Daily Chlorhexidine Bathing and Infection Rates in Critically-ill Patients

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1.0 STUDY SUMMARY

- **Title:** Daily Chlorhexidine Bathing and Infection Rates in Critically-ill Patients

- **Objectives:** To evaluate the effect of daily bathing with disposable chlorhexidine-impregnated bathing cloths, as compared to daily bathing with disposable standard non-chlorhexidine-impregnated bathing cloths, on the rates of healthcare-associated infections in critically-ill patients.

- **Hypothesis:** Daily bathing of the skin with chlorhexidine-impregnated bathing cloths will result in reduced rates of healthcare-associated infections in patients admitted to intensive care units (ICU).

- **Study Design:** Prospective, cluster randomized, crossover, controlled, double-blind design.
  
  1. Enrollment: 54 weeks
  2. ICUs will be cluster randomized to daily bathing of all patients with Sage® 2% Chlorhexidine Gluconate Cloths or to daily bathing with Sage Comfort Bath® Cleansing Washcloths. Each ICU will crossover between treatment assignments three times during the study period with a two week washout period with each crossover (Depicted in Figure 1).
  3. Data on rates of healthcare-associated infections will be collected prospectively for each ICU during the study period.

- **Treatment Arms:**
  
  1. Intensive care units will be randomized to one of two treatment arms
  2. The infection control staff will be blinded to which treatment arm the ICU is receiving.
  3. Patients will receive daily bathing with Sage® 2% Chlorhexidine Gluconate Cloths or daily bathing with Sage Comfort Bath® Cleansing Washcloths for the duration of the 10 week bathing assignment for the given ICU. A two week period of bathing with Sage Comfort Bath® Cleansing Washcloths will serve as a washout period prior to crossover.

**Figure 1:**

- **Treatment Arm 1:** Patients in an ICU randomized to treatment arm 1 will be bathed with single use, no rinse, disposable cloths impregnated with 2% chlorhexidine gluconate solution (Sage® 2% Chlorhexidine Gluconate Cloths). Bathing of the skin of the arms, chest, abdomen, back, both legs, perineum, and buttocks will be performed daily and as needed after patients become soiled. The face and neck will not be bathed in this manner but will be bathed with water-moistened washcloths. All other infection control and cleaning procedures will be performed per the current practice in each intensive care unit.

- **Treatment Arm 2:** Patients in an ICU randomized to treatment arm 2 will be bathed with single use, no rinse, disposable cloths that do not contain chlorhexidine.
gluconate solution (Sage Comfort Bath® Cleansing Washcloths). Bathing of the skin
of the arms, chest, abdomen, back, both legs, perineum, and buttocks will be
performed daily and as needed after patients become soiled. The face and neck will
not be bathed in this manner but will be bathed with water-moistened washcloths.
All other infection control and cleaning procedures will be performed per the current
protocols in each intensive care unit.

- Sample Size/Statistical Considerations:
  1. The study is expected to accrue approximately 4000 patients (2000 in each treatment arm).
  2. Outcome variables will be compared for each treatment arm. These values will be evaluated
     with a paired t test (n=4000).
  3. The sample size was chosen based on the expected number of admissions to the participating
     ICUs during the study period. There will be approximately 2000 experimental subjects and
     2000 control subjects. Data collected from the calendar year 2011 showed that a composite
     rate of healthcare-associated infections was normally distributed with mean of 2.9 infections
     per 1000 patient-days and a standard deviation 0.86. If the true difference in the experimental
     and control means is 0.1, we will be able to reject the null hypothesis that the population
     means of the experimental and control groups are equal with probability (power) .957. The
     Type I error probability associated with this test of this null hypothesis is 0.05.

- Inclusion Criteria:
  1. All patients admitted to the medical, surgical, trauma, and neuro adult intensive care units

- Exclusion Criteria:
  1. Being cared for in the burn ICU or patients with TEN/SJS or burns being cared for in one of
     the non-burn intensive care units.
  2. Patients with known allergy to chlorhexidine gluconate
  3. Age < 18 years old
  4. Patients where daily bathing would not be safe

- Primary Endpoints: To evaluate the efficacy of daily bathing with chlorhexidine-impregnated
  bathing cloths, as compared with non-chlorhexidine-impregnated bathing cloths, as measured by the
  composite rate of the following infections:
    1. Central line-associated blood stream infections (CLABSI)
    2. Ventilator-associated pneumonia (VAP)
    3. Catheter-associated urinary tract infection (CAUTI)
    4. *C. difficile*-associated diarrhea

- Secondary Endpoints: To evaluate the effect of daily bathing with chlorhexidine-impregnated
  bathing cloths, as compared with non-chlorhexidine-impregnated bathing cloths, on the following:
  1. Rates of each individual site infection included in the composite calculation above
  2. Skin reactions
  3. In hospital mortality
  4. Hospital length of stay
  5. Intensive care unit length of stay
  6. Cultures positive for multi-drug resistant organisms (MDROs)
  7. Rates of blood culture contamination
  8. Subgroup analysis by intensive care unit
Safety Evaluations: This study involves the use of two widely available, individual, disposable cloth patient bathing systems that differ in the inclusion of 2% chlorhexidine-gluconate. Chlorhexidine-gluconate has no systemic absorption with topical use. Therefore, safety evaluation will include monitoring of the patient’s skin condition using existing hospital mechanisms.
### 2.0 ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>TEN</td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>SJS</td>
<td>Stevens-Johnson Syndrome</td>
</tr>
<tr>
<td>CLABSI</td>
<td>Central line-associated blood stream infection</td>
</tr>
<tr>
<td>APACHE</td>
<td>Acute Physiology and Chronic Health Evaluation</td>
</tr>
<tr>
<td>VAP</td>
<td>Ventilator-associated pneumonia</td>
</tr>
<tr>
<td>CAUTI</td>
<td>Catheter-associated urinary tract infection</td>
</tr>
<tr>
<td>MDROs</td>
<td>Multi-drug resistant organisms</td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin-resistant <em>Enterococcus</em></td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>MICU</td>
<td>Medical intensive care unit</td>
</tr>
<tr>
<td>SICU</td>
<td>Surgical intensive care unit</td>
</tr>
<tr>
<td>BSI</td>
<td>Blood stream infection</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>VUMC</td>
<td>Vanderbilt University Medical Center</td>
</tr>
</tbody>
</table>
3.0 INTRODUCTION

3.1 Background:

Healthcare-associated infections are the most common adverse event in hospitalized patients. As many as 10% of patients admitted to acute care hospitals may have their course complicated by a healthcare associated infection, which contributes to increased morbidity, length of stay, and use of healthcare resources. Patients cared for in intensive care units are at risk for healthcare-associated infection due to their underlying critical illness as well as the presence of indwelling invasive devices. For instance, the placement of central venous catheters poses a risk for developing central line-associated blood stream infections. Indwelling bladder catheters increase the risk for infections of the urinary tract (CAUTI). Endotracheal intubation with mechanical ventilation places the patient at risk for ventilator-associated pneumonia. Also, this patient population is frequently placed on broad-spectrum antibiotics, which increase the risk for acquired C. difficile diarrhea and multidrug resistant organism (MDROs). Much effort is devoted to decreasing the rates of these healthcare-associated infections in intensive care units. Several lines of evidence suggest that efforts to decrease levels of patient bacterial colonization result in decreased rates of healthcare-associated infections.

3.2 Chlorhexidine Gluconate:

Chlorhexidine gluconate is a water-soluble, cationic biguanide. It affects membrane integrity at low concentrations and causes cell death by precipitating cytoplasmic contents at higher concentrations. It has broad activity against Gram-positive, Gram-negative, and anaerobic bacteria as well as yeast and some lipid enveloped viruses, including HIV. Chlorhexidine is a commonly used topical disinfectant for preparing patients prior to surgery and bathing cloths impregnated with chlorhexidine have been developed for patient use at home prior to surgery. These bathing cloths are disposable, single use, no rinse cloths that have been impregnated with 2% chlorhexidine gluconate – a concentration with in vitro cidal activity for a multitude of common pathogens (Sage® 2% Chlorhexidine Gluconate Cloths). The cloths are designed to wash the skin and reduce the burden of bacterial colonization of the skin prior to surgery.

3.3 Chlorhexidine Bathing and Infection:

There have been 10 studies published to date that examine the use of daily bathing with chlorhexidine-impregnated cloths, as compared to standard bathing, for the reduction of health care-associated infections or rates of colonization with selected pathogens. These data are summarized in Table 1. Eight of these studies employed a quasi-experimental pre and post intervention design. The remaining two studies used a prospective, sequential group, clinical trial design. Seven of the eight studies using a pre and post intervention strategy showed a reduction in the rates of blood stream infections following the intervention. Vernon et al performed a prospective clinical trial that showed decreased rates of colonization with vancomycin-resistant Enterococcus (VRE) in the group receiving chlorhexidine bathing. Bleasdale et al performed a prospective crossover clinical trial of 863 patients and were able to show a reduction in the rates of blood stream infections in the group bathed with chlorhexidine. The overall strength of this evidence is low, based on the majority being quasi-experimental designs and multiple cointerventions. In addition, the variability in the outcomes measured makes interpreting the results of these studies collectively difficult. In addition, there have been two studies of chlorhexidine bathing presented in abstract form. Milstone et al used a prospective cluster randomized design to investigate the effect of daily chlorhexidine bathing, as compared with non-chlorhexidine bathing, on the development of bacteremia in a pediatric ICU population and found a trend toward reduced bacteremia in the group bathed with chlorhexidine that was not statistically significant. Climo et al report a multi-
center, cluster randomized, trial of chlorhexidine bathing in adult patients that resulted in decreased rates of bloodstream infections as well as decreased colonization with MDROs\textsuperscript{16}.

Publically available data collected from Vanderbilt’s ICUs during the calendar year 2011 showed that a composite rate of healthcare-associated infections was normally distributed with mean of 2.9 infections per 1000 patient-days and a standard deviation 0.86. As can be seen in Table 1, that composite rate for all HAIs is less than that of all published studies before intervention, and lower than that of most published studies after bathing intervention. This is a critical observation because the effectiveness of chlorhexidine bathing is uncertain in environments with low HAI rates.
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Setting</th>
<th>Design</th>
<th>Intervention</th>
<th>Outcome of interest</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vernon, et al 2006</td>
<td>1787</td>
<td>MICU of tertiary care hospital</td>
<td>Prospective, sequential group clinical trial</td>
<td>Daily soap and water bath compared to 2% chlorhexidine bath</td>
<td>Acquisition of VRE colonization</td>
<td>Decreased VRE colonization (from 26 to 9 per 1000 patient-days)</td>
</tr>
<tr>
<td>Popovich, et al 2009</td>
<td>NA</td>
<td>MICU of tertiary care hospital</td>
<td>Quasi-experimental pre and post intervention</td>
<td>Daily soap and water bath compared to 2% chlorhexidine bath</td>
<td>Rates of CLABSI</td>
<td>Decreased rates of CLABSI (from 5.31 to 0.69 per 1000 patient-days)</td>
</tr>
<tr>
<td>Popovich et al 2010</td>
<td>NA</td>
<td>SICU of tertiary care hospital</td>
<td>Quasi-experimental pre and post intervention</td>
<td>Daily soap and water bath compared to 2% chlorhexidine bath</td>
<td>Rates of CLABSI</td>
<td>No change in rates of CLABSI</td>
</tr>
<tr>
<td>Borer, et al 2007</td>
<td>320</td>
<td>MICU of tertiary care hospital</td>
<td>Quasi-experimental pre and post intervention</td>
<td>Daily soap and water bath compared to 4% chlorhexidine bath</td>
<td>Rates of Acinetobacter BSI</td>
<td>Decreased rates of BSI (from 4.6 to 0.6 per 1000 patient-days)</td>
</tr>
<tr>
<td>Climo, et al 2009</td>
<td>5320</td>
<td>6 ICUs at at 4 tertiary care centers</td>
<td>Quasi-experimental pre and post intervention</td>
<td>Daily soap and water bath compared to 2% chlorhexidine bath</td>
<td>Rates of colonization and BSI with MRSA and VRE</td>
<td>Decreased colonization with MRSA and VRE and decreased VRE BSI but not MRSA BSI</td>
</tr>
<tr>
<td>Munoz-Price, et al 2009</td>
<td>NA</td>
<td>Long-term acute care hospital</td>
<td>Quasi-experimental pre and post intervention</td>
<td>Daily soap and water bath compared to 2% chlorhexidine bath</td>
<td>Rates of CLABSI</td>
<td>Non-significant decrease in CLABSI (9.5 to 3.8 per 1000 patient-days)</td>
</tr>
<tr>
<td>Dixon, et al 2010</td>
<td>144</td>
<td>SICU at a level 1 trauma center</td>
<td>Observational cohort with experimental controls</td>
<td>Daily soap and water bath compared to 2% chlorhexidine bath</td>
<td>Rates of CLABSI</td>
<td>Decreased rates of CLABSI (12.07 to 3.17 per 1000 patient-days)</td>
</tr>
<tr>
<td>Evans, et al 2010</td>
<td>539</td>
<td>Trauma ICU</td>
<td>Quasi-experimental pre and post intervention</td>
<td>Daily bathing with wash cloths with and without chlorhexidine</td>
<td>Rates of CLABSI</td>
<td>Decreased rates of CLABSI (8.4 to 2.1 per 1000 patient-days)</td>
</tr>
<tr>
<td>Kassakian, et al 2011</td>
<td>14,801</td>
<td>4 General medicine wards at a tertiary care center</td>
<td>Quasi-experimental pre and post intervention</td>
<td>Daily soap and water bath compared to 2% chlorhexidine bath</td>
<td>Rates of MRSA and VRE infections</td>
<td>64% reduction in MRSA and VRE infections</td>
</tr>
<tr>
<td>Bleasdale, et al 2007</td>
<td>836</td>
<td>MICU of tertiary care hospital</td>
<td>Crossover clinical trial</td>
<td>Daily soap and water bath compared to 2% chlorhexidine bath</td>
<td>Rates of BSI</td>
<td>Decreased rates of BSI (from 10.4 to 4.1 per 1000 patient-days)</td>
</tr>
</tbody>
</table>
4.0 OBJECTIVES

4.1 Primary Endpoints: To evaluate the efficacy of daily bathing with chlorhexidine-impregnated bathing cloths, as compared with non-chlorhexidine-impregnated bathing cloths, as measured by the composite rate of the following infections:

1. Central line-associated blood stream infections
2. Ventilator-associated pneumonia
3. Catheter-associated urinary tract infection
4. *C. difficile*-associated diarrhea

4.2 Secondary Endpoints: To evaluate the effect of daily bathing with chlorhexidine-impregnated bathing cloths, as compared with non-chlorhexidine-impregnated bathing cloths, on the following:

1. Rates of each individual site infection used in the composite rate above
2. Skin reactions
3. In hospital mortality
4. Hospital length of stay
5. Intensive care unit length of stay
6. Cultures positive for multi-drug resistant organisms (MDROs)
7. Rates of blood culture contamination
8. Subgroup analysis by intensive care unit

5.0 STUDY DESIGN

5.1 Study Description

This is a single center, multiple ICU, cluster randomized, controlled, crossover study to evaluate the impact of daily bathing of critically-ill patient’s skin with cloths impregnated with 2% chlorhexidine gluconate, as compared to non-chlorhexidine-impregnated bathing cloths, on the development of healthcare-associated infections. Only subjects being cared for in an ICU will be eligible.

In addition, subjects will receive standard ICU care including all infectious control practices in place in the ICU that the subject is admitted to. This will include appropriate hand hygiene, contact isolation for patients known to be colonized or infected with MDROs, standardized bundles for central venous catheter insertion, measures to prevent the development of VAP (including oral care with chlorhexidine gluconate), and use of antibiotics at the discretion of the clinician caring for the patient.

Every patient admitted to one of the four participating ICUs who meet none of the exclusion criteria will be enrolled in the study. Patients will be enrolled prior to receiving their first bath in the ICU. Patients will continue bathing with the assigned cloths as long as they physically remain in the ICU, regardless of whether or not they get transferred off the ICU team prior to being cared for outside of the ICU, or until a crossover event occurs.

The study consists of daily bathing of patient’s skin with one of two single use, no rinse, disposable bathing cloths. Sage® 2% Chlorhexidine Gluconate Cloths are impregnated with a 2% chlorhexidine solution while the Sage Comfort Bath® Cleansing Washcloths do not contain chlorhexidine gluconate. Bathing of the skin of the arms, chest, abdomen, back, both legs, perineum, and buttocks will be performed daily and as needed after patients become soiled. The face and neck will not be bathed in this
manner but will be bathed with water-moistened washcloths. In situations where extensive soiling occurs, the soiled material will be cleaned per usual ICU practice (often with washcloths and water). At the end of the cleaning, the area will be wiped down with the study cloths.

5.1.1 Schematic of the Study Design

![Schematic Figure 5.A]

5.1.2 Study Bathing Administration and Design

The participating ICUs will be randomized to daily bathing of all patients admitted that do not meet an exclusion criteria with either non-chlorhexidine-impregnated bathing cloths (Sage Comfort Bath® Cleansing Washcloths) or with bathing cloths impregnated with 2% chlorhexidine gluconate solution (Sage® 2% Chlorhexidine Gluconate Cloths). Following 10 weeks of the assigned bathing group, a two week washout period will begin. During this period, all patients will be bathed daily with the non-chlorhexidine-impregnated bathing cloths. Healthcare-associated infections that occur during the washout period will not be counted toward either bathing group. Following the washout period, each ICU will crossover into the opposite bathing group for a 10 week period. There will be a total of three crossovers for each ICU with a two week washout period preceding each crossover. Therefore, each ICU will employ each bathing technique for two 10 week periods during the study (depicted in Figure 5.1.1).

The Sage Comfort Bath® Cleansing Washcloths and Sage® 2% Chlorhexidine Gluconate Cloths differ in appearance and scent. These differences between the bathing cloths make blinding of the nursing staff and care partners performing the bathing impossible. However, the Infection control staff responsible for distinguishing VAP, CLABSI, and blood stream contamination, etc. will be blinded to the bathing assignment in each ICU.

Each bath makes use of six bathing cloths. One cloth each is used to bath the arms and chest, abdomen, back, each leg, and buttocks and perineum. This will be performed daily on each patient enrolled in the study. In addition, bathing can be repeated on a given day if needed due to soiling. If extensive soiling, the bathing with the study cloths should occur after cleaning of the soiled area by usual ICU practice. Bathing will continue in this manner for the duration of a patient’s stay in the ICU or until the conclusion of a given bathing assignment within that ICU.

The assessment of safety will include collection of adverse events. Given the lack of systemic absorption of topical chlorhexidine gluconate, adverse events are expected to be limited to the skin. Skin abnormalities will be tracked using existing reporting methods in each ICU.

The assessment of efficacy will include collection of data on the rates of infection. The primary endpoint is the composite endpoint of rates of CLABSI, VAP, CAUTI, and *C. difficile* diarrhea. The Vanderbilt
University Medical Center Department of Infection Control and Prevention collects these data using standardized methods and definitions and will make them available to the study.

### 5.1.3 Post-Study Follow-Up Period

Patients will be followed for mortality outcomes until the earlier of hospital discharge or day 28. Subjects that are discharged alive from the hospital prior to day 28 will be presumed to be alive at day 28.

### 5.2 Treatment Arms

#### 5.2.1 Treatment Arm 1

Patients in an ICU randomized to treatment arm 1 will be bathed with single use, no rinse, disposable cloths impregnated with 2% chlorhexidine gluconate solution (Sage® 2% Chlorhexidine Gluconate Cloths). Bathing of the skin of the arms, chest, abdomen, back, both legs, perineum, and buttocks will be performed daily and as needed after patients become soiled. The face and neck will not be bathed in this manner but will be bathed with water-moistened washcloths. All other infection control and cleaning procedures will be performed per the current protocols in each intensive care unit.

#### 5.2.2 Treatment Arm 2

Patients in an ICU randomized to treatment arm 2 will be bathed with single use, no rinse, disposable cloths that do not contain chlorhexidine gluconate solution (Sage Comfort Bath® Cleansing Washcloths). Bathing of the skin of the arms, chest, abdomen, back, both legs, perineum, and buttocks will be performed daily and as needed after patients become soiled. The face and neck will not be bathed in this manner but will be bathed with water-moistened washcloths. All other infection control and cleaning procedures will be performed per the current protocols in each intensive care unit.

### 5.3 Administration of Study Medications

#### 5.3.1 Study Intervention Preparation and Administration

Participating ICUs will be randomized to daily bathing of all patients admitted that do not meet an exclusion criteria with either non-chlorhexidine-impregnated bathing cloths (Sage Comfort Bath® Cleansing Washcloths) or with bathing cloths impregnated with 2% chlorhexidine gluconate solution (Sage® 2% Chlorhexidine Gluconate Cloths). These cloths will be distributed to the appropriate ICUs and will be the only bathing cloth available in the ICU during the study period. Each bath makes use of six bathing cloths. One cloth each is used to bathe the arms and chest, abdomen, back, each leg, and buttocks and perineum. This will be performed daily on each patient enrolled in the study. In addition, bathing can be repeated on a given day if needed due to soiling. Bathing will continue in this manner for the duration of a patient’s stay in the ICU or until the conclusion of a given bathing assignment within that ICU.

### 6.0 STUDY POPULATION AND ENROLLMENT

#### 6.1 Participant Enrollment

All patients admitted to a participating ICU during the study period that do not meet exclusion criteria will be enrolled in the study. Patients will be enrolled at the time of admission and prior to receiving their...
first bath in the ICU. Based on the admission rates to the participating ICUs in recent years, approximately 4000 subjects are expected to be enrolled during the study period.

6.2 Inclusion Criteria

Participant eligibility is determined based on the selection of criteria detailed below:

1. All patients admitted to the participating adult intensive care units

6.3 Exclusion Criteria:

Patients meeting any of the following criteria will not be eligible for participation in the study:

1. Being cared for in the burn ICU or patients with TEN/SJS or burns being cared for in one of the non-burn intensive care units.
2. Patients with known allergy to chlorhexidine gluconate
3. Age < 18 years old
4. Patients where daily bathing would not be safe

6.4 Informed Consent

Chlorhexidine is a non-prescription product available in retail stores and on the internet. Chlorhexidine soap is also widely used in clinics and doctors’ offices. Both bathing cloths used in this study are readily available and are widely used in healthcare settings in the US and both are considered within the range of usual care. Currently, the medical and surgical ICUs at Vanderbilt University Medical Center use the Sage® 2% Chlorhexidine Gluconate Cloths for bathing while the trauma and neuro ICUs use the Sage Comfort Bath® Cleansing Washcloths. Both bathing systems are safe and pose minimal risk to patients. Because of the minimal risk posed to patients and the common use of both bathing cloths in practice, a waiver of informed consent will be requested. In addition to this being minimal risk due to both arms being used in clinical practice, obtaining informed consent prior to participation will not be feasible as patients will need to be enrolled prior to their first bath in the ICU, which is done at the time of admission. Obtaining informed consent before the first bath will be impossible in most of these patients who will not be able to consent for themselves (i.e. would require surrogate consent). Also, because ICUs are randomized as opposed to individual patients, subjects who refuse consent would need to be placed in an ICU that has been randomized to standard bathing cloths. The current practice at VUMC is to admit a patient to the ICU most appropriate for their care requirements. The need to potentially move patients that do not consent to a different ICU would pose an additional barrier to obtaining consent and might compromise care.

6.5 Randomization and the Blind

The four participating ICUs will be randomized to the initial bathing group using a computer randomization program. Following the initial randomization, each ICU will crossover between bathing groups three times during the study period. Individual patients will not be randomized for the purposes of this study. Patients that are transferred between two participating ICUs will be treated according to the bathing assignment for the unit in which they currently are cared for however they will be analyzed by their original bathing assignment for all subsequent analyses. Similarly, a patient transferred from a participating ICU to a non-participating ICU will be analyzed according to their initial bathing assignment for all subsequent analyses. All infections that occur during the two week washout period will not be counted toward either bathing assignment and will be excluded from analysis.
The Sage Comfort Bath® Cleansing Washcloths and Sage® 2% Chlorhexidine Gluconate Cloths differ in appearance and scent. These differences between the bathing cloths will make blinding of the nursing staff and care partners performing the bathing impossible. However, the Infection control staff responsible for distinguishing VAP, CLABSI, and blood stream contamination, etc. will be blinded to the bathing assignment in each ICU.

6.6 Excluded Medications

No medications will be excluded during the study period.

6.7 Concomitant Medications

All medications administered as part of standard care will be allowed.

6.8 Criteria for Discontinuation or Withdrawal

The primary reason for treatment discontinuation will be noted in the medical record:

A. Adverse Event: The participant has experienced an adverse event that the investigator believes requires early termination because continued participation imposes an unnecessary risk to the participant’s health.

6.9 Procedures for Discontinuation or Withdrawal of a Participant

Participants who prematurely discontinue from the study will be bathed with soap and water for the remainder of their ICU stay, since the presumed reason for discontinuation will be reaction to chlorhexidine-impregnated or non-chlorhexidine-impregnated cloths. Their data will be included in subsequent analyses.

7.0 STUDY PLAN

7.1.1 Demographics and Medical History

Demographics will include the age, gender, ethnicity, and race as described by the participant or participant’s legally authorized representative.

7.1.2 Mortality Assessment

Participant survival will be assessed at the earlier of hospital discharge or 28 days. Participants who are discharged alive from the hospital prior to day 28 will be assumed to be alive at study day 28. No additional efforts to contact these participants to ascertain their status will be undertaken.

7.1.3 Infection Rates

The Vanderbilt University Medical Center Department of Infection Control and Prevention track incidents of nosocomial infections, including CLABSI, VAP, CAUTI, and *C. difficile* diarrhea. Infection Control Staff designate these infections according to CDC definitions existing at the time of the infection. These data will be available for every incident occurring in the participating ICUs during the study period.

7.1.4 Isolation of MDROs
The Vanderbilt University Medical Center Department of Infection Control and Prevention track all cultures positive for Multi-drug resistant organisms (organisms resistant to more than one class of antibiotics) and this data will be available for all participating ICUs during the study period in the REDCap database.

### 7.1.5 Blood Culture Contamination

The Vanderbilt University Medical Center Department of Infection Control and Prevention track rates of blood culture contamination defined as \( \leq 50\% \) of all blood culture sets obtained from one patient on the same day that grow one of the following organisms: coagulase-negative staphylococci, alpha-hemolytic streptococci, Micrococcus species, Propionibacterium species, Corynebacterium species, and Bacillus species. These data will be available for all participating ICUs during the study period in the REDCap database.

### 7.1.6 Collection and Banking of Organisms Causing Infections

All bacterial isolates causing healthcare-associated infections during this study period will be collected by the VUMC Microbiology laboratory and stored in a \(-80^\circ\) freezer for possible subsequent analyses.

### 7.2 Schedule of Observation and Procedures

#### 7.2.1 Baseline Assessments

Eligibility of participants will be assessed based on the inclusion and exclusion criteria prior to the initiation of bathing.

#### 7.2.2 Bathing

Patients will be enrolled in the study prior to receiving their first bath in the ICU to which they are admitted. Bathing will be continued daily and as needed for soiling for the duration of the subject’s stay in that ICU or until a crossover event with a washout period.

#### 7.2.3 Immediate Post-Study Evaluation Period (18-36 hours)

Subjects will be monitored during the bathing period and data will be collected on the primary and secondary study endpoints as well as monitoring for adverse events.

#### 7.2.4 Post-Study Follow-Up Period

The survival status of participants will be assessed at 28 days. If participants are discharged from the hospital alive prior to study day 28, they will be considered alive at study day 28.

### 8.0 PROTOCOL DEVIATIONS

Protocol deviations will be recorded and reported to the local IRB in a timely manner. If the protocol deviation placed the participant at increased risk, it will be reported to the IRB within 3 business days. If the protocol deviation resulted in no increased risk, the event will be reported to the IRB at continuing review.

### 9.0 ADVERSE EVENTS
9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an intervention, whether or not the incident is considered to be related to the intervention. Given the topical administration of the study drug, incidences of skin eruptions and ulcerations will be systematically collected and will not be considered adverse events.

The Principal Investigator will be responsible for overseeing the safety of this trial on a daily basis. He will be available at any time for questions from the bedside nurses, who will also be monitoring the patients continuously for adverse events. In addition, a Data Safety and Monitoring Board (DSMB) consisting of experienced clinician clinical investigators in critically ill patients with experience monitoring clinical trials in such patients, will be available to oversee the study. Since there will be no interim analyses of the data for efficacy, the major role of the DSMB will be to monitor the trial for safety. In addition, the DSMB will also be available to review serious adverse events in a timely manner. They will be asked to be available for rapid access by the investigators in the case of the need to evaluate serious adverse events or any other major unanticipated or safety related issues. Furthermore, in cases of serious adverse events, the DSMB will have the ability to pause the trial to investigate possible safety issues and/or suggest changes to the design of the study to abrogate any safety issues.

9.2 Pre-Existing Conditions

Pre-existing conditions that are present before the start of bathing will be considered concurrent medical conditions and should NOT be recorded as adverse events. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication may be recorded as an adverse event at the discretion of the investigator.

9.3 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that meets all the following criteria:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
- Requires inpatient hospitalization
- Prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Important medical event that requires an intervention to prevent any of a-f above.

9.4 Adverse Event Collection Period

Collection of adverse events will commence from the time that the participant is first bathed. Routine collection of adverse events will continue until the patient leaves the ICU.

10.0 STATISTICAL METHODS
10.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will include date of birth, age, and gender. Descriptive statistics, including mean and standard deviation, median, intraquartile ranges, minimum and maximum, and the number and percent of subjects in specified categories will be used to summarize the demographic and baseline variables for both treatment arms. These will be compared between treatment groups using two-sample t-test for continuous variables and Chi-square test (or Fisher’s Exact Test) for categorical variables. Characteristics of variables will be analyzed to ensure normal distribution. If they are not normally distributed, log transformation will be utilized in an attempt to normalize the distribution. If this is not effective, then non-parametric statistical methods will be utilized for the analysis. All statistical analyses will be done using standard statistical software.

10.2 Sample Size

Based on the number of admissions to the participating ICUs in recent years, this study is expected to accrue approximately 4000 patients. This sample size was chosen based on the expected number of admissions to the participating ICUs during the study period. There will be approximately 2000 experimental subjects and 2000 control subjects. Data collected from the calendar year 2011 showed that a composite rate of healthcare-associated infections was normally distributed with mean of 2.9 infections per 1000 patient-days and a standard deviation 0.86. If the true difference in the experimental and control means is 0.1, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) .957. The two-sided Type I error probability associated with this test of this null hypothesis is 0.05.

10.3 Primary Endpoints

The primary clinical endpoint for this study is composite rate of healthcare-associated infections including CLABSI, VAP, CAUTI, and C. difficile diarrhea.

Primary efficacy variables will be evaluated by comparing the composite rates of healthcare-associated infections that occurred during periods of non-chlorhexidine bathing with the rates during periods of chlorhexidine bathing in each ICU.

10.4 Secondary Endpoints

Secondary endpoints will include analyses for each infection individually (CLABSI, VAP, CAUTI, and C. difficile diarrhea). Other outcome variables, including hospital length of stay, ICU length of stay, rates of bloodstream contamination, and mortality at 28 days will similarly be compared between subjects bathed using standard bathing cloths versus those bathed with chlorhexidine-impregnated bathing cloths. All of these analyses will be conducted using paired t tests (n=16).

11.0 ETHICS

11.1 Ethical Conduct of the Trial

This study will be conducted with the highest respect for individual participants according to the protocol, the World Medical Association Declaration of Helsinki, the Guideline for Good Clinical Practice, and the Belmont Report. Furthermore, the study will be conducted in accordance with the Common Rule (45
CFR 46), as guided by the Department of Health and Human Services via the Office of Human Research Protections.

11.2 Institutional Review Board

The investigator will submit all relevant documents to the IRB for the protocol’s review and approval. The study, protocol, and waiver of consent must be approved by the local IRB prior to commencing the study. Written approval by the IRB of the protocol must be obtained prior to enrollment of any participants. If any member of the IRB has direct participation in this trial, he or she must refrain from any IRB discussions or votes pertaining to this study.

Conduct of this study will adhere to all the requirements stipulated by the IRB. This may include notification to the IRB regarding: protocol amendments, recruitment materials, local safety reporting requirements, and closure of the study.

11.3 Participant Information and Waiver of Informed Consent

Chlorhexidine is a non-prescription product available in retail stores and on the internet. Chlorhexidine soap is also widely used in clinics and doctors’ offices. Both bathing cloths used in this study are readily available and are widely used in healthcare settings in the US and both are considered within the range of usual care. Currently, the medical and surgical ICUs at Vanderbilt University Medical Center use the Sage® 2% Chlorhexidine Gluconate Cloths for bathing while the trauma and neuro ICUs use the Sage Comfort Bath® Cleansing Washcloths. Both bathing systems are safe and pose minimal risk to patients. Because of the minimal risk posed to patients and the common use of both bathing cloths in practice, a waiver of informed consent will be requested. In addition to this being minimal risk due to both arms being used in clinical practice, obtaining informed consent prior to participation will not be feasible as patients will need to be enrolled prior to their first bath in the ICU which is done at the time of admission. Obtaining informed consent before the first bath will be impossible in most of these patients who will not be able to consent for themselves (i.e. would require surrogate consent). Also, because ICUs are randomized as opposed to individual patients, subjects who refuse consent would need to be placed in an ICU that has been randomized to standard bathing cloths. The current practice at VUMC is to admit a patient to the ICU most appropriate for their care requirements. The need to potentially move patients that do not consent to a different ICU would pose an additional barrier to obtaining consent and might compromise care. Since the only bathing cloths available in each ICU during the study period will be the study cloths, participants will be bathed with the study cloths regardless. As such, removal from the study will only occur in participants who experience an adverse event.

12.0 DATA HANDLING AND RECORDKEEPING

12.1 Participant Confidentiality

Vanderbilt affirms and upholds the principle of the participant’s right to protection against invasion of privacy. Throughout this study, a participant’s source data will only be linked to the clinical study database or documentation via a unique study identification number. As permitted per HIPAA regulations, limited participant attributes such as sex, age, or gender may be used to verify the accuracy of the participant’s unique identification number. Copies of any participant source documents provided to entities outside of Vanderbilt University Medical Center will have all personally identifiable information removed (e.g., participant name, address, date of birth, etc.)

12.2 Case Report Forms
Clinical and research data will be entered into the REDCap electronic record. As such, no written CRFs will be needed.

12.3 Record Retention

The investigator will keep all study-specific documents, an identification log of all participating patients, and any non-electronic source worksheets, and in a locked and secure office or storage space until at least 3 years after the completion of the study. Most of the data will be housed in the participant’s electronic medical record.

13.0 COMPENSATION AND TREATMENT FOR INJURY

Participants will not be compensated for injury beyond immediate treatment of any study-related adverse events at Vanderbilt Hospital.
REFERENCES


