to those reported in the current study, a simpler, less expensive approach that focuses on basic hygiene practices seems best.

ARTICLE INFORMATION

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Daily Chlorhexidine Bathing in the CCU: Should You Do It?

Andrew F. Shorr, MD, MPH | March 03, 2015

This is Andy Shorr from Washington, DC, with the Pulmonary and Critical Care Literature Update.

Today I want to discuss an article in the January 27, 2015, issue of *JAMA* by Noto and colleagues.[1] These authors investigated the impact of daily chlorhexidine bathing on the prevention of catheter-associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonias (VAP), and *Clostridium difficile* infections in patients in critical care units (CCUs).

These authors sought to replicate or refute the findings of an earlier study published in the *New England Journal of Medicine* by Climo and colleagues.[2] In that study, the investigators showed that chlorhexidine bathing substantially reduced the risk for hospital-acquired infection, primarily bloodstream infections, which was their focus, and the acquisition of certain resistant pathogens, namely methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).

The study by Climo and colleagues was not limited to CCUs, however. That study was criticized for including patients in a bone marrow transplant unit. In addition, they conducted active surveillance looking at acquisition, which also was criticized because that is not always done. Finally, in that study, it was unclear whether the bloodstream infections that were prevented were real bloodstream infections or skin contaminants causing blood culture contamination. Hence, although chlorhexidine bathing has been widely adopted because of the first study, questions remain about its actual efficacy.

Perhaps more important, chlorhexidine bathing is associated with direct costs and the potential for promoting resistance. For example, certain organisms that produce carbapenemases can become resistant to chlorhexidine, and the use of chlorhexidine could create selection pressure to produce more carbapenem-resistant Enterobacteriaceae (CREs), for which we have very few treatment options.

New Study Finds No Benefit From Chlorhexidine Bathing

The group from Vanderbilt University in Nashville, Tennessee, conducted a pragmatic randomized controlled trial.[1] They randomly assigned, in a crossover fashion, five CCUs to use chlorhexidine bathing or bathing with a non-antimicrobial-impregnated device. Then they looked at a composite endpoint of central line-associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), VAP, and *C difficile* infections

The study was very well done. Obviously, the investigators could not blind the CCU providers or the people recording data, and the unit of randomization was the CCU. However, each CCU crossed over from antimicrobial disinfection to regular bathing, back and forth three times, and the study included CCUs of various types (a neurology CCU, a medical CCU, etc) but only focused on CCUs.

The study included about 9000 patients overall. They excluded the patients who were only enrolled during the washout period when patients were bathed with non-antimicrobial disposable cloths. Again, they measured a pooled endpoint.

This study found no impact of chlorhexidine bathing on their combined endpoint of CLABSI, CLAUTI, VAP, and *C difficile* infection. Pooling those four complications may not make biologic sense because no evidence has suggested that chlorhexidine bathing will affect anything but CLABSIs. However, if the rate of all of these events is low in a given CCU, it is important to pool these infections to see whether you have missed something, or whether there is a signal you might not have otherwise seen.

Overall, these investigators saw absolutely no difference with chlorhexidine bathing vs without. In one of their specified subgroup analyses, the rate of VAP was doubled during one period of chlorhexidine bathing. They conducted several analyses, adjusting for a number of variables. In terms of their secondary endpoints, which were hospital length of stay, mortality, and other important considerations, they found no difference.

This important study should lead us to question the practice of chlorhexidine bathing, which we all leapt to doing after the publication of the initial study.[2] I believe we should go back and decide whether we really want to use a universal decontamination approach with chlorhexidine considering the potential risks. The true benefits are not clear. In the end, this is a very thought-provoking article in the January 27, 2015, issue of *JAMA*.

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Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Chlorhexidine Bathing and Health Care–Associated Infections
A Randomized Clinical Trial

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IMPORTANCE Daily bathing of critically ill patients with the broad-spectrum, topical antimicrobial agent chlorhexidine is widely performed and may reduce health care–associated infections.

OBJECTIVE To determine if daily bathing of critically ill patients with chlorhexidine decreases the incidence of health care–associated infections.

DESIGN, SETTING, AND PARTICIPANTS A pragmatic cluster randomized, crossover study of 9340 patients admitted to 5 adult intensive care units of a tertiary medical center in Nashville, Tennessee, from July 2012 through July 2013.

INTERVENTIONS Units performed once-daily bathing of all patients with disposable cloths impregnated with 2% chlorhexidine or nonantimicrobial cloths as a control. Bathing treatments were performed for a 10-week period followed by a 2-week washout period during which patients were bathed with nonantimicrobial disposable cloths, before crossover to the alternate bathing treatment for 10 weeks. Each unit crossed over between bathing assignments 3 times during the study.

MAIN OUTCOMES AND MEASURES The primary prespecified outcome was a composite of central line–associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), ventilator-associated pneumonia (VAP), and *Clostridium difficile* infections. Secondary outcomes included rates of clinical cultures that tested positive for multidrug-resistant organisms, blood culture contamination, health care–associated bloodstream infections, and rates of the primary outcome by ICU.

RESULTS During the chlorhexidine bathing period, 55 infections occurred: 4 CLABSI, 21 CAUTI, 17 VAP, and 13 *C difficile*. During the control bathing period, 60 infections occurred: 4 CLABSI, 32 CAUTI, 8 VAP, and 16 *C difficile*. The primary outcome rate was 2.86 per 1000 patient-days during the chlorhexidine and 2.90 per 1000 patient-days during the control bathing periods (rate difference, −0.04; 95% CI, −1.10 to 1.01; $P = .95$). After adjusting for baseline variables, no difference between groups in the rate of the primary outcome was detected. Chlorhexidine bathing did not change rates of infection-related secondary outcomes including hospital-acquired bloodstream infections, blood culture contamination, or clinical cultures yielding multidrug-resistant organisms. In a prespecified subgroup analysis, no difference in the primary outcome was detected in any individual intensive care unit.

CONCLUSION AND RELEVANCE In this pragmatic trial, daily bathing with chlorhexidine did not reduce the incidence of health care–associated infections including CLABSIs, CAUTIs, VAP, or *C difficile*. These findings do not support daily bathing of critically ill patients with chlorhexidine.

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Editorial

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Infections acquired during hospitalization (health care–associated infections) are associated with increased hospital length of stay, rates of death, and increased costs.[1-3] Substantial effort is devoted to preventing infections through practices designed to reduce the transmission of nosocomial pathogens, such as hand hygiene, bundles for insertion and care of devices, and isolation of patients with multidrug-resistant organisms.[4,5]

The skin of hospitalized patients is a reservoir for pathogens. Invasion by skin flora is thought to be a mechanism contributing to health care–associated infections.[6] Chlorhexidine is a broad-spectrum topical antimicrobial agent that, when used to bathe the skin, may decrease the bacterial burden thereby reducing infections. Several observational and quasi-experimental studies have found that daily bathing with chlorhexidine results in decreased skin colonization with multi-drug resistant organisms, decreased rates of bloodstream infections, and reduced *Clostridium difficile* infections.[7] A recent multicenter cluster-randomized trial demonstrated that bathing patients with chlorhexidine reduced multidrug-resistant organism acquisition and hospital-acquired bloodstream infections,[8] and chlorhexidine bathing is incorporated into some expert guidelines.[9] These results, however, have not been replicated and the effect of chlorhexidine bathing on other infections is unclear. Furthermore, chlorhexidine increases costs. Unnecessary exposure may result in the development of chlorhexidine resistance.[10,11] Therefore, we conducted a cluster-randomized trial to evaluate the effect of chlorhexidine bathing on the rates of multiple health care–associated infections among critically ill adults.

CAUTI *catheter-associated urinary tract infection*

CLABSI *central line–associated bloodstream infection*

ICU *intensive care unit*

VAP *ventilator-associated pneumonia*

Methods

Study Design

We performed a pragmatic cluster randomized, crossover, controlled study involving patients admitted to 5 adult intensive care units (ICUs) at a tertiary care medical center between July 2012 and July 2013. The neurological unit had 34, the surgical unit 34, and the trauma unit 31 ICU and step-down beds. The cardiovascular unit had 27 and the medical unit had 34 ICU beds. Each unit is staffed by critical care nurses and nurse practitioners with 24-hour physician coverage. Units performed once-daily bathing of all patients with cloths impregnated with 2% chlorhexidine (2% Chlorhexidine Gluconate Cloths, Sage Products) or with disposable nonantimicrobial cloths (Comfort Bath, Sage Products) as a control. Due to differences in the scent and appearance of the cloths, blinding of patients, treating physicians, nurses, and unit staff was not possible. Infection control personnel responsible for adjudicating infection outcomes according to standardized definitions were blinded to the treatment assignments. Each unit was randomized to a bathing sequence by generating 5 numbers from 1 to 2 at random using software available at http://www.randomizer.org. Each number in the sequence corresponded to 1 of the 5 ICUs. Those assigned a 1 began with chlorhexidine bathing and those assigned a 2 began with control bathing. Bathing assignment alternated thereafter. Bathing treatments were performed for a 10-week period followed by a 2-week washout period during which patients were bathed with nonantimicrobial disposable cloths, before crossover to the alternate bathing treatment for 10 weeks. Each unit crossed over between bathing assignments 3 times during the study (**Figure 1**).

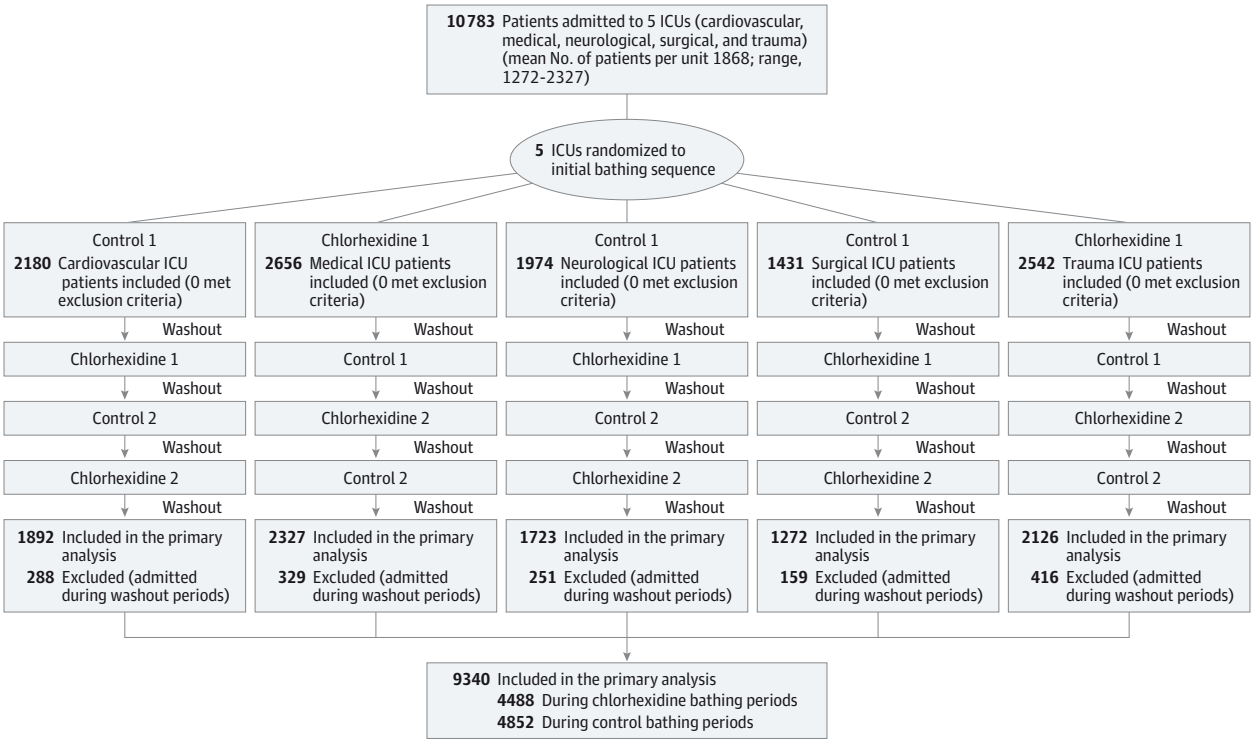
Bathing was performed once daily according to the manufacturer's instructions with sequential cloths used to rinse all body surfaces. Patients who became soiled after the initial daily bath were allowed to be bathed a second time in that day with bathing cloths maintaining the randomization. The face was not bathed to avoid exposure of the mucous membranes to chlorhexidine. The cardiovascular ICU used chlorhexidine cloths for a single, preoperative bathing of patients undergoing cardiac surgery regardless of the unit treatment assignment at the time. However, routine daily bathing of patients was performed according to the study bathing assignment. All other units were supplied only with the assigned cloths and the alternate cloths were not available during each bathing period. Prior to the study, 2 units were using daily chlorhexidine bathing in routine care and 3 were not. Before the study began, nurses on each unit were instructed to use only the available cloths and were reminded of proper bathing technique. All other infection control and cleaning procedures, including the use of contact precautions for patients colonized or infected with multidrug-resistant organisms, were performed according to the usual practice of each unit throughout the study period. Active surveillance for multidrug-resistant organism colonization was not done.

All patients admitted to the cardiovascular, medical, neurological, surgical, and trauma ICUs during the study period were included. Patients were excluded if they were known to have an allergy to chlorhexidine, were admitted with burns or toxic epidermal necrolysis or Stevens-Johnson syndrome, or the treating physician thought bathing would be unsafe. Patients admitted during a washout period were excluded from the primary analysis.

The study was approved by the Vanderbilt University Institutional Review Board with waiver of consent.

This study was conceived as an institutional quality improvement project and underwent institutional review board review as is our practice, with approval of the study design, end points, and analysis plan on May 7, 2012 (study protocol is available in Supplement 1). Patient enrollment began July 19, 2013. After patient enrollment was completed, the researchers realized the novel design and size of this study might be of interest to others and registered the study at clinicaltrials.gov on January 8, 2014; this occurred before any data analyses were conducted. The study end points are concordant with the protocol approved by the institutional review board, a detailed statistical analysis plan dated November 26, 2013, those specified in the trial

Figure 1. Recruitment, Randomization, and Patient Flow of Chlorhexidine Bathing Study



A total of 10 783 patients were admitted to the participating intensive care units (ICUs) during the study period. Each ICU was randomized to an initial bathing treatment for a 10-week period followed by a 2-week washout prior to crossover into the alternate bathing treatment. Each unit crossed between treatments 3 times during the study period. Therefore, each unit received 2 nonsequential 10-week periods of chlorhexidine bathing alternating with 2 nonsequential 10-week periods of control bathing. The 1443 patients admitted during washout periods were excluded from the analysis per protocol. The number of patients admitted to each ICU is shown.

registration, and the results reported in this article. Health care–associated bloodstream infections were added as a secondary end point because these data became available electronically during the course of the study. The complete data set was available to investigators for analysis on February 4, 2014. No data analyses were conducted during the study or prior to trial registration.

Study Outcomes and Definitions

Because individual health care–associated infections are rare events, the analysis plan specified a composite primary outcome including central line–associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), possible or probable ventilator-associated pneumonia (VAP), or *C difficile* infection. Infections were determined using Centers for Disease Control and Prevention National Healthcare Safety Network definitions by trained infection control personnel, who were blinded to the bathing assignment.[12] Secondary outcomes included the rates of each individual infection included in the primary outcome, in-hospital mortality, hospital and ICU length of stay, rates of clinical cultures positive for multidrug-resistant organisms (number of positive cultures per 1000 patient-days), blood culture contamination (number of contaminants per 1000 patient-days), health care–associated bloodstream infections, and rates of the primary outcome by ICU. Additional definitions of infection-related outcomes are available in the online eAppendix in Supplement 2.

Statistical Analysis

The study was conducted over 1 year. The approximately 10 000 patients expected to be admitted to the participating ICUs based on the previous year's admissions would provide at least 95% power to detect a change in the primary outcome of 0.1 infections per 1000 patient-days. Using an intention-to-treat-design, each patient was analyzed according to the bathing assignment of the unit at the time of admission regardless of length of stay or the number of days he/she was bathed. Patients whose hospital stay bridged a crossover event, and therefore changed bathing treatment, were analyzed according to their initial bathing assignment. The primary analysis was a comparison of the infection rate (number of infections per 1000 patient-days) between groups using a Poisson regression model. All events meeting an outcome definition were included. Therefore, repeated infections from an individual patient were included as events in the analysis. Several patients contributed to multiple events: 5 to the primary outcome, 24 with clinical cultures that tested positive for multidrug-resistant organisms, 23 for health care–associated bloodstream infections, and 34 for blood culture contamination.

Table 1. Baseline Demographics and Clinical Characteristics

	Control (n = 4852)	Chlorhexidine (n = 4488)	*P* Value
Age, median (IQR), y[a]	57.0 (42-68)	56.0 (42-68)	.82
Men, No. (%)[b]	2805 (57.8)	2586 (57.6)	.85
Race, No. (%)[b]			
White	4045 (83.4)	3668 (81.7)	.16
Black	592 (12.2)	593 (13.2)	
Other	62 (1.3)	58 (1.3)	
Unknown	153 (3.2)	169 (3.8)	
Admission ICU, No. (%)[b]			
Medical	1215 (25.0)	1112 (22.9)	.37
Trauma	1072 (22.1)	1054 (21.7)	
Cardiovascular	986 (20.3)	906 (18.7)	
Neurological	925 (19.1)	798 (16.5)	
Surgical	654 (13.5)	618 (12.7)	
Baseline laboratory data			
Creatinine, median (IQR), mg/dL[a]	0.98 (0.78-1.34)	0.98 (0.78-1.32)	.96
Hemoglobin, mean (SD), g/dL[a]	12.09 (2.45)	12.08 (2.45)	.92
WBC × 1000/mL, median (IQR)[a]	10.8 (7.80-15.30)	10.8 (7.70-15.00)	.18
Serum lactate, median (IQR), mg/dL[a]	9.91 (7.21-17.12)	9.91 (6.31-17.12)	.53
Expected mortality, median (IQR), %[a]	1.39 (0.40-6.42)	1.39 (0.38-6.14)	.049
Comorbidities, No. (%)			
Respiratory disease[b]	3633 (74.9)	3447 (76.8)	.03
Cardiovascular disease[b]	3669 (75.6)	3328 (74.2)	.10
Renal disease[b]	1338 (27.6)	1242 (27.7)	.92
Diabetes mellitus[b]	1273 (26.3)	1176 (26.2)	.97
Malignancy[b]	1005 (20.7)	950 (21.2)	.59

Abbreviations: Expected mortality, University HealthSystem Consortium–expected mortality; ICU, intensive care unit; IQR, interquartile range; WBC, white blood cell count.

Conversion factors: to convert creatinine from mg/dL to µmol/L, multiply by 88.4; lactate from mg/dL to mmol/L, multiply by 0.111.

[a] *P* value derived using Mann-Whitney U test.

[b] *P* value derived using uncorrected Pearson χ^2 test; missing data, University HealthSystem Consortium–expected mortality (n = 156), lactate (n = 5669), hemoglobin (n = 151), creatinine (n = 108).

Prespecified secondary analyses included tests for a chlorhexidine effect for each individual infection comprising the primary outcome, differences in hospital and ICU length of stay as well as rates of health care-associated bloodstream infections, blood culture contamination, and cultures positive for multidrug-resistant organisms using a Mann-Whitney U test or Poisson model where appropriate. Adjusted estimates of chlorhexidine effect were obtained using a logistic and Poisson model. Covariates included age, sex, race (white, nonwhite, or unknown), admission ICU, study time, University HealthSystem Consortium-expected mortality,[13] comorbid conditions, and admission white blood cell count, along with bathing assignment. Race was collected from an administrative database based on patient self-reporting. Effectiveness of chlorhexidine was also assessed by comparing the primary outcome occurrence rate within each ICU using Poisson regression. Sensitivity analyses were performed including an analysis in which patients receiving both bathing treatments were excluded, an as-treated analysis to account for a study protocol violation, and a group-level analysis performed on the unit clusters as opposed to analyses of individual patients. A logistic regression model with the same covariates and primary predictors of treatment assignment described above including an interaction term for treatment assignment and infection status was used to estimate the effect of chlorhexidine on the outcome of in-hospital mortality as well as its interaction with our primary outcome. All tests were 2-tailed with a significance threshold of $P < .05$. The statistical analysis was performed with R (version 2.10.1, http://www.r-project.org, the R Foundation for Statistical Computing) and IBM SPSS Statistics (version 22).

Results

Enrollment and Patient Characteristics

A total of 10 783 patients were admitted to the 5 participating ICUs during the study period (Figure 1). None met exclusion criteria. The 1443 patients admitted during washout periods were excluded from the analysis per protocol. Therefore, 9340 patients were included in the primary analysis with 4488 patients in the chlorhexidine bathing periods and 4852 patients in the control bathing periods. Baseline patient characteristics were balanced between the control and intervention periods with regard to age, sex, race/ethnicity, comorbid conditions, and baseline laboratory data (**Table 1**).

Primary Outcome

A total of 55 infections occurred during the chlorhexidine bathing period (4 CLABSI, 21 CAUTI, 17 VAP, and 13 *C difficile*) and 60 infections during the control bathing periods (4 CLABSI, 32 CAUTI, 8 VAP, and 16 *C difficile* infections). The rate of the primary outcome was 2.86 per 1000 patient-days during chlorhexidine bathing and 2.90 per

Table 2. Primary and Secondary Outcomes

	Control			Chlorhexidine			Rate Difference (95% CI)	*P* Value
	Rate (95% CI)	No. of Events	No. of Patients	Rate (95% CI)	No. of Events	No. of Patients		
Intention-to-treat analysis								
No. of patients			4852			4488		
Patient-days, No.	20 720.5			19 201.5				
Composite primary outcome[a]	2.90 (2.16 to 3.63)	60	58	2.86 (2.11 to 3.62)	55	52	−0.04 (−1.10 to 1.01)	.95
Infections per 1000 patient-days								
CLABSI[a]	0.19 (0.004 to 0.38)	4	4	0.21 (0.004 to 0.41)	4	4	0.02 (−0.26 to 0.30)	.91
CAUTI[a]	1.54 (1.01 to 2.08)	32	31	1.09 (0.63 to 1.56)	20	21	−0.45 (−1.16 to 0.26)	.22
Clostridium difficile[a]	0.77 (0.39 to 1.15)	16	16	0.68 (0.31 to 1.05)	13	13	−0.09 (−0.62 to 0.44)	.72
VAP[a]	0.39 (0.12 to 0.65)	8	8	0.89 (0.46 to 1.31)	17	17	0.5 (0.0013 to 0.999)	.05
HA-BSI[a]	5.45 (4.45 to 6.46)	113	95	5.00 (4.00 to 6.00)	96	80	−0.45 (−1.87 to 0.97)	.53
Blood culture contamination[b]	5.45 (4.45 to 6.46)	113	96	4.84 (3.86 to 5.83)	93	73	−0.61 (−2.02 to 0.80)	.40
Clinical cultures positive for MDROs[a,d]	5.41 (4.40 to 6.41)	112	85	4.84 (3.86 to 5.83)	93	79	−0.57 (−1.97 to 0.83)	.43
Length of stay, mean (95% CI), d[c]								
ICU	2.39 (1.21 to 4.95)			2.56 (1.24 to 5.09)			0.169 (−0.01 to 0.321)	.12
Hospital	5.0 (2.0 to 9.0)			5.0 (2.0 to 9.0)			0 (0 to 0)	.38
In-hospital mortality, No. (%)[e]	449 (9.25)		449	367 (8.18)		367	−1.07 (−2.22 to 0.07)	.07
In-hospital mortality adjusted[f]								.32
As-treated analysis								
No. of patients			5091			4253		
Patient-days, No.	21 507.5			18 464.4				
Composite primary outcome[a]	2.84 (2.12 to 3.55)	61	59	2.98 (2.19 to 3.77)	55	52	0.14 (−0.92 to 1.20)	.79
Infections per 1000 patient-days								
CLABSI[a]	0.19 (0.004 to 0.37)	4	4	0.22 (0.004 to 0.43)	4	4	0.03 (−0.25 to 0.31)	.83
CAUTI[a]	1.53 (1.01 to 2.06)	33	32	1.14 (0.65 to 1.62)	21	20	−0.39 (−1.11 to 0.33)	.28
Clostridium difficile[a]	0.74 (0.38 to 1.11)	16	16	0.70 (0.32 to 1.09)	13	13	−0.04 (−0.57 to 0.49)	.88
VAP[a]	0.37 (0.11 to 0.63)	8	8	0.92 (0.48 to 1.36)	17	17	0.55 (0.05 to 1.05)	.04
HA-BSI[a]	5.35 (4.37 to 6.32)	115	97	4.93 (3.92 to 5.94)	91	76	−0.42 (−1.83 to 0.99)	.56
Blood culture contamination[b]	5.25 (4.29 to 6.22)	113	96	4.82 (3.82 to 5.82)	89	70	−0.43 (−1.82 to 0.96)	.54
Clinical cultures positive for MDROs[d]	5.35 (4.37 to 6.32)	115	88	5.03 (4.01 to 6.06)	93	79	−0.31 (−1.72 to 1.10)	.67
Length of stay, mean (95% CI), d								
ICU[a]	2.36 (1.20 to 4.89)			2.61 (1.28 to 5.22)			0.247 (.102 to 0.394)	.004
Hospital[c]	5.0 (2.0 to 9.0)			5.0 (2.0 to 9.0)			0 (0 to 0)	.92
In-hospital mortality, No. (%)[e]	474 (9.31)		474	346 (8.14)		346	−1.17 (−2.3 to −0.03)	.046
In-hospital mortality adjusted[f]								.051

Abbreviations: CAUTI, catheter-associated urinary tract infection; CLABSI, central line–associated bloodstream infection; HA-BSI, health care–associated bloodstream infection; ICU, intensive care unit; MDROs, multidrug-resistant organisms; VAP, probable and possible ventilator-associated pneumonia.

[a] *P* value derived using Poisson regression.

[b] Blood culture contamination is expressed as number of contaminated blood cultures per 1000 patient-days.

[c] *P* value derived using Mann-Whitney U test.

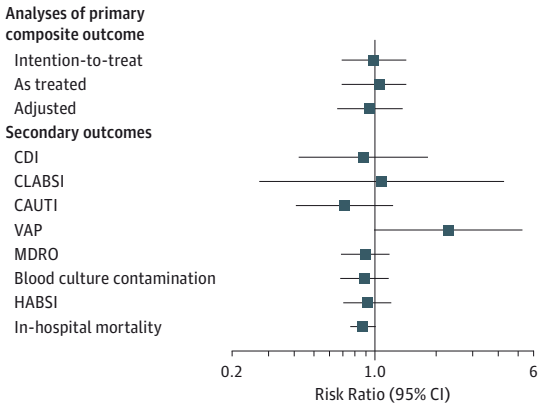
[d] MDROs are expressed as clinical cultures positive for MDROs per 1000 patient-days.

[e] *P* value derived using uncorrected Pearson χ^2 test.

[f] *P* value calculated after adjusting for University HealthSystem Consortium–expected mortality in logistic regression model.

1000 patient-days during control bathing (rate difference, −0.04; 95% CI, −1.10 to 1.01; *P* = .95). After adjusting for age, sex, race/ethnicity, unit of admission, time, comorbid conditions, and admission white blood cell count, no significant difference between groups in the rate of the primary outcome was detected (adjusted risk ratio in treatment group, 0.94; 95% CI, 0.65 to 1.37; *P* = .83) (**Table 2**, **Figure 2**). Five patients who developed more than 1 infection were included in the primary outcome during the study (3 during chlorhexidine and 2 during control bathing).

Figure 2. Effect of Chlorhexidine Bathing on Primary and Secondary Outcomes



The chlorhexidine effect on intention-to-treat, as-treated, and adjusted analyses of the primary outcome of the composite rate of central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), probable and possible VAP (ventilator-associated pneumonia), and *Clostridium difficile* infection (CDI) are shown. Intention-to-treat analyses of secondary outcomes, which are components of the primary outcomes, are shown. HA-BSI indicates health care–associated bloodstream infection; MDRO, multidrug-resistant organisms. For crude data, see Table 2.

Secondary Outcomes

No significant difference in the rate of health care–associated bloodstream infections was seen between the chlorhexidine and control periods (5.00 and 5.45, respectively; rate difference, −0.45; 95% CI, −1.87 to 0.97; P = .53; Table 2, Figure 2). In addition, no significant differences in the rates of blood culture contamination (4.84 per 1000 patient-days and 5.45 per 1000 patient-days; rate difference, −0.61; 95% CI, −2.02 to 0.80; P = .40) or clinical cultures positive for multidrug-resistant organisms (4.84 and 5.41 per 1000 patient-days; rate difference, −0.57; 95% CI, −1.97 to 0.83; P = .43) were found between the chlorhexidine and control periods (Table 2 and eTable 3 in Supplement 2, Figure 2). When analyzed independently, the individual infections comprising the primary outcome were not significantly different between intervention and control bathing periods and no difference in ICU or hospital length of stay was observed (Table 2). In-hospital mortality was 8.18% in the chlorhexidine bathing periods and 9.25% in the control periods (difference in percent, −1.07%; 95% CI, −2.22% to 0.07%; P = .07).

In a prespecified subgroup analysis by ICU, no difference in the rate of the primary outcome was detected in any individual ICU in the chlorhexidine bathing and control periods (**Table 3** and **Table 4** and **Figure 3**). A significant reduction in blood culture contamination (2.37 and 8.25 per 1000 patient-days during chlorhexidine and control periods, respectively; rate difference, −5.88; 95% CI, −9.41 to −2.35; P = .003) was detected in the cardiovascular ICU during periods of chlorhexidine bathing without a significant reduction in health care–associated bloodstream infections (2.71 and 4.42 per 1000 patient-days during chlorhexidine and control periods, respectively; rate difference, −1.71; 95% CI, −4.63 to 1.21; P = .26). The rates of health care–associated bloodstream infections, blood culture contamination, or clinical cultures positive for multidrug-resistant organisms did not differ between intervention and control periods in any other unit. Although infection-related outcomes did not differ, the trauma ICU had a significant reduction in in-hospital mortality during periods of chlorhexidine bathing (6.17% vs 8.58%; difference in percent, −2.41%; 95% CI, −4.64% to −0.19%; P = .03). After adjusting for the University HealthSystem Consortium–expected mortality rate, the adjusted odds ratio was 0.85 (95% CI, 0.51-1.39; P = .51).

Three post hoc analyses were performed: (1) an as-treated analysis to address a protocol violation in the cardiovascular ICU where 235 patients bathed with the incorrect cloths were analyzed according to the bathing treatment they received rather than the bathing treatment they were assigned (Table 2), (2) an analysis in which the 658 patients whose hospital stay spanned a crossover event were excluded and therefore received both bathing treatments (eTable 1 in Supplement 2), and (3) a group-level analysis performed on the unit clusters as opposed to the analyses of individual patients (eTable 2 in Supplement 2). In each of these analyses, no difference between groups was detected for the primary outcome, health care–associated bloodstream infections, blood culture contamination, or clinical cultures testing positive for multidrug-resistant organisms. When the infections comprising the primary outcome were analyzed individually, a statistically significant increase in possible or probable VAP was detected during periods of chlorhexidine bathing in all post hoc analyses (as-treated: 0.37 and 0.92 per 1000 patient-days in chlorhexidine and control bathing periods, respectively, rate difference, 0.55; 95% CI, 0.05-1.05; P = .04; analysis excluding patients who received both bathing treatments: 0.24 and 0.84 per 1000 patient-days in chlorhexidine and control bathing periods, respectively, rate difference, 0.6; 95% CI, 0.09-1.11; P = .03; and group-level analysis performed on the unit clusters: 0.41 and 0.95 per 1000-patient days in chlorhexidine and control bathing periods, respectively, rate difference, 0.54; 95% CI, 0.02-1.06; P = .047; Table 2 and eTables 1 and 2 in Supplement 2).

A nonsignificant reduction in-hospital mortality was present during chlorhexidine bathing periods in the primary intention-to-treat analysis (9.25% vs 8.18% during control and chlorhexidine bathing periods, respectively, rate difference, −1.07; 95% CI, −2.2 to 0.07; P = .07). In-hospital mortality was significantly reduced during chlorhexidine bathing periods in 2 post hoc analyses (as-treated analysis, 8.14% and 9.31% in chlorhexidine and control periods, respectively, rate difference, −1.17; 95% CI −2.3 to −0.03; P = .046; analysis excluding patients who received both bathing treatments, 7.99% and 9.24% in the chlorhexidine and control periods, respectively, 95% CI, −1.25; −.02 to .001; P = .04, Table 2 and eTable 1 in Supplement 2). This reduction in in-hospital mortality was not present after adjusting for baseline variables (as-treated analysis adjusted P = .051, analysis excluding patients who received both bathing treatments adjusted P = .31; eTables 4, 5, and 6 in Supplement 2).

Table 3. Primary and Secondary Outcomes for Cardiovascular and Medical Intensive Care Units[a]

	Control			Chlorhexidine				
	Rate (95% CI)	No. of Events	No. of Patients	Rate (95% CI)	No. of Events	No. of Patients	Rate Difference (95% CI)	*P* Value
Cardiovascular ICU								
No. of patients			986			906		
Patient-days	3392.3			2954.8				
Primary outcome[b]	2.06 (0.53 to 3.59)	7	6	0.68 (0 to 1.61)	2	2	−1.38 (−3.17 to 0.41)	.16
Infections per 1000 patient-days								
CLABSI[b]	0.59 (0 to 1.41)	2	2	0.34 (0 to 1.00)	1	1	−0.25 (−1.30 to 0.80)	.65
CAUTI[b]	1.18 (0.02 to 2.33)	4	4	0	0	0	−1.18 (−2.34 to −0.024)	
Clostridium difficile[b]	0	0	0	0.34 (0 to 1.00)	1	1	0.34 (−0.32 to 1.00)	
VAP[b]	0.29 (0 to 0.87)	1	1	0	0	0	−0.29 (−0.87 to 0.29)	
HA-BSI[b]	4.42 (2.18 to 6.66)	15	12	2.71 (0.83 to 4.58)	8	7	−1.71 (−4.63 to 1.21)	.26
Blood culture contamination[a,b]	8.25 (5.20 to 11.31)	28	21	2.37 (0.61 to 4.12)	7	5	−5.88 (−9.41 to −2.35)	.003
Clinical cultures positive for MDROs[a,b]	3.24 (1.33 to 5.16)	11	9	1.69 (0.21 to 3.18)	5	4	−1.55 (−3.97 to 0.87)	.23
In-hospital mortality, No. (%)[c]	81 (8.22)		81	57 (6.29)		57	−1.93 (−4.36 to 0.41)	.11
In-hospital mortality adjusted[d]								.87
Medical ICU								
No. of patients			1215			1112		
Patient-days	4575.5			4544.8				
Primary outcome[b]	2.62 (1.14 to 4.11)	12	12	1.98 (0.69 to 3.27)	9	9	−0.64 (−2.61 to 1.33)	.52
Infections per 1000 patient-days								
CLABSI[b]	0.22 (0 to 0.65)	1	1	0	0	0	−0.22 (−0.64 to 0.21)	
CAUTI[b]	0.87 (0.02 to 1.73)	4	4	1.32 (0.26 to 2.38)	6	6	0.45 (−0.91 to 1.81)	.52
Clostridium difficile[b]	1.31 (0.26 to 2.36)	6	6	0.44 (0 to 1.05)	2	2	−0.87 (−2.08 to 0.34)	.18
VAP[b]	0.22 (0 to 0.65)	1	1	0.22 (0 to 0.65)	1	1	0 (−0.61 to 0.61)	>.99
HA-BSI[b]	8.31 (5.66 to 10.95)	38	31	5.72 (3.52 to 7.92)	26	20	−2.59 (−6.03 to 0.85)	.14
Blood culture contamination[a,b]	10.71 (7.71 to 13.71)	49	41	9.02 (6.26 to 11.78)	41	31	−1.69 (−5.77 to 2.39)	.42
Clinical cultures positive for MDROs[a,b]	7.43 (4.93 to 9.93)	34	28	7.48 (4.97 to 10.00)	34	31	0.05 (−3.49 to 3.59)	.98
In-hospital mortality, No. (%)[c]	186 (15.31)		186	159 (14.3)		159	−1.01 (−3.90 to 1.88)	.49
In-hospital mortality adjusted[d]								.33

Abbreviations: CAUTI, catheter-associated urinary tract infection; CLABSI, central line–associated bloodstream infection; ICU, intensive care unit; MDROs, multidrug-resistant organisms; VAP, probable and possible ventilator-associated pneumonia; HA-BSI, health care–associated bloodstream infection.

[a] Blood culture contamination expressed as number of contaminated blood cultures per 1000 patient-days; MDROs expressed as clinical cultures positive for MDROs per 1000 patient-days

[b] *P* value derived using Poisson regression.

[c] *P* value derived using uncorrected Pearson χ^2 test.

[d] *P* value calculated after adjusting for University HealthSystem Consortium–expected mortality in logistic regression model.

Discussion

In this single-center, multi-ICU, cluster randomized, crossover study, once daily bathing with chlorhexidine did not reduce the rate of the composite primary outcome of infections including CLABSI, CAUTI, possible or probable VAP, or infection with *C difficile*. Other infection-related secondary outcomes, including health care-associated bloodstream infections, blood culture contamination, and clinical cultures positive for multi-drug resistant organisms were also not improved by chlorhexidine. Chlorhexidine bathing is widely practiced in an effort to reduce health care–associated infections and has been incorporated into some expert guidelines.[9] Yet chlorhexidine use incurs a cost and exposure to chlorhexidine may increase microbial resistance.[10,11] Therefore, the finding that chlorhexidine bathing did not reduce infections in this study suggests that such bathing may not be necessary, resulting in cost saving and avoidance of unnecessary exposure without adversely affecting clinical outcome.

In contrast to the findings of the current study, Climo et al[8] performed a multicenter, cluster randomized, crossover trial of daily chlorhexidine bathing of 7727 patients admitted to 9 ICUs or bone marrow units and reported a significant reduction in methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) acquisition, health

Table 4. Primary and Secondary Outcomes for Neurological, Surgical, and Trauma Intensive Care Units[a]

	Control			Chlorhexidine				
	Rate (95% CI)	No. of Events	No. of Patients	Rate (95% CI)	No. of Events	No. of Patients	Rate Difference (95% CI)	*P* Value
Neurological ICU								
No. of patients			925			798		
Patient-days	4622.8			4123.6				
Primary outcome[b]	3.24 (1.60 to 4.89)	15	14	3.15 (1.44 to 4.87)	13	11	−0.09 (−2.46 to 2.28)	.94
Infections per 1000 patient-days								
CLABSI[b]	0	0	0	0	0	0	0	
CAUTI[b]	3.24 (1.60 to 4.89)	15	14	2.18 (0.76 to 3.61)	9	8	−1.06 (−3.23 to 1.11)	.35
Clostridium difficile[b]	0	0	0	0.97 (0.02 to 1.92)	4	4	0.97 (0.02 to 1.92)	
VAP[b]	0	0	0	0	0	0	0	
HA-BSI[b]	6.06 (3.81 to 8.30)	28	24	5.82 (3.4 to 8.15)	24	18	−0.24 (−3.47 to 2.99)	.89
Blood culture contamination[a,b]	4.11 (2.26 to 5.96)	19	17	5.82 (3.49 to 8.15)	24	21	1.71 (−1.26 to 4.68)	.26
Clinical cultures positive for MDROs[a,b]	5.84 (3.64 to 8.04)	27	19	3.40 (1.62 to 5.17)	14	14	−2.44 (−5.27 to 0.39)	.1
In-hospital mortality No. (%)[c]	61 (6.59)		61	54 (6.77)		54	0.18 (−2.20 to 2.54)	.89
In-hospital mortality adjusted[c]								.67
Surgical ICU								
No. of patients			654			618		
Patient-days, No.	4343.0			3479.1				
Primary outcome[b]	2.99 (1.37 to 4.62)	13	13	1.72 (0.34 to 3.10)	6	6	−1.27 (−3.40 to 0.86)	.26
Infections per 1000 patient-days								
CLABSI[b]	0.23 (0 to 0.68)	1	1	0	0	0	−0.23 (−-0.68 to 0.22)	
CAUTI[b]	0.69 (0 to 1.47)	3	3	0.57 (0 to 1.37)	2	2	−0.12 (−1.24 to 1.00)	.84
Clostridium difficile[b]	2.07 (0.72 to 3.43)	9	9	0.29 (0 to 0.85)	1	1	−1.78 (−3.25 to −0.31)	.06
VAP[b]	0	0	0	0.86 (0 to 1.84)	3	3	0.86 (−0.12 to 1.84)	
HA-BSI[b]	4.61 (2.59 to 6.62)	20	18	3.45 (1.50 to 5.40)	12	12	−1.16 (−3.97 to 1.65)	.43
Blood culture contamination[a,b]	1.38 (0.28 to 2.49)	6	6	2.30 (0.71 to 3.89)	8	6	0.92 (−1.02 to 2.86)	.35
Clinical cultures positive for MDROs[a,b]	6.45 (4.06 to 8.84)	28	17	6.32 (3.68 to 8.97)	22	17	−0.13 (−3.69 to 3.43)	.95
In-hospital mortality, No. (%)[c]	29 (4.43)		29	32 (5.18)		32	0.75 (−1.61 to 3.10)	.54
In-hospital mortality adjusted[d]								.78
Trauma ICU								
No. of patients			1072			1054		
Patient-days, No.	3787.0			4099.1				
Primary outcome[b]	3.43 (1.57 to 5.30)	13	13	6.10 (3.71 to 8.49)	25	24	2.67 (−0.36 to 5.70)	.09
Infections per 1000 patient-days								
CLABSI[b]	0	0	0	0.73 (0 to 1.56)	3	3	0.73 (−0.10 to 1.56)	
CAUTI[b]	1.58 (0.32 to 2.85)	6	6	0.98 (0.02 to 1.93)	4	4	−0.6 (−2.19 to 0.99)	.45
Clostridium difficile[b]	0.26 (0 to 0.78)	1	1	1.22 (0.15 to 2.29)	5	5	0.96 (−0.23 to 2.15)	.16
VAP[b]	1.58 (0.32 to 2.85)	6	6	3.17 (1.45 to 4.90)	13	13	1.56 (−0.58 to 3.70)	.16
HA-BSI[b]	3.17 (1.38 to 4.96)	12	10	6.34 (3.90 to 8.78)	26	23	3.17 (0.14 to 6.20)	.047
Blood culture contamination[a,b]	2.90 (1.19 to 4.62)	11	11	3.17 (1.45 to 4.90)	13	10	0.27 (−2.16 to 2.70)	.83
Clinical cultures positive for MDROs[a,b]	3.17 (1.38 to 4.96)	12	12	4.39 (2.36 to 6.42)	18	15	1.22 (−1.49 to 3.93)	.38
In-hospital mortality, No. (%)[c]	92 (8.58)		92	65 (6.17)		65	−2.41 (−4.64 to −0.19)	.03
In-hospital mortality adjusted[d]								.51

Abbreviations: CAUTI, catheter-associated urinary tract infection; CLABSI, central line–associated bloodstream infection; ICU, intensive care unit; MDROs, multidrug-resistant organisms; VAP, probable and possible ventilator-associated pneumonia; HA-BSI, health care–associated bloodstream infection.

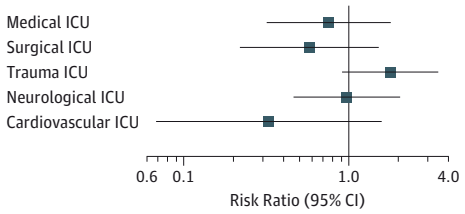
[a] Blood culture contamination is expressed as number of contaminated blood cultures per 1000 patient-days; MDROs, as clinical cultures positive for MDROs per 1000 patient-days.

[b] *P* value derived using Poisson regression.

[c] *P* value derived using uncorrected Pearson χ^2 test.

[d] *P* value calculated after adjusting for University HealthSystem Consortium–expected mortality in logistic regression model.

Figure 3. Effect of Chlorhexidine Bathing on the Primary Outcome by Intensive Care Unit



The chlorhexidine effect on the primary outcome of the composite rate of central line–associated bloodstream infection, catheter-associated urinary tract infection, probable and possible ventilator-associated pneumonia, and *Clostridium difficile* infection in a prespecified subgroup of the intention-to-treat analysis by intensive care unit (ICU) is shown. The vertical line depicts a risk ratio of 1. For crude data, see Table 3 and Table 4.

care-associated bloodstream infections, and CLABSI with chlorhexidine bathing. These studies differ in several ways. The duration of the chlorhexidine bathing intervention in the Climo study was 24 weeks compared with 10 weeks in the current study. It is possible that a longer intervention may have ecological consequences that reduce infectious outcomes. Climo et al performed active surveillance for MRSA and VRE colonization, and included bone marrow transplant units, neither of which were done in this study. Because bone marrow transplant places patients at high risk of infection, this may have altered outcomes. In addition, some of the infection rates were low in this study, and a lower limit to the rates of infection may exist beyond which chlorhexidine bathing no longer provides detectable benefit. The reduction in health care-associated bloodstream infections in the Climo study was driven primarily by a reduction in positive blood culture results caused by the skin commensal coagulase-negative staphylococci, and it is not clear if this observation was a result of blood culture contamination or true infection. Another recent study included chlorhexidine bathing as one of many interventions shown to reduce MRSA clinical isolates in a large cluster randomized trial of targeted vs universal decolonization of ICU patients.[14] The individual benefit from chlorhexidine bathing cannot be ascertained from this study, however.

In post hoc unadjusted analyses, in-hospital mortality was significantly reduced during periods of chlorhexidine bathing but not after adjustment for baseline variables (Table 2 and eTable 1 in Supplement 2). This finding also does not account for multiple comparisons. Furthermore, this in-hospital mortality difference is partially explained by differences in the University HealthSystem Consortium–expected mortality, which differ between bathing periods. Although it is possible that chlorhexidine bathing reduced the incidence of unmeasured infections, such as viral or surgical site infections, no clear mechanism for improved survival from chlorhexidine bathing exists in the absence of reduced infections.

This study has several strengths. The multiple crossover events allowed for assessment of 2 temporally separated intervention and control periods within each unit, which better accounts for intercluster variability while also controlling for seasonal variation in outcomes. The individual infections included in the primary outcome are rare events and a composite primary outcome was chosen to maximize the chance of detecting a difference between groups. Additionally, this study focused on patient-centered outcomes and tested the effect of chlorhexidine bathing on several infections other than bloodstream infection, CLABSI, and clinical cultures that tested positive for multidrug-resistant organisms, including *C difficile* infection, which has been impacted by chlorhexidine in a previous quasi-experimental study.[15] The limitations to this study include the inability to blind staff administering baths to the treatment group; however, personnel responsible for adjudicating infections were blinded to the treatment. Additionally, this is a single-center study that included multiple ICUs encompassing a diverse patient population and a large sample size. Of the infections included in the Medicare Hospital Compare website (http://www.medicare.gov/hospitalcompare), Vanderbilt University Medical Center is similar to national benchmarks, suggesting these findings are generalizable to other medical centers. This trial was designed as an effectiveness rather than an efficacy trial whereby the interventions were performed as a component of routine patient care rather than by dedicated study personnel. Therefore, bathing adherence was not assessed, and it is unclear if this may have affected outcomes. Active surveillance for multidrug-resistant organism acquisition is not routinely performed in our ICUs and was not a component of this study but has been included as an outcome in previous studies.[8,15-19]

Conclusions

In this pragmatic trial, daily bathing with chlorhexidine did not reduce the incidence of health care-associated infections including CLABSI, CAUTI, VAP, or *C difficile*. These findings do not support daily bathing of critically ill patients with chlorhexidine.

ARTICLE INFORMATION

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Study concept and design: Noto, Domenico, Rice, Bernard, Wheeler.
Acquisition, analysis, or interpretation of data: Noto, Domenico, Byrne, Talbot, Rice, Wheeler.
Drafting of the manuscript: Noto, Domenico, Byrne, Rice.
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