

## TITLE PAGE

**Title:** Chlorhexidine bathing and Clostridium difficile infection in a surgical intensive care unit

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## **Author Contributions**

LNB served as the lead investigator on study design, data collection, and interpretation of the findings. JTS was the principal investigator on IRB protocol of the original CHG-BATH trial and developed the hypothesis for this study. JTS and BAS co-developed the study database, verified the data, performed statistical analyses, and were involved with interpretation of all analyses. LNB, JTS, RJO, SWL, and EAG assisted with the acquisition of infection outcomes (adjudication committee) and evaluation of the data. 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. LNB wrote the first draft of the manuscript. All authors revised the protocol and the manuscript for intellectual content and approved the final version of the manuscript.

The primary results from this trial were presented as a platform presentation at the Midwest Pharmacy Resident Conference, Omaha, Nebraska, United States in May 2016, and as a poster at the American Society of Health System Pharmacists Summer Meeting, Baltimore, Maryland in June 2016.

## **ABSTRACT**

### **Background**

*Clostridium difficile* is the most common causative pathogen for hospital-acquired infections (HAIs) in the intensive care unit (ICU). This study evaluated the effect of chlorhexidine bathing every other day in preventing hospital-acquired *Clostridium difficile* infection (CDI) using data from the chlorhexidine-bath (CHG-BATH) randomized trial.

### **Methods**

The primary endpoint was the proportion of patients acquiring CDIs among patients at risk for incident CDIs. Infections detected > 48 hours after randomization were classified as incident CDIs. Infections detected prior to or within 48 hours of randomization were classified as prevalent CDIs.

### **Results**

Of 38 patients (11.7%) who met criteria for potential CDI and underwent adjudication, 24 (7.4%) received oral or enema vancomycin, 18 (5.5%) had a positive *Clostridium difficile* molecular assay, 14 (4.3%) received an ICD-9-CM code for CDI, and 2 (0.6%) had possible pseudomembranous colitis on histopathology reports. The prevalence of CDI was 3.7% (6 of 164) in the soap and water arm and 4.3% (7 of 161) in the chlorhexidine arm. Compared with daily soap and water bathing, 2% chlorhexidine bathing every other day was not associated with the prevention of hospital-acquired CDI (1.3% [2 of 152] soap and water versus 2.0% [3 of 148] chlorhexidine,  $P=0.68$ ).

## **Conclusion**

It is inconclusive if there was an association between chlorhexidine bathing and incidence of CDI among surgical ICU patients in this study as statistical power was limited. There are limited published data evaluating the association between chlorhexidine bathing and CDI, and this study provides data for future systematic reviews and meta-analyses.

**KEYWORDS:** *Clostridium difficile*, chlorhexidine, Chlorhexidine bathing, hospital-acquired infections, nosocomial infections, intensive care unit, ICU, surgical intensive care unit, SICU

## INTRODUCTION

Routine bathing of intensive care unit (ICU) patients with chlorhexidine gluconate has been shown to reduce the incidence of hospital-acquired blood stream infection (BSI) by 28% to 44% in multiple randomized trials (1-5). Our research team previously conducted the **CH**lorhexidine **G**luconate **BATH**ing (CHG-BATH) trial, a single-center, pragmatic, randomized controlled trial, which concluded that chlorhexidine bathing every other day decreased the risk of acquiring of four hospital-acquired infections (HAIs) (primary blood stream infection [BSI], catheter-associated urinary tract infection [CAUTI], ventilator associated pneumonia [VAP] and incisional surgical site infection [SSI]) compared to soap and water bathing by 44.5% in surgical ICU patients (5).

*Clostridium difficile* is the most commonly reported causative pathogen for HAIs in the ICU (6). Patients with advanced age, long duration of hospitalization, long exposure to antimicrobials, and exposure to multiple antimicrobials have shown to be at increased risk for CDI (7-10). However, the effectiveness of chlorhexidine bathing for prevention *Clostridium difficile* infection (CDI) remains unclear (11, 12). CDI was not included as an infectious outcome in the CHG-BATH trial. This study evaluates the effects of chlorhexidine bathing every other day in preventing hospital-acquired CDI using data from patients enrolled in the CHG-BATH trial.

## **METHODS**

### CHG-BATH trial

The CHG-BATH trial was approved by the Houston Methodist Hospital Institutional Review Board, which also approved this additional analysis. The CHG-BATH trial was a single-center, open-label, randomized clinical trial conducted in a 24-bed surgical ICU at Houston Methodist Hospital, a tertiary academic medical center. All adult patients admitted to the surgical ICU from 07/2012 through 05/2013 with an anticipated surgical ICU stay  $\geq 48$  hours were included. Patients with a Braden Scale for Predicting Pressure Sore Risk score  $>9$ , were pregnant, had skin irritation, had known chlorhexidine allergy, or stayed in the ICU  $>48$  hours prior to screening were excluded. Randomized patients were bathed with 1) daily soap and water or 2) every other day with 2% chlorhexidine gluconate alternating with every other day soap and water during the intervention period. Intervention period started at randomization and ended at surgical ICU discharge, day 28, or death, whichever occurred first. Patients and bedside clinicians were aware of treatment-group assignment, but investigators who determined efficacy and safety outcomes were blinded. Additional detailed inclusion and exclusion criteria, study design, patient recruitment, and bathing procedures have been previously reported (5).

### Study design

Retrospective data from the CHG-BATH trial was evaluated for hospital-acquired CDI. CDI surveillance (molecular assay, colonoscopy, and biopsy of colon tissue) was



performed by the treating medical team per standard-of-care. *Clostridium difficile* in stool was detected using the *Illumigene*® *C. difficile* molecular diagnostic system (95% sensitivity, 95% specificity) (13). We hypothesized that among surgical ICU patients enrolled in the CHG-BATH trial, patients randomized to chlorhexidine bathing every other day would have a lower incidence of hospital-acquired CDI compared to patients randomized to soap and water bathing.

### Study outcomes

The primary endpoint was the proportion of patients acquiring a CDI among patients at risk for an incident CDI. Infections detected > 48 hours after randomization and prior to the end of follow-up were classified as incident CDI. Infections detected prior to randomization or within 48 hours of randomization were classified as prevalent CDI. Patients were not at risk for incident CDI if they had a prevalent infection or were enrolled in the study for <48 hours. The 48-hours threshold between prevalent and incident infections accounts for the latency time between exposure to a pathogen and clinical symptoms required for detection and is consistent with the 48-hour latency period in CDC surveillance criteria (1, 14). The secondary endpoint was the proportion of patients with at least one HAI of the composite endpoint of five HAIs (CDI, primary BSI, CAUTI, VAP, or incisional SSI).

All patients included in this modified intention-to-treat analysis were screened for the CDI outcome using the criteria adapted from Clinical Practice Guidelines for CDI in adults (7). At least two independent, blinded investigators evaluated patient medical

records for CDI for all study patients with one or more criteria for potential CDI: 1) had a positive *Clostridium difficile* molecular assay, 2) received an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for CDI, 3) received oral antibiotics (vancomycin, fidaxomicin, or neomycin), or 4) had radiological evidence of pseudomembranous colitis during the hospital admission. The adjudication committee consisted of an infection prevention specialist (EAG), infectious diseases pathologists (RJO and SWL), and clinical pharmacists (LNB and JTS). All patients were classified as no CDI, prevalent CDI, or incident CDI. Complex cases and discrepancies were finalized by majority vote at arbitration meetings.

### Statistical analyses

According to previous studies (2, 15), the incidence of CDI in ICU patient were between 4%-6%. Given a higher severity of illness and mortality in the CHG-BATH trial (5), it is estimated that there would be 8% incident CDIs detected in the control arm. Using an independent sample test of two proportions with a fixed sample size of 325 and an estimated incidence of 8% in the control arm, the study had 80% power to detect a 6.5% absolute risk reduction. Primary and secondary outcomes were evaluated using the Pearson's Chi Square test or Fisher's exact test (two-sided  $\alpha=0.05$ ). Analyses were performed using Stata version 13 (StataCorp LP, College Station, TX, United States).

## RESULTS

A total of 325 patients (164 soap and water versus 161 chlorhexidine) were included in the modified intention-to-treat analysis. Demographics have been described previously<sup>5</sup> and additional information is summarized in Table 1. Of 38 patients (11.7%) who met criteria for potential CDI and underwent adjudication, 24 (7.4%) received oral or enema vancomycin, 18 (5.5%) had a positive *Clostridium difficile* molecular assay, 14 (4.3%) received an ICD-9-CM code for CDI, and 2 (0.6%) had possible pseudomembranous colitis on histopathology reports. Infection outcomes are summarized in Table 2. For the primary outcome, there was no significant difference in incidence of CDI among patients at risk for CDI between study arms (1.3% [2 of 152] soap and water versus 2.0% [3 of 148] chlorhexidine,  $P=0.68$ ). None of the 5 incident CDIs had complications of mega colon or perforation that required surgical intervention. When adding CDI to the four prior infections in the primary study, chlorhexidine bathing was associated with a non-significant reduction in the proportion of patients with at least one HAI in the composite endpoint of the five infections (18.9% [31 of 164] soap and water versus 11.2% [18 of 161] chlorhexidine,  $P=0.052$ ).

## DISCUSSION

This study was a secondary analysis of data from the CHG-BATH trial, and the outcome of CDI was chosen after the CHG-BATH trial was completed (5). This is the second randomized trial and the third clinical study assessing the association between chlorhexidine bathing and CDI (11, 12). A previously published single-center randomized trial did not find a reduction in the incidence rate of a composite endpoint of four HAIs (central-line associated BSI, CAUTI, VAP and CDI) or incidence rate of CDI between chlorhexidine bathing and control arms in the intention-to-treat analysis (11). However, chlorhexidine bathing was associated with a lower incidence rate of CDI in a subgroup of surgical ICU patients (rate of CDI per 1000 days at risk; 0.29 chlorhexidine versus 2.07 control,  $P=0.06$ ); although this association was not statistically significant (11). In a quasi-experimental, staged, dose-escalation study, chlorhexidine bathing was associated with a significant decrease in CDI in both acutely and critically ill patients compared to baseline soap and water bathing (12).

Strengths of the CHG-BATH trial were a pragmatic design, random allocation to treatment group assignments, and implementation of the chlorhexidine bathing intervention using bedside clinical staff (5). The CDI outcome was evaluated using a rigorous and blinded adjudication process.

There were several limitations that should be considered when evaluating the results of this study. There were potential risk for information bias because of the study's

retrospective design. This study was conducted in a single ICU at a tertiary hospital, which may have limited generalizability of the results. There was possible for surveillance bias as *Clostridium difficile* molecular assay screening was not standardized per protocol and was used in a minority of patients (see Table 1); however, screening was balanced between study arms. The *a priori* power analysis overestimated CDI incidence in the control group, and the study was not adequately powered to detect a clinically meaningful association between chlorhexidine bathing and CDI incidence.

## **CONCLUSION**

The results of this study were inconclusive regarding the potential association between chlorhexidine bathing and the incidence of CDI because the statistical power of the analysis was limited. There are limited published randomized trial data evaluating the association between chlorhexidine bathing and CDI. This study may help in designing future studies and may provide data for future systematic reviews and meta-analyses on this topic.

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The primary results from this trial were presented as a platform presentation at the Midwest Pharmacy Resident Conference, Omaha, Nebraska, United States in May 2016, and as a poster at the American Society of Health System Pharmacists Summer Meeting, Baltimore, Maryland in June 2016 and Society of Critical Care Medicine – Texas Chapter Annual Symposium, Houston, Texas in September 2016.

## **DISCLOSURES**

LNB received a fellowship from Texas Southern University in 2012 supporting her effort on the CHG-BATH trial. JTS received an intramural grant from Houston Methodist Research Institute to support the CHG-BATH trial. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.



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