Pilot Study: Safety of Chlorhexidine (CHG) Baths in Patients Less Than 2 Months of Age

Introduction

Literature provides overwhelming evidence supporting the use of chlorhexidine gluconate (CHG) a rapid onset, broad spectrum, topical antiseptic for reducing healthcare-associated infections (HAIs). CHG is believed to be superior to other forms of antiseptics because, when it is applied to the skin surface, it leaves a lasting residue on the skin. This residue cannot readily be removed with alcohol, a commonly used antiseptic during lab draws and frequently performed invasive procedures, and thus CHG provides prolonged protection against both gram-positive and gram-negative organisms. Additionally, reports indicate CHG is well tolerated in patients greater than 2 months of age. However, there is limited evidence to support the use of topically applied CHG in infants less than 2 months of age, or 48 weeks' postmenstrual age (PMA), because of potential safety concerns in this population.

The purpose of this investigation will be to describe the safety of bi-weekly CHG baths in a sample of Newborn Intensive Care Unit (NICU) and pediatric Cardiac Intensive Care Unit (CICU) patients less than 2 months of age by measuring the incidence of skin problems, other adverse events and CHG blood levels.

Definition. In this proposal 2 months of age is equivalent to 2 months' post-term gestation, or 48 weeks PMA. All other references to age will be presented in the number of week's PMA.

Background and Significance

HAI Prevention and CHG. Decreasing HAIs has been a long-standing challenge for health care institutions and a primary focus for governing bodies such as The Centers for Medicare and Medicaid Services (CMS), The Healthcare Infection Control Practices Advisory Committee (HICPAC), and The Joint Commission (TJC). There have been many national, statewide and multi-centered collaborative studies with the main focus being the reduction of HAIs, specifically central line associated blood stream infections (CLABSIs). Additionally, significant research has also been dedicated to finding products and developing practices that will help to minimize and maybe even eliminate the occurrence of HAIs.

One product that has been frequently studied and widely published is CHG. CHG is used for skin antisepsis before surgery, before central venous catheter (CVC) insertion, and for routine patient bathing. The majority of published evidence overwhelmingly supports CHG use for skin antisepsis. The use of CHG on the skin leads to significant reductions in colonization by organisms including methicillin resistant staphylococcus aureus (MRSA) and vancomycin resistant enterococcus (VRE), among others. Multiple studies have been conducted in pediatric and adult intensive care units comparing CHG against other products. One study (Mimoz, 2007) found CHG to be superior over povidone-iodine for CVC insertion and routine CVC care (dressing changes). Other studies, (Vernon, 2006; Bleasdale, 2007; Milstone, 2013) compared daily bathing with 2% CHG cloths against standard soap and water baths. All of these studies found significant decreases in bloodstream infections (BSIs) and/or skin colonization when skin asepsis was performed through daily bathing with CHG. Also, Lee et al (2013) looked at CHG blood concentrations in a small sample (12 subjects) of PICU patients undergoing daily bathing with 2% CHG-impregnated bathing cloths. All study participants were greater than 2 months of age. Blood samples were taken on (approximately) days 1, 4, 7 and weekly after daily CHG bathing had been initiated. Sixty-nine subjects had serum CHG levels of less than 4.5, 9 had CHG levels between 4.5-16.9, and 3 had CHG levels greater than 17. While these investigators found that CHG was absorbed into the blood streams of the subjects, there was no evidence of accumulation of CHG with repeated exposures over time. According to the investigators, when the high serum levels were repeated, half of the tests showed no evidence of CHG in the bloodstream.

In response to these studies and others, CHG use for skin antisepsis has become a widely accepted practice, and it is now part of the Centers for Disease Control and Prevention (CDC) CVC maintenance bundle for patients greater than 2 months of age.

CHG use in Young Infants. Mature, intact skin is a natural barrier to a host of infectious organisms. Skin that is free of these infectious organisms is necessary for invasive procedures like surgery and the insertion of CVCs. However, the permeable and fragile skin of the preterm infant and those infants less than 2 months of age remain problematic to healthcare providers. Even once commonly used products lead to problems; for instance, povidone-iodine solutions have been noted to alter thyroid function when absorbed, and isopropyl-alcohol solutions have led to extensive skin injury including burns. (Harpin and Rutter 1982)

Although evidence suggests that CHG is safe and efficacious to use in adult and pediatric patients greater than 2 months of age, many pediatric providers remain cautious about its use in infants less than 2 months of age. This caution stems from 2 landmark events. The first occurred when the topically applied antibacterial agent hexachlorophane (HCP) was used. HCP reportedly caused neurotoxicity in newborns and animals, generating fear amongst healthcare providers (Powell et al 1973). The second occurred when the US Food and Drug Administration (FDA) revised the labeling on CHG products as "not recommended for use in infants under 2 months of age" in response to the problems with HCP. As a result, there has been limited studies' investigating the use of CHG in infants less than 2 months of age.

Infection Control in NICU and CICU. Despite multiple infection prevention initiatives including yearly mandatory education through Net learning, staff education days and skills days, the number of CLABSIs remains problematic in Boston Children's Hospital (BCH) intensive care units. Since 2012, the NICU at Boston Children's Hospital has experienced 6 CLABSIs and the pediatric Cardiac ICU has had 21. Of these reported CLABSIs, 40% (11/27) occurred in infants less than 2 months of age. Furthermore, these HAIs may be directly related to increased morbidity and mortality for these hospitalized infants.

More recently, the FDA revised the labeling of CHG to "use with care in premature infants and infants under 2 months of age" (FDA Medwatch-internet, last revised 2012; O'Grady et al 2011). Additionally, HAIs remain a significant problem in this patient population. Moreover anecdotal and published reports suggest that some caring for these young infants are using CHG without data to support its safety.

Review of Literature. Our review of studies examining use of CHG in young infants has yielded more questions than answers. In one study by Cowen et al (1979), 34 infants were bathed with 4% Hibitane CHG (also called Hibiscrub), followed by a water rinse. They concluded that CHG levels were present in the blood of term and preterm newborns that were exposed to 4% Hibitane CHG baths. However, the investigators hypothesized that many blood samples were contaminated since CHG cannot be washed off with alcohol that is used on the skin before obtaining the blood samples. Another, Aggert et al (1981) studied both term and preterm infants exposed to 1% CHG solution for neonatal cord care. The umbilical cord was treated with 1% CHG and 3% zinc oxide powders. This treatment was repeated every 4 hours for a minimum of 9 days. Blood samples were obtained on approximately days 5 and 9 of the study, when other lab work was being obtained. The results demonstrated greater absorption of CHG in the preterm population, heightening concern for use of CHG products in preterm infants.

In 2009, Tamma et al surveyed 100 United States NICUs about CHG use in their units. Of the 90 NICUs that responded, 55 NICUs reported using CHG (61%), with the most frequent use being CVC dressing changes (78%). A surprising 49 % (27/55) did not report limiting CHG use for weight, gestational age or chronological age. Also 28 of the NICUs reported skin reactions like erythema and burns resulting from CHG use. More specifically, burns were primarily reported to have occurred when CHG was used on

infants weighing less than 1500 grams (13/15; 76%).

In 2012, Popovich studied CHG concentrations on the skin after daily CHG bathing compared to microbial density on the skin. The CHG levels on the skin did not show evidence of accumulation after repeated exposure through bathing and levels returned to baseline within 24-hours after exposure. Though of note, Popovich also concluded that the presence of untoward organisms on the skin was inhibited up to 3 days later, and was significantly lower than patients who were bathed with soap and water.

Untoward, Adverse Events Associated with CHG. While chlorhexidine has become a widely utilized antiseptic, it is not used without risk. With the assistance of Alison Clapp MLIS, the hospital librarian, an extensive literature search for untoward or adverse events associated with CHG revealed a number of concerning documents citing problems including mild skin irritation, Allergic Contact Dermatitis (ACD) and anaphylaxis. Most notably though, the more serious reactions were related from direct exposure to multiple products containing CHG and CHG impregnated devices (Khoo & Oziemski, 2010; Kutzscher, 2012), or direct contact between the CHG product and the mucous membranes of the individual. (Khan et al, 2011). In general, there were no serious events associated with CHG bathing cloths, with most reports citing only mild skin reactions. (Vernon et al, 2006; Bleasdale et al, 2007; Darmstadt et al, 2007; Sankar et al, 2009; Milstone et al, 2013).

Purpose Statement

Daily CHG baths are a proven method for preventing HAIs in patients greater than 2 months of age and older. However, CHG has been shown to be absorbed through the skin of premature and term infants and safe CHG bloodstream levels are not known. Thus the use of CHG in infants less than 2 months of age remains controversial.

Like many ICUs across the nation, the ICUs at Boston Children's Hospital have been using CHG on a limited basis for CVC insertion and CVC dressing changes on all babies greater than 28 weeks PMA for almost 2 years. During this time, we have not observed any untoward effects to the skin's surface. Though despite our best efforts, HAIs remain problematic, and thus we remain reluctant to expand the use to daily CHG baths without a better understanding of the risks and benefits. In effort to secure the benefit of CHG baths while minimizing risk of bloodstream absorption, our study team has elected to investigate the safety of twice-weekly 2% CHG baths in a sample of newborns (36 weeks PMA or older, less than 2 months of age or 48 weeks PMA, with a CVC). This study will examine the safety of twice weekly CHG baths and provide data to support a larger study that will examine efficacy. The research questions to be answered by this study are as follows:

Research Question 1:

Are twice weekly CHG baths safe for use in a sample of infants 36 weeks PMA or older, and less than 2 months of age (48 weeks PMA) with a CVC?

Hypothesis 1:

CHG will be safe for use in a sample of infants 36 weeks PMA or older, and less than 2 months of age (48 weeks PMA) with a CVC as evidenced by an adverse event rate less than 10%.

Research Question 2:

Does twice weekly CHG baths lead to rising (cumulative) CHG blood levels, liver function tests (LFTs -AST/ALT) and Serum Creatinine over time in a sample of infants 36 weeks PMA or older, and less than 2 months of age (48 weeks PMA) with a CVC?

Hypothesis 2:

Twice weekly CHG baths do not lead to rising (cumulative) CHG blood levels, LFTs (AST/ALT)

and Serum Creatinine over time in a sample of infants 36 weeks PMA or older, and less than 2 months of age (48 weeks PMA) with a CVC.

Methods

Study Design: A pilot study using a single arm trial design.

Study Sample: Our convenience sample will include 50 infants. Infants admitted to the NICU or pediatric CICU will be eligible to participate.

Inclusion criteria.

- Greater than/equal to 36 weeks PMA (gestational age + chronological age)
- Less than/equal to 48 weeks PMA (gestational age + chronological age)
- Greater than/equal to 3 days of age
- Existing or soon to be placed, peripheral or surgical CVC
- Permission to participate in trial by attending physician
- Parent or legal guardian informed consent to participate in the trial

Exclusion criteria.

- Infant with a large open lesion or severe skin condition (i.e., Myelomeningocele, Gastroschisis, lymphatic malformation, open chest, ostomies and/or mucus fistulas or Icthyosis)
- Infants with active seizure disorders
- Infants with Hypoxic Ischemic Encephalopathy
- Infants with severe multi-system organ failure or Liver failure as defined by documentation of abnormal liver function tests: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) Gamma-glutamyltransferase (GGT) and L-lactate dehydrogenase (LD).
- HCT </= 28%: Respiratory support (mechanical ventilation, continuous positive airway pressure or high flow nasal cannula with FiO2 > 25% Oxygen by nasal cannula > 1 liter/min) or HCT </= 25%: No respiratory support.
- Infant with renal impairment as defined by: documented serum Creatinine greater than 0.7, renal disorders (renal agenesis, polycystic kidney disease, dysplastic kidneys, acute renal injury).
- Infants deemed clinically unstable by their physician such as patients that are extremely fragile and wouldn't tolerate the stimulation of the bathing process or those infants being considered for withdrawal of care.

Setting: Boston Children's Hospital (BCH), a non-profit, Magnet® certified pediatric teaching and research hospital, is a 395 bed hospital that admits over 17,000 patients per year. This study will be conducted in our 24-bed Level IV NICU and a 29 bed pediatric CICU; both serve as tertiary care referral centers for critically ill infants.

During 2012, BCH NICU admitted 616 critically ill infants; 463 infants were admitted to the medical service and 153 were admitted to the surgical service. (NICU, 2012) The average length of stay was 12.7 days with a range of 2- 273 days. The BCH NICU admits infants up to 64 weeks PMA (6 months), though more than 98.7% of infants admitted during 2012 were less than 48 weeks PMA (2 months), and 86.5% were admitted at less than 44 weeks PMA (1 month). The NICU patient population consists of infants with complex medical and surgical conditions, with a vast range of diagnoses including, but not limited to Prematurity (41.4%), Respiratory distress-multiple causes (17%), rule out seizures (5%) and Patent Ductus Arteriosus (2%). In 2012, the NICU maintained an average of 3187 central lines days

though this number does not reflect the presence of multiple simultaneous central lines on any given patient.

In 2012, BCH pediatric CICU admitted 1364 critically ill children with 377 admissions being less than 2 months of age (48 weeks PMA; CICU 2012). The average LOS for this age group was between 9-15 days. The pediatric CICU maintained 6,917 CVCs, and nearly 100% of infants requiring surgical correction for their cardiac anomaly have at least 1 CVC placed.

Study Procedures**:**

Enrollment. Study nurses will be responsible for screening patients and identifying potential study subjects. Bedside nurses, nurse practitioners or physicians will ask parents of potential study subjects if they are interested in hearing about the study. To obtain consent, the study nurses (trained in obtaining consents) will approach parents interested in hearing about the study. The study nurses will explain the study and allow for questions to be answered. Parents will be given ample opportunity to make their decision (few days- depending on the infant's age and predicted length of treatment with CVC). Parents who wish to have their infant participate will be asked to sign informed consent/HIPPA forms. A copy of the consent and HIPPA form will be given to the parents and a copy will be placed in their medical records. The original consent and HIPPA forms will be maintained in a locked file cabinet behind a locked door in the NICU accessible only to members of the study team. Once informed consent and HIPPA forms are signed, a prescriber will place a standing order to facilitate commencement of bi-weekly CHG baths and blood collection procedures.

CHG Bath Cloth Supply, Labeling, Accountability and Storage.

- A supply of 2% CHG impregnated bath cloths will be purchased for this study by the NICU and Pediatric CICU and delivered directly to the Investigational Drug Service (IDS) pharmacy.
- The investigational pharmacist will properly label all bath cloths according to 21CFR 312.6 with the following statement "Caution: New drug—limited by federal (or United States) law to investigational use".
- Each label will bear a unique identifying number for the drug product so that it may be tied to each patient receiving the study drug. An additional label will be generated at the same time to track the product.
- Properly labeled bath cloths with the additional label will be delivered by IDS Pharmacy staff and placed directly into the 7 North study cloth warmer behind a locked door. (The cloth warmer will be housed in an on-call room adjacent to the NICU that has very limited access. It is behind two locked doors that require code and ID card for entry; this location was deemed the "most secure" area without being too far from the NICU by members of the study team).
- Properly labeled bath cloths with the additional label will be delivered by ISD Pharmacy staff and placed directly into the locked study cloth warmer in the CICU. (The cloth warmer will be housed in a locked unit that requires ID card for entry and a locked warmer that requires a code to enter, and only study team members will have access to the code).
- To ensure all bath cloths are warmed prior to use, the PI or her designee will document the warmer temperature on the CHG Warmer Temperature Log (Appendix A) daily. One CHG Warmer Temperature log will be kept with each warmer in the NICU and the CICU.
    - The warmer temperature of 100°F (37.8ºC) is in compliance with the package label and is compliant with the FDA's recommendation. The PI and one alternate (co-investigator) will have the passcode key that is required to adjust the set temperature. The Sage warmer is also equipped with status indicators for heating each individual package. A red light blinks to indicate when the CHG Cloths are to be disposed (after 84 hours in the warmer).

- Nurses performing the CHG bath intervention in the NICU and pediatric CICU will sign and date the extra label bearing the unique identifying number and place it on the CHG Bath Data Collection Tool (Appendix B). The nurses will also sign and date the label of the product package.
- After use, the used/soiled bath cloths will be disposed of in standard waste receptacles, and the empty packaging will be placed in a sealed container in a locked cabinet located in the Annex before return to IDS pharmacy.

CHG bath training. Experienced and trained NICU and pediatric CICU RNs who are familiar with the ICU equipment will administer the study intervention (CHG baths). The RNs will receive training to administer baths at a maximum of 2 times a week (Monday and Thursday). The RNs will wash around any tubes, drains and wires that need to stay in place during the bathing procedure. If needed, wires and leads can be changed at this time to allow thorough cleansing of all intact skin surfaces. The bathing procedure is as follows:

- Assess whole body for any skin lesions before bathing
- Apply clean diaper to the study subject and fold the diaper down to the abdominal crease in the front and the level of the iliac crest in the back
- Perform bath using pre-warmed 2% CHG impregnated rinse-free cloths by Sage Inc. Each package is for individual use only
- Cleanse body downward, starting at the neck
- Rub area to be cleansed with a back and forth motion
- Use 1 cloth for neck, arms, and legs (stopping at ankles to prevent wiping of feet/heels)
- Use second cloth for torso and back

CHG Bath Intervention. Subjects whose parents consent for this study will receive a CHG bath twice weekly. The CHG baths will be performed by 1 of 5 trained study nurses on each unit to ensure a standard bathing technique. Baths will be performed every Monday and Thursday during the day shift, for up to 12 weeks post enrollment or until the CVC is removed or the patient is discharged. Nurses will use pre-warmed 2% CHG impregnated non-sterile cloths from Sage Products Inc. CHG bath cloths will be pre-warmed to 100^{o}F (37.8^{o}C) in the warmers provided by Sage Products Inc. Baths will entail cleaning the infants with 2 CHG bathing cloths (1 package) beginning at the neck, working down the body toward the feet. Nurses will be instructed not to use the CHG cloths on the face, scalp, or over open body orifices or wounds, including the genitalia and anus (where bloodstream absorption is enhanced). The genital and anal areas will be protected by placing a clean diaper on the study subject prior to initiation of CHG bath. Cleansing of the feet/heels with CHG will be avoided due to the possibility of blood sample contamination as explained by Cowen et al (1979). Nurses will document completion of the CHG baths on the CHG Bath Data Collection Tool that will be kept at each participant's bedside. When a bath needs to be delayed for clinical reasons, it will be done as close to the scheduled time as possible.

Cleansing between CHG baths: Cleansing of infants between CHG baths may be required if they become soiled. These baths or partial baths will be done per NICU standard of care using (non-CHG) Comfort Cloths by Sage Products Inc. and documented on the CHG Exposure and Comfort Cloth Bath Log (Appendix C).

CHG Exposure: Infant participants have the potential for additional CHG exposures for central line insertions, dressing changes, and perioperative bathing. Additional CHG exposures will be recorded on the CHG Exposure and Comfort Cloth Bath Log.

Monitoring for Adverse Events

Full Body Skin Assessment. Study nurses will perform a full body skin assessment for skin irritation or open areas on infants prior to each bath. Following each bath, bedside nurses will conduct a full body assessment every 12 hours for the duration for the study (with the last assessment performed 36 hours after the last bath or prior to discharge- whichever occurs first). Full body assessment for altered skin integrity will be documented on the CHG Skin Assessment Log (Appendix D) provided for each participant. Full body assessment revealing untoward or adverse findings will also be recorded on the CHG Adverse Event Reporting Tool- Alteration in Skin Integrity (Appendix E) and reported to the PI.

CHG Measurement. Serum CHG levels will be quantified weekly by a clinical chemistry fellow with expertise using High Performance Liquid Chromatography coupled with tandem mass spectrometry (LC-MC/MS). Briefly, CHG will be extracted from 200uL of serum following deproteinization with 0.1% formic acid and addition of a deuterated CHG internal standard. Reversed phase HPLC separation and elution will be performed using a Waters Acquity® UPLC system with a C18 column. Detection and quantification will be achieved on a Waters Quattro^{TM} triple-quadropole mass spectrometer by electrospray ionization in positive ion mode (Chapman, et al 2013).

CHG blood levels. CHG blood level assays will be performed to determine CHG levels in study participants; but will not be used to inform clinical decision-making since safe blood levels of CHG are not known. Thus CHG blood level assays will not be used as the primary method of determining adverse reactions.

Instead, we will employ the current standard of care for determining adverse reactions to topically applied CHG, which is the visual and clinical assessment of nursing and medical staffs for symptoms of an adverse reaction. In this study, visual and clinical assessments for symptoms of an adverse reaction will serve as our primary measure for safety.

We plan to examine associations between CHG blood levels and other adverse reactions (skin irritation or open areas, abnormalities in liver and renal function tests) to help determine safe blood levels in infants 36 weeks PMA or older and less than 48 weeks PMA. Clinical decisions regarding potential reactions will be based on the evidence of adverse events from the visual and clinical assessments for symptoms of an adverse reaction.

Presently, there are no certified calibrators or standards available for CHG blood levels. Complete validation of the assay for CHG blood levels for use in clinical decision-making would require significant regulatory processes. This would include comparing our assay to those in the literature so that any clinical decision points could be established based on the published in vitro and in vivo data.

In this study, analysis of CHG blood levels will be conducted using a liquid chromatography-mass spectrometry system in the Department of Lab Medicine, assay development laboratory at Boston Children's Hospital. The developed assay for CHG blood levels will not be conducted under the CLIA accreditation of the laboratory and is for research use only (RUO). As such, data from this assay cannot be used for individual patient decision-making (such as discontinuing CHG exposure).

Assay from our laboratory will allow us to measure CHG at 5 ng/mL or even lower; providing greater detail and understanding of the kinetics of absorption and elimination. This is comparatively better than most studies in the literature. In the majority of published studies, CHG in the blood was not quantifiable since the lower limits of quantification, for their instruments, was 20 ng/mL.

If validation were to be conducted using the available instrumentation in the main clinical laboratory, which would allow clinical decision making from individual results, the current clinical mass spectrometers would perform similar to those in the literature. They would be unable to detect CHG in many samples due to insufficient limits of quantification. This is because these clinical laboratory instruments are a generation behind that in the assay development laboratory.

Moreover, utilizing the assay development laboratory will also allow greater flexibility regarding when analyses can be conducted for this study. Testing in the assay development laboratory is more flexible from timing and cost perspectives, and will be conducted weekly based on sample availability; as opposed to the fixed schedule in the main clinical laboratory.

Assessment of Liver and Renal Function. Most drugs or chemicals are excreted from the body via the hepatic or renal systems. Therefore, standard LFTs, namely AST and ALT, and the Serum Creatinine levels will be monitored on all subjects. If these labs have been obtained as part of the standard of care, the results will be used by the study team and not repeated in order to minimize additional blood loss or iatrogenic anemia. However, if the study subject's diagnosis did not warrant monitoring of these labs, they will be obtained weekly with the CHG blood level.

Procedures for Obtaining CHG, ALT, AST and HCT levels. A single CHG level will be obtained at baseline and then weekly on Fridays for the remainder of the study for each study participant. Every Friday additional labs will be obtained to monitor liver and renal function (AST, ALT, Serum Creatinine) and HCT for anemia.

Often these lab values are obtained as part of routine care in the ICU. If these labs have not been obtained, they will be added to the weekly labs that will require an additional 1.0 mLs. The study personnel performing the bath will assess the need for the additional labs and notify the bedside nurse so that these labs can be obtained at the appropriate time as per the CHG Study Research Order (Appendix F). The study labs will be drawn with other lab work via central line whenever possible. If no other lab work is scheduled to be obtained, or if the central line gauge is too small (less than 2.6 Fr), then the labs will be obtained at the designated time by heel stick. When no other lab work is to be obtained, infants will need 1-2 heel sticks per week for a required sample of 1- 1.5 mLs in order to limit access of CVC and minimize risk of infection. Standard heel sticks are safely performed on patient care units using the lateral aspect of the infants' pre-warmed heel. Blood levels will be recorded on the CHG Lab Work Log (Appendix G) and entered into a computerized database. Lab specimens for this study will be tracked by utilizing a CHG Study Lab Requisition Form (Appendix H) that bears the patients study ID number followed by a unique specimen identifier (i.e. Patient ID "#CHG001" followed by unique lab identifier "3456").

Assessment for Iatrogenic Anemia. CHG levels being obtained for this study require 0.5mL for each sample. The volume of blood for the ALT/AST/ Serum Creatinine level is 0.5 mL and the hematocrit (HCT) is 0.5mls. The minimum total blood volume obtained per week will be 0.5 mL, and the maximum total blood volume obtained per week will be 1.5 mLs. If a study participant were to remain in the study for the maximum length of time (12 weeks) the maximum amount of blood obtained for the study will be 18 mLs (0.5mL at baseline, 1.5 mL weekly for CHG levels, ALT, AST, serum creatinine and HCT). If the HCT and Serum Creatinine have already been obtained as part of the infant's routine ICU bloodwork as is often the case (and not for the study), the maximum blood obtained for the study is 12.5 mLs (0.5mL at baseline, 1 mL weekly for CHG levels, ALT, AST).

To put this in perspective, the average blood volume for a full term or near term newborn is 80mL/kg (160 mL for a 2 Kg infant). Infants born at 36 weeks gestation, weigh between 2.5-3.5 Kg with an average weight of approximately 2.8 Kg, thus their estimated blood volume is 224 mLs. Iatrogenic

anemia occurs when blood loss exceeds 20 % in a 48-hour period (44.8 mL in a 2.8 Kg infant). Thus, it is unlikely that an infant would sustain iatrogenic anemia from participating in this study. However, blood volume removed will be maintained on the CHG Lab Work Log for each study subject throughout study participation (in order to monitor blood volume removed for study lab work). If the study labs are consistently added on to the study subject's routine lab work, and thought to pose an additional clinical risk in terms of blood loss, the DSMC and the FDA will be notified.

Although iatrogenic anemia is unlikely to result from participating in this study our patient population is at risk for the development of anemia from a number of potential contributors including: blood loss sustained from invasive procedures such as surgery, low iron stores, bone marrow suppression or intracranial hemorrhage. This warrants monitoring for anemia during the course of this investigation. For the purpose of this study anemia is defined as HCT </= 28% with respiratory support (mechanical ventilation, continuous positive airway pressure or high flow nasal cannula with FiO2 > 25% or Oxygen by nasal cannula > 1 liter/min) or HCT </= 25%: no respiratory support. To monitor infants for the development of anemia during the study, we will be obtaining weekly HCT levels on infants that do not have a weekly HCT levels documented in their medical record. A plan for the management of infants with anemia has been put in place and is outlined later in this protocol under Table 1: Management of Adverse Events to CHG Baths.

Data Collection. Data collection will be performed by study nurses in the NICU and pediatric CICU. Data collection procedures by the study nurses will consist of:

1. Assigning study ID numbers.
2. Recording bi-weekly CHG baths on the CHG Bath Data Collection Tool.
3. Maintaining an on-line password protected database that will be used to record participants CHG blood levels, AST, ALT, HCT, serum Creatinine and untoward/adverse skin events and CLABSIs.
4. Recording the incidence and severity of untoward/adverse skin reactions and adverse events experienced by study subjects on the CHG Adverse Event Reporting Tool-Alteration in Skin Integrity or CHG Adverse Event Reporting Tool-Events Not Related to Skin (Appendix I).
5. Maintaining a computerized log to track the development of skin reactions, elevated CHG and other blood levels, anemia and hours/days of onset of adverse event from time study initiated.
6. Maintaining a computerized log of all CHG levels (this will be maintained by the study personnel in the laboratory).

The study PIs will be responsible for following up on adverse events and contacting the Data and Safety Monitoring Committee (DSMC) for consultation.

Phototherapy. To track study participants who are receiving phototherapy we will include a data collection point on the CHG Skin Assessment Log. This data collection point will enable the RN completing every 12 hours skin assessments to indicate if the infant is receiving phototherapy. This will allow the investigators to determine if a relationship between CHG level and phototherapy exists.

Study Participation Ends. Infants will remain in the study up to 48 weeks PMA (maximum of 12 weeks), upon hospital discharge/transfer, or until the CVC is removed.

Data Management and Quality Control. The Cardiovascular and Critical Care Nursing Research Group (CCCNRG) will be responsible for all data management procedures and will provide support to the research team during the course of the investigation. The CCCNRG employs experienced research personnel. Also all study staff will be CITI program trained. Study staff will have access to designated desk spaces and hospital maintained computer and printing systems.

Standard procedures to ensure accurate and reliable collection of data will include well designed forms with clear instructions, training of staff, and on-going monitoring of all study activities. A manual of operations that describes the purpose of the study, eligibility criteria, and all intervention and assessment procedures will be developed by the study investigators. Study staff will be trained by the study investigators to conduct informed consent, bathing technique, research assessments, and complete case report forms. Furthermore, the primary investigator will provide oversight of all research activities to ensure proper data collection procedures and to monitor staff performance.

Subject confidentiality will be maintained using unique study identification codes. The CHG Active Study Participant Log (Appendix J) will be used to assign ID numbers and to record the identifiers for contacting and tracking subjects. An electronic copy of the log will be kept by the data manager in a file accessible only to study staff, in a computer folder with restricted access. Identifiable data, such as patient name, contact information and medical record numbers will be recorded and stored separately from the research data.

All data will be recorded on hard copy case report forms (CRF) developed by the research team. A response will be required for all items on the CRF's. Options for "missing, not applicable or not done" will be coded on the CRF's with a specify option to explain the reason. All entries on the CRF's will be printed legibly in black ink. Corrections on CRF's will be made by drawing a single straight line through the incorrect entry and recording the correct data above or next to it. All corrections to data on the CRF's must be initialed and dated. Clarifications to data recorded on the CRF's will be printed above or next to the item, initialed and dated. Completed case report forms will be stored in individual subject folders in a locked file cabinet accessible by authorized study staff only.

Data collected on case report forms will be entered into the Oracle Health Sciences InForm data capture and management cloud platform (www.oracle.com). InForm is a comprehensive, integrated, open standards-based data capture and management platform that provides: 1) efficient and accurate data collection; 2) easy consolidation and transformation of data from multiple sources-EMR; 3) complete core data capabilities 4) advanced query management, study design and coding; and 5) full service deployment capabilities. InForm is HIPAA-certified and supports 21 CFR Part 11. The CCCNRG will be responsible for double data entry procedures. Double data entry will be conducted on a random sample of 10% forms to evaluate and correct entry errors. System security is maintained by requiring user authentication to gain access to the file on the hospitals private secure network. Only authorized users are permitted access to the data files, and daily server back-up activities are executed to ensure data recovery. The InForm platform and all electronic files will be saved on the hospital's limited access servers protected by hospital security and back up procedures. All exported data sets will undergo final data cleaning using SAS or similar packages using programmed logical routines unique to each data set. Outliers will be resolved prior to any data analysis. In addition, regular study status reports will be produced and reviewed by the PI to monitor recruitment, CRF data entry status, missing data frequencies, out of range values, adverse events and quality metrics.

Random observations of CHG baths will be performed throughout the entire study period by a designated clinician to ensure that all nurses are bathing the infants using the same technique. Each study team member actively bathing study subjects will be audited a minimum of once every two months. These observations will be documented on the CHG Bath Audit Tool (Appendix K) and scores of 15/15 points are acceptable. Any score lower than 15 will require retraining on the bathing technique. Also to facilitate reliable assessment of skin lesions, a CHG Erythema Assessment Tool (Appendix L) will be available for nurses to follow during their assessments (maintained at each study patients' bedside) (Figure 1.).

The sponsor-investigator will also engage the services of a qualified independent monitor to ensure the protection of the rights of human subjects, the safety of all subjects involved in the investigation and the quality and integrity of the data resulting from the trial. The independent monitor will conduct a pre-monitoring set-up visit and a monitoring visit after every fifth patient has been recruited and on the study for 1 week.

Data Analysis. With the support of a faculty statistician from the BCH Center for Patient Safety and Quality Research, we will use descriptive statistics including mean, median, range, and frequencies to describe the study sample and the findings (skin findings and adverse events). We will characterize the study sample on demographic and clinical characteristics. Our primary outcome measures will be proportion of subjects that experience any adverse event, and the rate of adverse events per 100 patient-days of follow-up. Our inferential statistics will calculate 95% confidence intervals around these estimates.

Research Question 1:

Are twice weekly CHG baths safe for use in a sample of infants 36 weeks PMA or older, and less than 2 months of age (48 weeks PMA) with a CVC?

Data Analysis 1:

Descriptive statistics including mean, median, range and frequencies will be used to describe adverse events (including skin reactions and other untoward events). We will characterize the demographic and clinical characteristics of subjects that experience adverse events, although we will not perform hypothesis tests of association. We will consider time-to-rash data using Kaplan-Meier estimators.

Research Question 2:

Does twice weekly CHG baths lead to rising (cumulative) CHG blood levels, liver function tests (LFTs -AST/ALT) and Serum Creatinine over time in a sample of infants 36 weeks PMA or older, and less than 2 months of age (48 weeks PMA) with a CVC?

Data Analysis 2:

Descriptive statistics including mean, median, range and frequencies will be used to describe CHG, LFTs and serum Creatinine blood levels over time. We will examine scatterplots and other graphical analysis of blood level dispersion over time to look for relationships.

Sample Size Justification. The primary quantitative goal of this study is estimation of the adverse event rate per 100 patient days. The study sample size will impact the precision of this estimate, and we will establish an upper bound on the rate if zero adverse events occur. In this context, we designed the study sample to expand the existing knowledge base.

Based on recent safety data (Quach, et al 2014) on roughly 200 neonates which recorded no adverse events, we assume the rate of adverse events using CHG bath is lower than 5 events per 1000 days of post-exposure follow-up. We propose following N=50 subjects over 7 days of post-exposure follow-up, for a total of 350 observation days. Assuming rates of 3.5 events or 1.0 events per 1000 days of follow-up, the probability that at least one subject will experience an adverse event is roughly 83% or 40% respectively. Using Monte Carlo simulations, the mean upper bound for estimable rates is 5.5 events per 1000 days.

Auditing and Inspecting:

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the Boston Children's Hospital IRB, the independent data monitor and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities.

Human Subjects:

BCH Committee for Clinical Investigation approval will be obtained before study procedures commence. All study staff will be Citi-program trained. Informed consent/HIPPA forms will be secured before initiation of any study procedures. A computerized database to track subjects through the research continuum will be developed and housed on a password-protected site behind the BCH firewall. Subjects will be assigned study ID numbers that will appear on all study materials and that will be utilized in place of subjects' names in the computerized database. A separate (electronic) CHG Study ID Assignment Log linking subject's names and ID numbers will be maintained by study personnel and kept in a locked cabinet behind a locked door. Only approved study personnel will have access to the log.

This study is considered greater than minimal risk with a potential for direct benefit. There is strong evidence that CHG will help prevent HAIs, however the safety profile for using CHG in infants less than 2 months of age (48 weeks PMA) is not known. To monitor for adverse events, the study team has developed a Data Safety Monitoring Plan (DSMP) and adverse event management plan (see Table 1). Adverse events to CHG baths include mild to severe skin lesions and possible absorption of CHG into the blood that could result in more serious problems such as respiratory, renal and liver problems or anaphylaxis. Thus the study team is taking a conservative approach. In an attempt to usurp the benefits associated with CHG while concurrently minimizing the likelihood of adverse events, study subjects will receive twice-weekly, instead of daily, CHG baths.

While these baths still place the subjects at risk for adverse events we believe twice-weekly baths will minimize these risks. To monitor for adverse events the study team has developed the following procedures:

1. Study RNs will perform a full body skin assessment for skin irritation or open areas prior to each bath.
2. Bedside RNs will complete skin assessments every 12 hours during the course of the study.
3. A plan is in place for Management of Adverse Events to the CHG Baths. (Table 1.)
4. To monitor for absorption into the blood, infants will have blood levels (CHG, ALT, AST, and Serum Creatinine) drawn at baseline and weekly and when an infant is removed from the study in response to an adverse event. In addition, infants will be monitored weekly for the development of iatrogenic anemia.

Data Safety Monitoring Plan:

The DSMC will review all adverse events experienced by the study subjects. All CHG levels obtained (up until the week prior to the meeting) will be available for review by the DSMC. The DSMC will consist of 5 expert clinicians throughout the institution including: a Clinical Nurse Specialist (skin care specialist), attending medical physician from the NICU or CICU, a Doctor of Pharmacy, an Infection Control expert and a Laboratory Medicine physician. They will assist the study team in making informed decisions about the management of adverse events, including study closure if warranted. At minimum, the PIs will contact members of the DSMC via email with a summary of the study findings, including available CHG levels, LFTs (AST/ALT), Serum Creatinine and HCT levels, at the following intervals during the course of the study:

- After the first 10 subjects have enrolled and participated in the study for a minimum of 2 weeks. During this meeting the DSMC will discuss the need to revise the plan (frequency) for obtaining LFTs, Serum Creatinine and HCT
- Following completion of the study by 25 subjects
- At the conclusion of the study

More frequent meetings may be required if serious adverse events are noted (Table 1, #5-8).

Adverse Event Management:

Criteria for Holding or Stopping the Study

Table 1 delineates criteria for holding and stopping rules for study subjects based on skin and lab and clinical assessments. Holding rules apply to study subjects that will no longer receive CHG baths, such as following the need for a blood transfusion, adverse event, or infants that become clinically unstable. Infants whose participation is placed on hold will have monitoring of daily vital signs (ranges), HCTs (if anemia was the cause of the hold), and documentation of significant clinical changes. This information will be recorded on the CHG Vital Sign and Clinical Monitoring Tool (Appendix M). Stopping rules apply to study participants that have had CHG baths placed on hold and have completed necessary monitoring described in holding rules. Furthermore, all adverse events will be recorded on the Adverse Event Reporting Tools.

Holding and Stopping Rules

Anemia/Blood Transfusions:

Holding rules for patients with anemia requiring blood transfusion. All study participants that require a blood transfusion while enrolled in the study will have CHG baths suspended until 1-week post transfusion and will have a pre- and post-transfusion assessment of vital signs (ranges-heart rate, respiratory rate, blood pressure, oxygenation requirement and means of respiratory support). A post-transfusion hematocrit will also be obtained, if not attained via standard of care, and documented on the CHG Blood Transfusion Tool (Appendix N). The CHG baths will resume 1-week post transfusion if study participant is deemed stable by both the study and medical teams.

Study participants that do not receive a blood transfusion or are deemed not stable will have monitoring of daily vital signs (ranges-heart rate, respiratory rate, blood pressure, oxygenation requirement and means of respiratory support), HCTs that are obtained as routine ICU care, and significant changes to clinical status for 1 month from cessation of CHG baths or until discharge, whichever comes first to assess for adverse events related to anemia.

Stopping rules for patients with anemia requiring blood transfusion. All study participants that have had CHG baths suspended and that do not receive a blood transfusion or are deemed unstable will be removed from the study after completing the clinical monitoring as described above.

Adverse Event (Other Than Anemia):

Holding rules for patients that experience an adverse event: All study participants that experience an adverse event, as described in table 1, and have CHG baths suspended due to the adverse event will have 2 CHG levels obtained within 1 week of CHG bath (recorded on CHG Lab Work Log), unless the previous level was not detectable. These infants will also have monitoring for adverse event symptom resolution and daily vital signs (ranges-heart rate, respiratory rate, blood pressure, oxygenation requirement and means of respiratory support) for 1 month from cessation of CHG baths or until discharge, whichever comes first.

Stopping rules for patients that experience an adverse event. All study participants that have CHG baths suspended due to an adverse event will be removed from the study after completing the clinical monitoring as described above.

Clinical Instability:

Holding rules for patients that become clinically unstable. For the safety of the study participant bathing will be suspended for infants demonstrating significant or acute impairment of their clinical status as indicated by their medical team. For example, patients requiring volume resuscitation due to blood and fluid losses, or a patient in the immediate post-operative period will not be bathed until return to baseline stability. These patients will have 2 CHG levels obtained within 1 week of last CHG bath, unless previous level was non-detectable. Infants deemed not appropriate for participation by either the study team or medical team will have monitoring of daily vital signs (ranges-heart rate, respiratory rate, blood pressure, oxygenation requirement and means of respiratory support) for 1 month from cessation of CHG baths or until discharge, whichever comes first.

Stopping rules for subjects that become clinically unstable. Study subjects whose clinical status does not return to baseline, as assessed by both the study and medical teams will be removed from the study after completing the clinical monitoring for 1 month as described above.

Table 1: Management of Adverse Events to CHG Baths

Erythema Assessment (see CHG Erythema Assessment Tool for visual comparisons)			
Finding	**Action**	**Follow Holding and Stopping Rules**	**Reporting**
1. Mild redness X1	None	*Not Applicable*	No immediate action; Send email update to PI; include in monthly DSMP report
2. Mild redness X2, persistent redness leading up to 2nd bath, or moderate redness:	Discontinue CHG baths (unless rash is limited only to diaper area)	*Adverse Event (Other Than Anemia)*	Immediately reportable to PI; include in monthly DSMP report
3. Raised rash	Discontinue CHG baths (unless rash is limited only to diaper area)	*Adverse Event (Other Than Anemia)*	Immediately reportable to PI; include in monthly DSMP report
4. Blister(s)	Discontinue CHG baths	*Adverse Event (Other Than Anemia)*	Immediately reportable to PI; meet with DSMC
5. Open area(s)	Discontinue CHG baths	*Adverse Event (Other Than Anemia)*	Immediately reportable to PI; meet with DSMC

6. Evidence of systemic event	Discontinue CHG baths	*Adverse Event (Other Than Anemia)*	Immediately reportable to PI; meet with DSMC
7. Anaphylaxis	Discontinue CHG baths	*Adverse Event (Other Than Anemia)*	Immediately reportable to PI; meet with DSMC
Lab Value Assessment			
AST >70 u/l	Discontinue CHG baths	*Adverse Event (Other Than Anemia)*	Immediately reportable to PI; meet with DSMC
ALT >60 u/l	Discontinue CHG baths	*Adverse Event (Other Than Anemia)*	Immediately reportable to PI; meet with DSMC
Serum Creatinine 0.7 mg/dl or greater	Discontinue CHG baths	*Adverse Event (Other Than Anemia)*	Immediately reportable to PI; meet with DSMC
HCT </= 28%: Respiratory support (mechanical ventilation, continuous positive airway pressure or high flow nasal cannula with FiO2 > 25% Oxygen by nasal cannula > 1 liter/min) HCT </= 25%: No respiratory support	Discontinue CHG baths	*Anemia/Blood Transfusions*	Immediately reportable to PI; Discuss with medical team; meet with DSMC
Other			
Clinical Instability	Discontinue CHG baths	*Clinical Instability*	Immediately reportable to PI; include in monthly DSMP report

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This study is being funded by the Program for Patient Safety and Quality, the Department of Lab Medicine Clinical Chemistry Training Program, and the American Association of Critical Care Nurses. The nursing departments from the participating units will purchase the 2% CHG cloths for this study. The Department of Newborn Medicine will fund all supplemental laboratory specimens.

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