Title: Effect of Chlorhexidine Bathing Every Other Day on Prevention of Hospital-Acquired Infections in the Surgical Intensive Care Unit: A Single Center, Randomized Controlled Trial

Short running head: Chlorhexidine bathing in surgical intensive care unit

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Author Contributions

JTS was the principal investigator on the grant and IRB protocol and served as the lead investigator on study design, patient enrollment, data collection, and interpretation of the findings; JTS managed the study database and wrote the first draft of the manuscript. LNB and VPP assisted with revising the protocol, training investigators, developing study forms, collecting data, enrolling patients, preparing information for the HAI adjudication committee, and adjudicating safety outcomes. BAS co-developed the study database, co-developed the statistical analysis plan, verified the data, performed all statistical analyses, and was involved with interpretation of all analyses. LRS and JAG were critical care pharmacists at Houston Methodist Hospital at the time of involvement and assisted with acquisition (adjudication committee) of infection and safety outcomes and assisted with evaluation of the data. EAG, SAH, RAO, and KID assisted with the acquisition of infection outcomes (adjudication committee) and evaluation of the data. JEB, JBB, ADM, and RMP assisted with patient enrollment, bathing compliance auditing, and data collection. MLJ provided consultation on the statistical analysis plan. MOB was the acting nurse educator in the SICU at the time of involvement and assisted with formulating the study hypothesis, writing the study protocol, obtaining IRB approval, and obtaining intramural grant support. SKT was a Clinical Research Nurse at the time of involvement and assisted with writing the study protocol, obtaining IRB approval, developing study forms, enrolling patients, and collecting data. CMA and NPW served the team as the senior methodologists and assisted with the design of the work, the acquisition of infection outcomes (adjudication committee), and the interpretation of findings. All authors had full access to all the data in the study and take responsibility for

the integrity of the data and the accuracy of the data analysis. All authors revised the manuscript for intellectual content and approved the final version of the manuscript.

The primary results from this trial were presented at the Society of Critical Care Medicine Critical Care Congress in January 2015, which was held in Phoenix, Arizona, United States.

Competing interest statement

JTS received an intramural grant from Houston Methodist Research Institute supporting this research. LNB received a fellowship from Texas Southern University supporting her effort on this trial. All authors report no other financial relationships with any organizations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

MeSH Keywords: chlorhexidine; nosocomial infections; ventilator-associated pneumonia; urinary tract infection; surgical wound infection; bacteremia; surgical intensive care

ABSTRACT:

Objective: To test the hypothesis that compared with daily soap and water bathing, 2% chlorhexidine gluconate bathing every other day for up to 28 days decreases the risk of hospital-acquired catheter-associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP), incisional surgical site infection (SSI), and primary bloodstream infection (BSI) in surgical intensive care unit (SICU) patients.

Design: This was a single-center, pragmatic, randomized trial. Patients and clinicians were aware of treatment-group assignment; investigators who determined outcomes were blinded.

Setting: 24-bed SICU at a quaternary academic medical center

Patients: Adults admitted to the SICU from 07/2012 through 05/2013 with an anticipated SICU stay ≥48 hours were included.

Interventions: Patients were randomized to bathing with 2% chlorhexidine every other day alternating with soap and water every other day (treatment arm) or to bathing with soap and water daily (control arm).

Measurements and Main Results: The primary endpoint was a composite outcome of CAUTI, VAP, incisional SSI, and primary BSI. Of 350 patients randomized, 24 were excluded due to prior enrollment in this trial and 1 withdrew consent. Therefore, 325 were analyzed (164 soap and water versus 161 chlorhexidine). Patients acquired 53 infections. Compared to soap and water bathing, chlorhexidine bathing every other day decreased the risk of acquiring infections (hazard ratio=0.555, 95% CI 0.309 to 0.997, P=0.049). For patients bathed with soap and water versus chlorhexidine, counts of incident hospital-acquired infections were 14 versus 7 for CAUTI, 13 versus 8 for VAP, 6 versus 3 for incisional SSIs, and 2 versus 0 for primary BSI; the effect was consistent

across all infections. The absolute risk reduction for acquiring a hospital-acquired infection was 9.0% (95% CI 1.5% to 16.4%, P=0.019). Incidences of adverse skin occurrences were similar (18.9% soap and water versus 18.6% chlorhexidine, P=0.95).

Conclusions: Compared with soap and water, chlorhexidine bathing every other day decreased the risk of acquiring infections by 44.5% in SICU patients.

INTRODUCTION

An estimated 1,700,000 hospital-acquired infections (HAIs) occur in the United States each year, with an annual cost of up to $147 billion dollars.(1, 2) A growing body of evidence supports the conclusion that bathing intensive care unit (ICU) patients with chlorhexidine gluconate, a topical antiseptic that rapidly kills common HAI-causing pathogens, prevents colonization from HAI-causing pathogens, prevents bloodstream infections (BSIs), and may prevent other types of HAIs.(3-21) A 2012 meta-analysis, which included one randomized trial and eleven quasi-experimental studies, reported a 64% reduction (pooled odds ratio = 0.44, 95% CI 0.33 to 0.59) in incident BSIs with chlorhexidine bathing in adult ICU patients.(21) In this meta-analysis, the treatment effect was consistent for both chlorhexidine solution and chlorhexidine-impregnated cloths; however, the effect was strongest for medical ICU patients and there was less evidence for surgical intensive care unit (SICU) patients. Data from several quasi-experimental studies suggests that chlorhexidine bathing may prevent non-BSI HAIs, but this has not been confirmed in a randomized trial.(10, 11, 16, 19, 20, 22, 23)

In 2013, three multicenter trials that randomized either ICUs or hospitals found that compared to daily bathing with soap and water, daily bathing with chlorhexidine reduced BSIs by 28% to 44%.(17, 18, 24) However, these trials did not examine a treatment effect of chlorhexidine for prevention of catheter-associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP), or incisional surgical site infections (SSI) and did not evaluate the treatment effect of chlorhexidine bathing at the individual patient level. In 2015, the effectiveness of chlorhexidine bathing was challenged by a

single-center, cluster-randomized crossover trial of daily bathing using chlorhexidine-impregnated cloths in critically ill adults that did not find a reduction in the composite outcome of central line-associated BSI, CAUTI, VAP and *Clostridium difficile;* however, the impact of ascertainment bias in that study is unclear.(25)

In 2011, the Houston Methodist Research Institute funded the CHlorhexidine Gluconate BATHing (CHG-BATH) trial. We believed a clinical trial was warranted as there was clinical equipoise regarding the effectiveness of chlorhexidine bathing in SICU patients. The objective of this trial was to evaluate the comparative effectiveness of bathing with chlorhexidine versus soap and water for the prevention of four HAIs (CAUTI, VAP, incisional SSI, and primary BSI) in SICU patients.

MATERIALS AND METHODS

Trial design

The CHG-BATH trial was a pragmatic, single-center, open-label, randomized trial conducted in a 24-bed SICU at Houston Methodist Hospital, a quaternary academic medical center. The SICU provides care for general surgical patients and a large liver failure population before and after liver transplant. We tested the hypothesis that compared to soap and water daily bathing, 2% chlorhexidine gluconate bathing on ICU admission and every 48 hours during SICU care for up to 28 days will decrease the risk of acquiring four HAIs (CAUTI, VAP, incisional SSI, and primary BSI) in SICU patients.

Patients and bedside clinicians were aware of treatment-group assignment, but investigators who determined efficacy and safety outcomes were blinded. No interim analyses for efficacy were planned. This trial was supported by an intramural grant, approved by the hospital's Institutional Review Board with a waiver of informed consent, and registered prior to enrollment (#NCT01640925). This trial could not be practically carried out without a waiver of informed consent, and a waiver was provided for this minimal risk study.

Patients were randomized within 48 hours of SICU admission. Patients were bathed per protocol during the bathing period, which started at randomization and ended at SICU discharge, day 28, or death, whichever occurred first. Patient-level information was collected daily during the observation period, which includes the bathing period plus up to 48 hours of additional follow-up.

The original protocol allowed for patients readmitted to the SICU to be re-randomized into the trial; however, prior to analyzing the data, the research team excluded non-index randomizations to maintain independence among units of randomization.

Recruitment and eligibility criteria

All patients admitted to the SICU from 07/2012 through 05/2013 were screened for eligibility. Adults (≥18 years old) with an anticipated SICU stay ≥48 hours were eligible. Patients with a Braden Scale for Predicting Pressure Sore Risk (26) score <9 (highest risk), pregnancy, skin irritation that precluded chlorhexidine bathing, chlorhexidine allergy, or a SICU stay of >48 hours prior to screening were ineligible.

Bathing procedure

Beginning on the day of randomization, patients received daily washbasin-based baths per protocol until SICU discharge, day 28, or death, whichever occurred first. In the control arm, patients were bathed daily with soap and water. In the treatment arm, patients were bathed with chlorhexidine every other day (starting study day 1) alternating with soap and water every other day. Prior to trial initiation, all SICU nurses and patient care assistants were educated on the protocol. A charge nurse or nursing manager audited bathing compliance daily. The protocol mandated that washbasins be discarded after each study bath (in both arms) to prevent colonization.(27)

Soap and water baths were predominately provided with non-medicated Bedside-Care® Easicleanse™ Bath washcloths (Coloplast, Minneapolis, Minnesota, USA), which are compatible with chlorhexidine (http://www.coloplast.us/); alternatively, Dial™ soap and disposable cloths were used. This procedure was also used to provide soap and water baths every other day in the chlorhexidine arm. These soap and water baths were the standard of care in this SICU prior to trial initiation. Patients in both study arms also received ad-hoc soap and water baths to cleanse bodily fluids such as urine, feces, and blood. Ad-hoc baths were restricted to soiled skin areas only. The frequency of use of ad-hoc baths was not recorded.

Chlorhexidine bathing consisted of the following steps. First, Bedside-Care® Easicleanse™ Bath washcloths were used to remove soiled material from skin and to cleanse face, open wounds, and perianal areas. The washbasin was emptied and filled with a 2% chlorhexidine solution created by mixing 8 ounces of warm tap water with 8 ounces (two 4-ounce bottles) of Bactoshield® chlorhexidine 4% Surgical Scrub (STERIS corporation, Mentor, Ohio, USA). Disposable or terrycloth washcloths submerged into the 2% chlorhexidine solution were used to bathe the entire body except for the face, perianal mucous membranes, and open wounds. The chlorhexidine was allowed to air-dry without rinsing to create a chlorhexidine barrier.

Trial outcomes

Primary efficacy endpoint

The primary endpoint was acquisition of an incident CAUTI, VAP, incisional SSI, or primary BSI (definitions for each infection are available in Supplemental Digital Content –Text 1 and Figures 1-4). Infections detected more than 48 hours after randomization and prior to the end of follow-up were classified as incident infections. Infections detected prior to or within 48 hours of randomization were classified as prevalent infections. Surveillance for infection (cultures and imaging) was ordered per routine care and was not standardized per protocol. The 2008 Centers for Disease Control and Prevention (CDC) surveillance definitions were used, with a modification to the definition of abnormal temperature to include <36°C and >38°C.(28, 29) For CAUTI, we adopted the March 2010 CDC update and 2013 CDC requirement of symptoms within 1 day of urine culture.(28, 30) Pneumonias detected after 48 hours of mechanical ventilation were classified as VAP.(28, 31) Since chlorhexidine bathing was hypothesized to decrease SSIs involving the incision, only superficial or deep incisional SSI were included as outcomes; organ/space infections were not included. However, organ/space SSIs that drained through the incision were classified as incisional SSIs.(28) If a patient developed two infections of the same type (e.g. two BSIs); the second infection was not included. If a patient developed two incident infections of different types (e.g. VAP and CAUTI), both infections were included.

Time at risk for an incident HAI

The time-at-risk for each HAI type was the summation of all hours within the observation period during which patients also met infection-specific criteria. Infections detected within 48 hours after randomization were classified as prevalent infections, and the first

48 hours after randomization were not included in the calculation of time-at-risk. Patients were at risk for BSI during the entire observation period. Patients were at risk for incisional SSI for 30 days after National Healthcare Safety Network qualifying surgeries without implant and 365 days after surgeries with implant.(30, 32) Patients were at risk for CAUTI if a urinary bladder catheter was present or had been used within the previous 48 hours. Patients were at risk for VAP after 48 hours of airway invasion with an endotracheal or tracheostomy tube and remained at risk until removal of the airway tube.

Secondary endpoints

Efficacy endpoints were rates of CAUTI, VAP, incisional SSI, and primary BSI per 1,000 days at risk, in-hospital mortality, and length of time from randomization until first SICU discharge and hospital discharge. Safety endpoints were incident adverse skin occurrences (e.g. non-infectious rashes, blisters, ulcers, indurations, urticaria, erythema, and exfoliation); severity was graded using National Cancer Institute criteria.(33) Nurses evaluated skin conditions every 4 hours during SICU care. Skin occurrences detected prior to randomization were classified as prevalent, and those detected after randomization were classified as incident. Investigators blinded to treatment-group assignment categorized the perceived association of the skin occurrences with bathing as not related, unlikely, possibly, probably, or definitely.(34)

Sample size

The number of patients needed to achieve 80% power was estimated at 320 using Pearson's Chi-squared (66% relative risk reduction; proportion infected, 15% with control, 5% with chlorhexidine) and 171 using Cox proportional hazards regression (hazard ratio reduction of 0.66; 0.15 probability of infection with control) using a two-sided 5% significance. The enrollment goal was set at 350 patients.

Randomization

Prior to trial launch, the principal investigator created the randomization table by sorting 175 letter A's (chlorhexidine) and 175 letter B's (soap and water) using "=RAND()" function in Microsoft Excel 2007. Investigators consecutively numbered 350 folders and filled each with treatment-group specific materials. Investigators opened folders only after a patient was enrolled and study numbers were assigned in order. Folder contents were not visible prior to opening.

Outcome assignment

To prevent misclassification, two adjudication committee members independently reviewed every patient case using standardized flow sheets to detect HAIs (details are available in Supplemental Digital Content –Text 1 and Figures 1-4). This 8-member adjudication committee consisted of an internist (CMA), a pulmonologist (NPW), infection prevention specialists (EAG and KID), surgeons (SAH and RAO), and critical care pharmacists (JAG and LRS). Complex cases were discussed at arbitration meetings, and a majority vote was used to finalize outcome decisions. One investigator

(VPP, LNB, JAG, or LRS) reviewed patient data to detect and grade skin occurrences. Reviewers for HAIs and skin occurrences were blinded.

Statistical analysis

Primary outcome

The primary outcome used Cox regression analysis of a multiple outcomes failure model stratifying the baseline hazard function on infection type and providing an overall hazard rate ratio for the four infection types (two-sided alpha of 0.05).(35) This analysis was conducted with a modified intention-to-treat (modified-ITT) population and was not adjusted for baseline variables. All other analyses were planned *a priori*, but were considered exploratory. All analyses were performed using Stata version 13 (StataCorp LP, College Station, TX, United States).

Secondary outcomes

Proportions of patients with incident skin occurrence(s) or in-hospital mortality were compared using Chi-squared tests. For each individual infection type, a hazard rate ratio was calculated using survival models and infection rates were compared using Poisson regression. Lengths of hospital or SICU stay were compared using the t-test.

Sensitivity analyses

Sensitivity analyses were conducted to test the robustness of results of the primary analysis. The primary analysis was conducted within per-protocol (received ≥1 study bath) and compliant (received ≥80% of study baths) groups. Proportions of patients with

incident infection(s) were analyzed with Pearson's Chi-squared test. Additional sensitivity analyses are described and reported in the Supplemental Digital Content – Text 3,

Patient involvement

Patients were not involved in the design of this study, development of outcomes, or recruitment of subjects. Results were not disseminated to study subjects.

Role of the funding source

This study was funded by an intramural grant from the Houston Methodist Research Institute, Houston, Texas, United States. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

RESULTS

Trial participants

Of 350 randomizations, 325 patients were included in the primary analysis (Figure 1). The mean APACHE II score was 26.5; 37.5% of included patients (122 of 325) had liver failure and 49.5% (161 of 325) had kidney dysfunction prior to enrollment. Treatment arms were balanced regarding age, race, pre-randomization hospital course, and severity of illness (Table 1 and Supplemental Digital Content – Table 2). However, patients in the chlorhexidine arm were more likely to have kidney dysfunction, liver failure, subclavian bloodstream catheters, invasive airway at randomization, and a SICU admission status of unscheduled surgery. Patients received 83.4% (1944 of 2332) of study baths and averaged 6 baths each (SD=6.6, range 0 to 28), which was similar (P=0.8) between arms (Supplemental Digital Content – Table 3). The online Supplemental Digital Content provides detailed information on surveillance of blood and urine cultures (Supplemental Digital Content – Table 4), amount of time at risk censored after detection of infection (Supplemental Digital Content – Table 5), and number of surgeries eligible for incisional SSI (Supplemental Digital Content – Table 6).

Primary outcome

Fifty-three incident HAIs (35 with soap and water versus 18 with chlorhexidine) were detected (organisms reported in Supplemental Digital Content – Tables 7 and 8). Compared to soap and water bathing alone, intermittent chlorhexidine bathing decreased the risk of acquiring HAIs (hazard ratio [HR]=0.555, 95% CI 0.309 to 0.997,

P=0.049) by 44% in an unadjusted primary analysis (Figure 2). The proportional-hazards assumption was met for this analysis (P=0.061).

Secondary outcomes

The incidence of adverse skin occurrences was 18.9% in the soap and water arm and 18.6% in the chlorhexidine arm, with no difference between arms (P=0.95) (Supplemental Digital Content – Table 9). Compared with patients bathed with soap and water, patients bathed with intermittent chlorhexidine experienced fewer CAUTIs (14 versus 7), VAPs (13 versus 8), incisional SSIs (6 versus 3), primary BSIs (2 versus 0) (Figure 3), and deaths during the study (23 versus 18, HR=0.85, 95% CI 0.46 to 1.58, P=0.60). However, these individual secondary outcomes were not powered and were not significantly different. Additional outcomes are reported in Supplemental Digital Content – Table 3.

Sensitivity analyses

In the test of proportions analysis, chlorhexidine bathing reduced the incidence of acquiring an HAI from an incidence of 18.3% (30 of 164) in the soap and water arm to an incidence of 9.3% (15 of 161) in the chlorhexidine arm (absolute risk reduction of 9.0%, 95% CI 1.5% to 16.4%, P=0.019). Analyses within per-protocol and compliant groups supported the primary analysis (Figure 2). Additional sensitivity analyses listed in Supplemental Digital Content –Text 3, Table 3, Table 10, Figure 5, and Figure 6 also support the results of the primary analysis.

DISCUSSION

This is the first trial evaluating chlorhexidine bathing in SICU patients that randomized on the patient level and enrolled patients who were predicted to require at least 48 hours of ICU care, which selected patients at highest risk for acquiring HAIs. In this trial, full-body bathing with chlorhexidine every other day reduced the risk of acquiring the composite outcome of four HAIs (CAUTI, VAP, incisional SSI, and primary BSI) in SICU patients by 44%. The absolute risk reduction for acquiring an HAI was 9%, equating to bathing 11 patients to prevent one HAI. Chlorhexidine bathing did not increase the risk of adverse skin occurrences or pressure ulcers.

Clinical relevance

Beginning in 2009, the United States Department of Health and Humans Services' HAI Action Plan established goals to reduce CAUTI by 25%, reduce central line-associated BSIs by 50%, reduce SSIs by 25%, and reduce VAP. (36, 37) The large magnitude of the estimated effect of chlorhexidine bathing every other day, as shown in our trial, meets these HAI prevention goals for SICU patients who are predicted to require at least 48 hours of ICU care.

Temporal effects of chlorhexidine

The rationale for bathing with chlorhexidine every other day was chosen to limit the risk of adverse skin occurrences, as no safety data was available from randomized trials when this trial was developed. However, it was reasonable to expect the effects of chlorhexidine to last for at least 48 hours, since it takes a median of 5 days for the skin

to recolonize following a chlorhexidine bath. (38-40) Following SICU admission, the average time to randomization was 14 hours and time to first study bath was 26 hours, and this expeditious enrollment and bathing may have been crucial to prevent HAIs.

Our protocol assumed that the latency period between inoculation of a pathogen and detection of infection was 48 hours. As expected, chlorhexidine bathing did not reduce the prevalence of infections detected within 48 hours of randomization and did reduce the incidence of infections occurring 48 hours or more after randomization. Our data provides rationale to classify infections that develop within 48 hours of randomization as prevalent infections, rather than incident infections, to prevent bias in future trials.

Biological plausibility: organism-specific effects of chlorhexidine

The most common organisms isolated among incident HAIs were *Candida* species (n=15), *Enterococcus* species (n=8), *Staphylococcus* species (n=7), and *Klebsiella pneumoniae* (n=7), which represent the most common ICU pathogens.(2) Compared with patients bathed with soap and water, patients bathed with intermittent chlorhexidine acquired fewer HAIs from *Candida* species (11 versus 4), *Enterococcus* species (6 versus 2), and *Staphylococcus* species (6 versus 1); however, counts of specific organisms were not powered for statistical analysis. These findings are biologically plausible as chlorhexidine rapidly kills *Staphylococcus*, *Enterococcus*, and *Candida* and decreases skin colonization density. (7, 41-45) Chlorhexidine bathing of critically ill patients decreases patients' skin colonization density of *Enterococcus* and decreases the risk of obtaining positive *Enterococcus* cultures on healthcare workers' hands. (46)

A reduction of *Candida* infections, predominately CAUTIs, was the largest organism-specific effect observed in our trial, and anti-fungal activity has been reported in three clinical studies. Two recent multicenter trials of chlorhexidine bathing reported 29% to 53% reductions in fungal BSIs.(17, 18) A third study of chlorhexidine bathing reported a reduction in *Candida* CAUTIs (P<0.001).(10) The causal association between chlorhexidine bathing and a reduction in both colonization and infection from staphylococci and enterococci has been widely demonstrated. (16-19, 22, 24, 47) Although at least one study reported a reduction in gram-negative bacteria with chlorhexidine bathing, there is less evidence that chlorhexidine bathing prevents hospital-acquired infections from gram-negative bacteria.(23)

Biological plausibility: infection-type specific effects of chlorhexidine

Routine antisepsis of healthcare workers' hands and pre-procedural antisepsis of local region of patients' skin are universally accepted strategies for preventing infections. (38, 48) Full-body bathing with chlorhexidine reduces colonization of HAI-causing pathogens on the skin of critically ill patients, who often have multiple inserting catheters and are highly vulnerable to infection either from their own microbiota or from patient-to-patient transmission. (46) The relationship between chlorhexidine bathing and prevention of BSI has been clearly established in three multi-center trials and a meta-analysis.(17, 18, 21, 24) Therefore, it seems plausible that chlorhexidine bathing may also prevent infections associated with other inserting catheters (CAUTI and VAP) or incision of the skin (incisional SSI).

In addition to the reductions in CAUTI, VAP, and SSI observed in this trial, the biological plausibility that chlorhexidine bathing decreases multiple HAIs is supported by several other recent studies. In a before-and-after study of 325 ICU patients with suspected sepsis, bathing with 2% chlorhexidine versus soap and water decreased the incidence of 3 HAIs (BSIs, VAP, and urinary tract infection) from 32% to 19% (P = 0.01); the effect was significant for all three individual infection types.(23) A before-and-after study of 1,007 of mixed medical/surgical ICU patients reported a 44% reduction in the combined rate of VAP, CAUTI, or central-line associated BSIs (P<0.001) with chlorhexidine bathing, with significant reductions for VAP (49% relative reduction, P = 0.036) and CAUTI (25% relative reduction, P<0.001).(10) A meta-analysis of two studies reported a 78% reduction in methicillin-resistant *Staphylococcus aureus* VAP with chlorhexidine bathing (P=0.006).(19) A meta-analysis of five studies evaluating perioperative skin antisepsis with chlorhexidine reported a 71% reduction in SSIs.(20)

Noto, et al. conducted the only previous randomized trial evaluating the effect of chlorhexidine bathing on CAUTI and VAP, and did not find an effect; however, there are several key differences between our trial and this trial.(25) Compared with Dr. Noto's trial, the incidence of infections among control patients in our trial was 13.4-fold greater for CAUTI (8.5%, 14 of 164 versus 0.6%, 31 of 4852) and 48-fold greater for VAP (7.9%, 13 of 164 versus 0.2%, 8 of 4852). Additionally, patients in our trial received an average of 4.4 more days of ICU care (7 versus 2.6), thus receiving a longer duration of exposure to chlorhexidine bathing. The data from these two trials indicate that

chlorhexidine bathing may have increased effectiveness in patients who are at high risk for infection and are predicted to require at least 48 hours of ICU care.

Intervention at the patient-level rather than group-level

Previous chlorhexidine bathing trials used cluster randomization and intervened at the group-level, and may be at risk for ecological inference fallacy if individual exposure to chlorhexidine was not accounted for in the analysis. Group-level interventions do not evaluate the effectiveness of prescribing chlorhexidine bathing to individual patients in healthcare settings where chlorhexidine bathing is not the standard of care either due to limited healthcare resources or other barriers. By randomizing on the patient level, our trial provides evidence that prescribing chlorhexidine bathing for individual patients prevents HAIs. It is unknown if the treatment effect observed in our trial was through decreasing the risk of infection from the patient's own microbiota, decreasing the risk of patient-to-patient transmission, or both.

Bathing product selection and frequency

Within our institution, the cost of each soap and water bath using a washbasin is $1.16, 2% chlorhexidine bath using a washbasin is $4.66, and 2% chlorhexidine-impregnated cloth bath without a washbasin is $6.69. (6, 49) Although previous trials utilized 2% chlorhexidine impregnated cloths,(17, 18) this trial utilized a 2% chlorhexidine solution to reduce costs. However, nurses may prefer bathing with 2% chlorhexidine cloths compared to bathing with chlorhexidine in washbasins. (49) Now that both products have shown effectiveness, chlorhexidine products can be selected by balancing cost

and satisfaction. Chlorhexidine bathing every other day reduced HAIs in this trial, which provides evidence that the treatment effect lasts for at least 48 hours after each bath.

Chlorhexidine bathing was provided every other day rather than daily in this trial due to concerns of increased risk of skin reactions; however, the incidence of skin occurrences was similar between treatment arms. Two large trials have demonstrated safety with daily bathing,(17, 18) and daily bathing may be preferred over every other day bathing due to the potential for a larger treatment effect. However, the comparable effectiveness of chlorhexidine bathing provided daily versus every other day is unknown. Additionally, the treatment effect of chlorhexidine bathing compared with soap and water bathing with washbasins may be different than if the control group consisted of non-medicated cloth bathing.

Strengths

This trial used a pragmatic design that ensured maximum generalizability by using minimal inclusion and exclusion criteria, causing minimal interference with normal processes of care (such as culture ascertainment and antimicrobial use), emphasizing the use of data routinely collected within the hospital's electronic medical record. This trial was conducted with minimal financial resources for research activities. Non-investigator bedside nurses and patient care assistants provided chlorhexidine bathing, investigators did not monitor the quality of baths provided, and concentrations of chlorhexidine in the bathing solution were not measured; while these attributes may

decrease the internal validity (potentially attenuating the treatment effect), they increase the external validity of this trial.

Investigators limited misclassification bias by having all patient cases reviewed independently by two adjudication committee members and limited observer bias by blinding adjudication committee members to treatment-group assignment. Times at risk for HAIs were calculated to the unit of hours to improve precision for survival analyses. A singular primary analysis was clearly defined prior to seeing the data that maintains an overall type 1 error of 0.05%. Although not powered for statistical analysis, mathematical reductions for each of the four infections were consistent with the primary analysis. The magnitude of the treatment effect observed in the primary analysis was supported by many sensitivity analyses.

Generalizability

This trial was conducted within a single SICU at one institution. Only patients with anticipated SICU stay of ≥48 hours were enrolled. Due to the trial's inclusion criteria and calculation of time-at-risk, these rates of infection are high and cannot be directly compared to rates that were calculated using different criteria. This SICU cares for many patients who have liver failure or have undergone solid organ transplant (liver, kidney, and pancreas), and these immunocompromised patients have a high risk of infection. Most surgeries involved the intra-abdominal cavity, which carries the greatest risk of SSIs. At our institution, cardiovascular surgery, thoracic surgery, and

neurosurgery patients are routinely admitted to other ICUs and are not represented in this cohort.

Limitations

This study was not powered to detect differences in the incidence of individual infection types, hospital length of stay, or in-hospital mortality. Although a large treatment effect was detected, the confidence intervals for this point estimate were wide. Although adjudicators of infection outcomes were blinded during official study activities, 2 of the 8 adjudicators provided direct care in the SICU (clinicians were not blinded), which may have led to inadvertent loss of blinding in some cases. Chlorhexidine susceptibility testing was not performed. Previous research identified major limitations of the VAP CDC criteria that were used in this trial. (50)Since adjudicators were blind to treatment group assignment, any potential misclassification of VAP outcomes is expected to have impacted both treatment groups equally.

The trial protocol did not standardize surveillance of HAIs (cultures and imaging), and non-standard surveillance could have caused under-ascertainment of HAIs that could have biased the results towards the null. Fortunately, surveillance of blood and urine cultures was similar between study arms, providing some evidence that surveillance bias would have impacted both arms equally. The trial protocol censored a patient's risk after the first infection of that type, and this censoring may have prevented detection of new incident HAIs. The impact of this potential bias would be greatest for the two most common HAIs, which were CAUTI and VAP. Since most incident HAIs were detected in

the soap and water arm, this impact of this limitation would be largest for the soap and water arm, which may have biased the treatment effect towards the null. Systemic antimicrobial therapy (especially use of prophylactic antimicrobials) was not standardized by the trial protocol. However, due to randomization, exposure to antimicrobials within 48 hours after randomization appeared similar, and it was unlikely that this bias accounted for the large magnitude of effect observed. Use of Dial™ soap was not measured; however, investigators believe it was used infrequently.

The protocol mandated that washbasins be discarded after each bath, but compliance with this mandate was not tracked. If washbasins were not appropriately discarded, pathogens may have colonized the washbasins. This colonization would be more likely to occur in the soap and water arm compared with the chlorhexidine arm, because chlorhexidine prevents colonization. (27, 51) This phenomenon can either be viewed as a potential bias or as part of the treatment effect of chlorhexidine bathing.

CONCLUSION

Full-body bathing with chlorhexidine every other day reduced the risk of acquiring the composite outcome of four HAIs (CAUTI, VAP, incisional SSI, and primary BSI) in SICU patients by 44.5%. Intermittent chlorhexidine bathing did not increase the risk of adverse skin occurrences. This inexpensive, safe, and easy to implement intervention prevents HAIs in SICU patients who are expected to require at least 48 hours of ICU care. The association between chlorhexidine bathing and prevention of multiple types of infection observed in this trial should be confirmed in another clinical trial of patients who have a high risk of acquiring HAIs.

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References

1. Marchetti A, Rossiter R: Economic burden of healthcare-associated infection in US acute care hospitals: Societal perspective. *J Med Econ* 2013;16:1399-1404

2. Magill SS, Edwards JR, Bamberg W, et al: Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014;370:1198-1208

3. Dixon JM, Carver RL: Daily chlorohexidine gluconate bathing with impregnated cloths results in statistically significant reduction in central line-associated bloodstream infections. *Am J Infect Control* 2010;38:817-821

4. Climo MW, Sepkowitz KA, Zuccotti G, et al: The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant staphylococcus aureus, vancomycin-resistant enterococcus, and healthcare-associated bloodstream infections: Results of a quasi-experimental multicenter trial. *Crit Care Med* 2009;37:1858-1865

5. Fraser TG, Fatica C, Scarpelli M, et al: Decrease in staphylococcus aureus colonization and hospital-acquired infection in a medical intensive care unit after institution of an active surveillance and decolonization program. *Infect Control Hosp Epidemiol* 2010;31:779-783

6. Holder C ZM: Daily bathing with chlorhexidine in the ICU to Prevent central Line–Associated Bloodstream Infections. *J Clin Outcomes Manage* 2009;16:509-513

7. McDonnell G, Russell AD: Antiseptics and disinfectants: Activity, action, and resistance. *Clin Microbiol Rev* 1999;12:147-179

8. Munoz-Price LS, Hota B, Stemer A, et al: Prevention of bloodstream infections by use of daily chlorhexidine baths for patients at a long-term acute care hospital. *Infect Control Hosp Epidemiol* 2009;30:1031-1035

9. Montecalvo MA, McKenna D, Yarrish R, et al: Chlorhexidine bathing to reduce central venous catheter-associated bloodstream infection: Impact and sustainability. *Am J Med* 2012;125:505-511

10. Martinez-Resendez MF, Garza-Gonzalez E, Mendoza-Olazaran S, et al: Impact of daily chlorhexidine baths and hand hygiene compliance on nosocomial infection rates in critically ill patients. *Am J Infect Control* 2014;42:713-717

11. Popovich KJ, Hota B, Hayes R, et al: Daily skin cleansing with chlorhexidine did not reduce the rate of central-line associated bloodstream infection in a surgical intensive care unit. *Intensive Care Med* 2010;36:854-858

12. Popovich KJ, Hota B, Hayes R, et al: Effectiveness of routine patient cleansing with chlorhexidine gluconate for infection prevention in the medical intensive care unit. *Infect Control Hosp Epidemiol* 2009;30:959-963

13. Popp JA, Layon AJ, Nappo R, et al: Hospital-acquired infections and thermally injured patients: Chlorhexidine gluconate baths work. *Am J Infect Control* 2014;42:129-132

14. Rupp ME, Cavalieri RJ, Lyden E, et al: Effect of hospital-wide chlorhexidine patient bathing on healthcare-associated infections. *Infect Control Hosp Epidemiol* 2012;33:1094-1100

15. Viray MA, Morley JC, Coopersmith CM, et al: Daily bathing with chlorhexidine-based soap and the prevention of staphylococcus aureus transmission and infection. *Infect Control Hosp Epidemiol* 2014;35:243-250

16. Evans HL, Dellit TH, Chan J, et al: Effect of chlorhexidine whole-body bathing on hospital-acquired infections among trauma patients. *Arch Surg* 2010;145:240-246

17. Climo MW, Yokoe DS, Warren DK, et al: Effect of daily chlorhexidine bathing on hospital-acquired infection. *N Engl J Med* 2013;368:533-542

18. Huang SS, Septimus E, Kleinman K, et al: Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med* 2013;368:2255-2265

19. Chen W, Li S, Li L, et al: Effects of daily bathing with chlorhexidine and acquired infection of methicillin-resistant staphylococcus aureus and vancomycin-resistant enterococcus: A meta-analysis. *J Thorac Dis* 2013;5:518-524

20. Karki S, Cheng AC: Impact of non-rinse skin cleansing with chlorhexidine gluconate on prevention of healthcare-associated infections and colonization with multi-resistant organisms: A systematic review. *J Hosp Infect* 2012;82:71-84

561 21. O'Horo JC, Silva GL, Munoz-Price LS, et al: The efficacy of daily bathing with
562 chlorhexidine for reducing healthcare-associated bloodstream infections: A meta-
563 analysis. *Infect Control Hosp Epidemiol* 2012;33:257-267

564 22. Bleasdale SC, Trick WE, Gonzalez IM, et al: Effectiveness of chlorhexidine bathing
565 to reduce catheter-associated bloodstream infections in medical intensive care unit
566 patients. *Arch Intern Med* 2007;167:2073-2079

567 23. Cassir N, Thomas G, Hraiech S, et al: Chlorhexidine daily bathing: Impact on health
568 care-associated infections caused by gram-negative bacteria. *Am J Infect Control* 2015;

569 24. Milstone AM, Elward A, Song X, et al: Daily chlorhexidine bathing to reduce
570 bacteraemia in critically ill children: A multicentre, cluster-randomised, crossover trial.
571 *Lancet* 2013;381:1099-1106

572 25. Noto MJ, Domenico HJ, Byrne DW, et al: Chlorhexidine bathing and health care-
573 associated infections: A randomized clinical trial. *JAMA* 2015;313:369-378

574 26. Bergstrom N, Braden BJ, Laguzza A, et al: The braden scale for predicting pressure
575 sore risk. *Nurs Res* 1987;36:205-210

576 27. Johnson D, Lineweaver L, Maze LM: Patients' bath basins as potential sources of
577 infection: A multicenter sampling study. *Am J Crit Care* 2009;18:31-8, 41; discussion 39-
578 40

28. Horan TC, Andrus M, Dudeck MA: CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309-332

29. Dellinger RP, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637

30. CDC/NHSN: CDC/NHSN surveillance definitions for specific types of infections. http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf Edition. 2013

31. American Thoracic Society, Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388-416

32. CDC/NSHN: Surgical site infection event: Procedure associated module. http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf Edition. 2014

33. HHS/NIH/NCI: Common terminology criteria for adverse events (CTCAE), version 4.03. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf Edition. 2010

34. Edwards IR, Aronson JK: Adverse drug reactions: Definitions, diagnosis, and management. *Lancet* 2000;356:1255-1259

35. Therneau TM, Grambsch PM: Modeling survival data: Extending the cox model. New York, Springer, 2000

599 36. National action plan to prevent health care-associated infections: Road map to
600 elimination. Washington, DC, Department of Health and Human Services, 2013

601 37. National action plan to prevent health- care-associated infections: Roadmap to
602 elimination. Washington, DC, Department of Health and Human Services, 2009

603 38. Byrne DJ, Napier A, Phillips G, et al: Effects of whole body disinfection on skin flora
604 in patients undergoing elective surgery. *J Hosp Infect* 1991;17:217-222

605 39. Hibbard JS: Analyses comparing the antimicrobial activity and safety of current
606 antiseptic agents: A review. *J Infus Nurs* 2005;28:194-207

607 40. Aly R, Maibach HI: Comparative study on the antimicrobial effect of 0.5%
608 chlorhexidine gluconate and 70% isopropyl alcohol on the normal flora of hands. *Appl*
609 *Environ Microbiol* 1979;37:610-613

610 41. Sakuragi T, Yanagisawa K, Dan K: Bactericidal activity of skin disinfectants on
611 methicillin-resistant staphylococcus aureus. *Anesth Analg* 1995;81:555-558

612 42. Frantz SW, Haines KA, Azar CG, et al: Chlorhexidine gluconate (CHG) activity
613 against clinical isolates of vancomycin-resistant enterococcus faecium (VREF) and the
614 effects of moisturizing agents on CHG residue accumulation on the skin. *J Hosp Infect*
615 1997;37:157-164

616 43. Wade JJ, Casewell MW: The evaluation of residual antimicrobial activity on hands
617 and its clinical relevance. *J Hosp Infect* 1991;18 Suppl B:23-28

618 44. Bobichon H, Bouchet P: Action of chlorhexidine on budding candida albicans:
619 Scanning and transmission electron microscopic study. *Mycopathologia* 1987;100:27-35

620 45. Hiom SJ, Furr JR, Russell AD, et al: Effects of chlorhexidine diacetate on candida
621 albicans, C. glabrata and saccharomyces cerevisiae. *J Appl Bacteriol* 1992;72:335-340

622 46. Vernon MO, Hayden MK, Trick WE, et al: Chlorhexidine gluconate to cleanse
623 patients in a medical intensive care unit: The effectiveness of source control to reduce
624 the bioburden of vancomycin-resistant enterococci. *Arch Intern Med* 2006;166:306-312

625 47. Derde LP, Cooper BS, Goossens H, et al: Interventions to reduce colonisation and
626 transmission of antimicrobial-resistant bacteria in intensive care units: An interrupted
627 time series study and cluster randomised trial. *Lancet Infect Dis* 2014;14:31-39

628 48. World Health Organization: WHO Guidelines on Hand Hygiene in Health Care: First
629 global patient safety challenge Clean Care Is Safer Care. 2009;

630 49. Ritz J, Pashnik B, Padula C, et al: Effectiveness of 2 methods of chlorhexidine
631 bathing. *J Nurs Care Qual* 2012;27:171-175

632 50. Stevens JP, Kachniarz B, Wright SB, et al: When policy gets it right: Variability in
633 u.s. hospitals' diagnosis of ventilator-associated pneumonia*. *Crit Care Med*
634 2014;42:497-503

635 51. Powers J, Peed J, Burns L, et al: Chlorhexidine bathing and microbial contamination
636 in patients' bath basins. *Am J Crit Care* 2012;21:338-342

637 **Tables**

638 **Table 1. Patient demographics and baseline variables**

Variable	Soap and water (n = 164)	Chlorhexidine (n = 161)
Age, mean years ± SD	60.2 ± 16.5	59.4 ± 15.9
Male sex, no. (%)	86 (52.4)	98 (60.9)
Weight, mean kg ± SD	83.8 ± 25.7	86.9 ± 28.0
Race, no. (%)		
Caucasian	96 (58.5)	96 (59.6)
African American	22 (13.4)	20 (12.4)
Hispanic	11 (6.7)	7 (4.4)
Asian	7 (4.3)	5 (3.1)
Other	28 (17.1)	33 (20.5)
Hospital course prior to randomization		
Hospital stay, mean days ± SD [a]	4.4 ± 7.17	4.2 ± 11.1
SICU stay, mean days ± SD [a]	0.6 ± 0.4	0.6 ± 0.5
Time from SICU admission to first study bath, mean days ± SD	1.1 ± 0.6	1.1 ± 0.6
Time from randomization to first study bath, mean days ± SD	0.5 ± 0.5	0.5 ± 0.5
SICU admission type(52), no. (%)		
Medical	95 (57.9)	79 (49.1)
Scheduled surgery	27 (16.5)	29 (18.0)
Unscheduled surgery	42 (25.6)	53 (32.9)
SICU admission severity of illness, mean ± SD		
SAPS II(52) [a]	44.2 ± 17.8	44.1 ± 16.2
SOFA(53)	7.0 ± 4.7	7.6 ± 4.5
APACHE II(54) [b]	26.1 ± 9.0	26.8 ± 9.1
Organ failure at baseline, no. (%)		
Acute/chronic liver failure [a,c]	57 (34.8)	65 (40.4)
Acute/chronic kidney dysfunction [a,c]	76 (46.3)	85 (52.8)
Count of central bloodstream catheters at randomization, mean ± SD [a,d]	0.9 ± 0.8	1.1 ± 0.8
Bloodstream catheters at randomization, no. (%)		
Peripheral line access	113 (68.9)	122 (75.8)

Intra-jugular access [a]	79 (48.2)	81 (50.3)
Femoral access [a,c]	28 (17.1)	35 (21.7)
Peripherally-inserted central catheter access [a]	27 (16.5)	27 (16.8)
Subclavian access [a,c]	20 (12.2)	28 (17.4)
Arterial catheter [a,e]	66 (40.2)	71 (44.1)
Invasive airway at randomization, no. (%) [a,c]	93 (56.7)	111 (68.9)
Orotracheal	88 (53.7)	105 (65.2)
Tracheostomy	3 (1.8)	5 (3.1)
Nasopharyngeal	2 (1.2)	1 (0.6)
Urine bladder catheter at randomization, no. (%)	140 (85.4)	139 (86.3)
Systemic antibiotics or antifungals within 48 hours after randomization, no. (%) [a,f]	145 (88.4)	141 (87.6)
Braden Scale for Predicting Pressure Sore Risk(26) at randomization, mean ± SD	14.5 ± 2.6	14.5 ± 2.9

APACHE II, Acute Physiology and Chronic Health Evaluation II; SAPS II, Simplified Acute Physiology Score II; SD, standard deviation; SOFA, sepsis-related organ failure assessment

[a] Using criteria specified before analysis (Table S1), investigators inspected 13 baseline variables for clinically relevant differences.

[b] APACHE II scores were calculated using the lowest Glasgow Coma Scale recorded during the 24 hours following ICU admission; however, Glasgow Coma Scale scores may have been influenced by sedation. Alternatively, APACHE II scores were calculated using the Glasgow Coma Scale score that was recorded immediately prior to initiation of intravenous opioids or sedatives (mean ± SD; 24.0 ± 8.7 soap and water vs. 24.3 ± 7.9 chlorhexidine).

[c] The five variables that were imbalanced according to these criteria were used as covariates in a sensitivity analysis.

[d] A central bloodstream catheter was defined as a venous or arterial catheter of the following types: intrajugular, femoral, subclavian, or peripherally-inserted central catheter

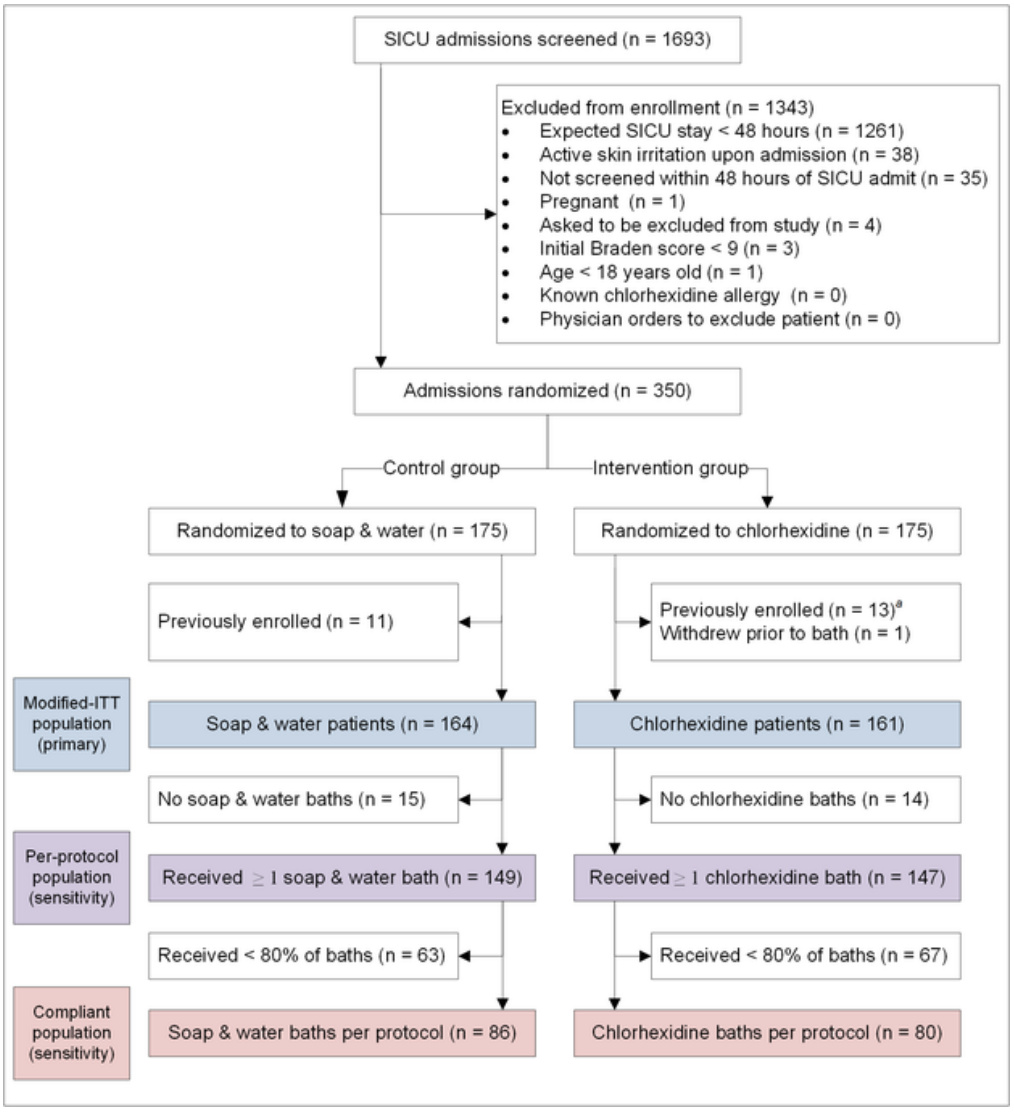
[e] The number of patients with bloodstream catheters in the radial or femoral artery. This is not mutually exclusive from the femoral access row above. For example, a patient

with a femoral arterial line would be counted in the femoral access row and the arterial catheter row.

[f] Detailed information on antibiotic exposure within the first 48 hours after randomization is available in the online data supplement (Table S2).

Figures

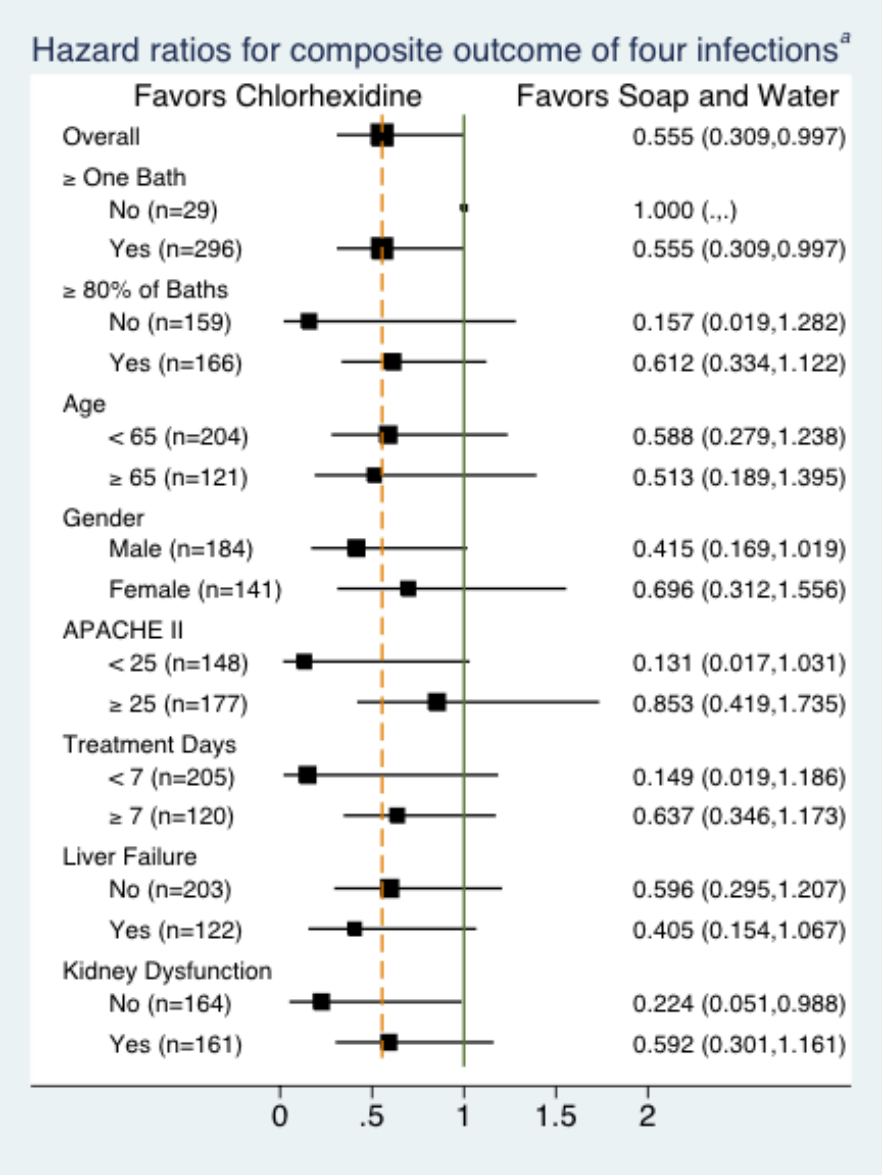
Figure 1. CONSORT diagram



Footnote: ITT, intention to treat; SICU, surgical intensive care unit

[a] Twelve patients were excluded because they were previously enrolled in the trial. One patient that was already active in the trial was erroneously randomized to the same study arm; the second randomization number was retired, and the patient continued the first randomization.

Figure 2. Forest plot of hazard-ratios by subgroups

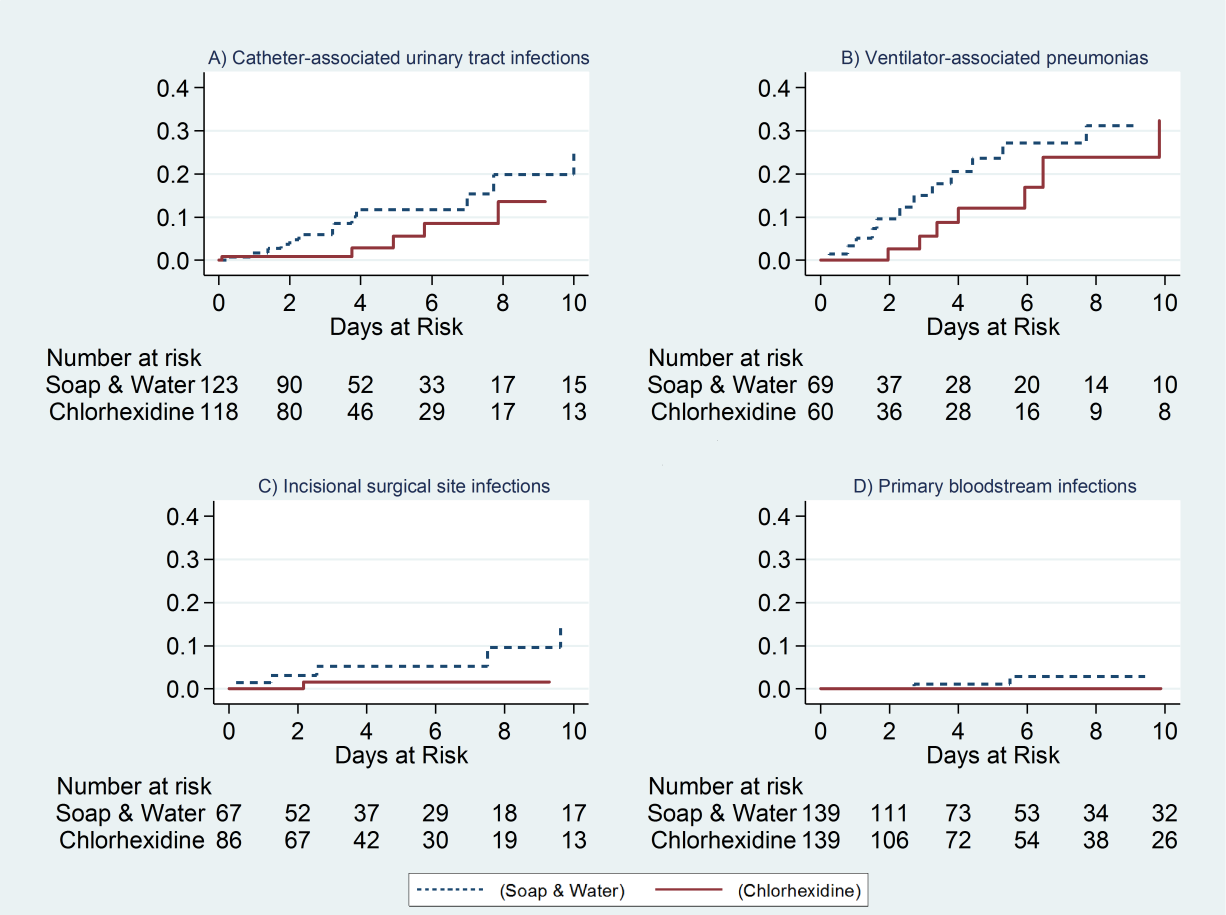


Footnote: APACHE II, Acute Physiology and Chronic Health Evaluation II.

The boxes represent the hazard ratios, and the lines represent 95% confidence intervals.

[a] The composite outcome of hospital-acquired infections includes CAUTI, VAP, incisional SSI, and primary BSI. The treatment effect was consistent across gender, duration of treatment, severity of illness, liver failure, and kidney dysfunction.

Figure 3. Kaplan-Meier of time to infection



Footnote: Soap and water is depicted with a dotted line and chlorhexidine is depicted with a solid line. The y-intercept (Days at risk = 0) represents 48 hours after randomization, which is the earliest time where an incident infection could be detected. Compared with soap and water, the risk for acquiring individual HAI was as follows: A) CAUTI HR=0.55 (95% CI 0.22 to 1.37, P=0.20), B) VAP HR=0.67 (95% CI 0.28 to 1.63, P=0.38), C) incisional SSI HR=0.50 (95% CI 0.12 to 2.02, P=0.33), and D) primary BSI HR=0.0 (95% CI 0 to upper bound unknown, P=1.0).