# Double-blind Randomized Placebo controlled Clinical trial evaluating effect of Chlorhexidine Gluconate 2% cloth baths vs Placebo cloth baths on the incidence of CLASBI in Outpatient HSCT Patients.

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Introduction:

Central line associated blood stream infections (CLABSIs) are one of the most deadly types of hospital-acquired infections (HAIs), with a mortality rate of 12% to 25%.[1] Nationally, hospital acquired CLASBIs are reported as a measure of patient safety through the National Healthcare Safety Network. The Center for Disease Control and Prevention (CDC) collects data and reports on CLABSIs among hospitalized patients aged 1 year or older and among patients receiving outpatient hemodialysis.[2] It is estimated that 84,551 to 204,901 CLABSIs occur each year resulting in 10,426 to 25,145 preventable deaths.[3] The cost of each CLABSI is estimated to range from $3,700 to $45, 254.[4] If the average mortality caused by CLABSIs is 18% (reported ranges 15-24%) and the average CLABSI rate is 5.3 per 1000 catheter-days, as many as 28 000 patients die of CLABSIs annually in ICUs alone.[3-5] Because of the high incidence, mortality rate and healthcare costs of CLABSIs, the Agency for Healthcare Research and Quality (AHRQ) sponsored a national patient safety imperative aimed at eliminating CLABSIs.[4] This program reviewed data from over 1000 hospitals in 44 states in the US including ICU, non-ICU and pediatric unit settings. It implemented a Comprehensive Unit-based Safety Program (CUSP) directed towards reducing central line associated blood stream infections. The program bundled interventions of establishing safety cultures on a unit level with utilization of safety teams and implementation of CLABSI reduction steps. These CLABSI reduction steps included: appropriate hand hygiene, full barrier precautions with line insertion, daily review of line necessity, chlorhexidine skin care, and avoidance of femoral site placement of central lines. With use of these methods, CLASBI rates were reduced 40%.[6] While much of healthcare is being diverted to the outpatient setting, no such efforts have been undertaken in evaluating outpatient CLABSIs with the exception of the dialysis population.

Individuals undergoing hematopoietic stem cell transplantation (HSCT) usually require central venous access for frequent infusions including chemotherapy and blood products as well as for hydration, electrolyte replacement, antibiotics, and parenteral nutrition. However, the benefits of having a central line must be balanced against the risk of complications, the most common of which is central line-associated bloodstream infections (CLABSIs).[7-9] Risk factors established for the development of CLASBI include prolonged hospitalization before catheter placement, prolonged duration of catheterization, microbial colonization of the insertion site or catheter hub, internal jugular or femoral catheterization, neutropenia, TPN, transfusion of blood products and frequent manipulations of the catheter. ([10-16]) Care of patients undergoing a HSCT is

complex and these individuals collect many of the known factors, which put them at risk for developing CLASBIs. As well, chemotherapy often induces mucositis resulting in translocation of enteric microorganisms into the bloodstream, which may then secondarily seed central venous access devices.[17,18] In an effort to reduce bacteremia in HSCT patients expected to have a prolonged period of neutropenia, antimicrobial prophylaxis with agents having activity against enteric pathogens is common practice.

With engraftment, the absolute neutrophil count rises, prophylactic antimicrobials are discontinued, and mucositis resolves. HSCT patients may be released to home requiring infusion of fluids, electrolytes, TPN, and sometimes antimicrobial agents. As well, these patients have frequent outpatient visits for transfusion of blood products. Due to chemotherapy induced phlebitis of peripheral veins, the central line is frequently the only intravenous access available to obtain blood for laboratory monitoring of the patient. Therefore, patients who have undergone HSCT have multiple persistent risk factors for the development of CLABSI, even after discharge from the inpatient setting.

Chlorhexidine is a broad-spectrum antiseptic agent active against both gram-positive and gram-negative bacteria as well as yeasts, and has been successfully assessed as an effective skin antiseptic alone or in combination with alcohol.[19-29] Due to its success in reducing hospital acquired CLABSIs, daily chlorhexidine baths have been implemented in the intensive care setting and in inpatient stem cell transplant units. In this study we aim to evaluate whether or not continued skin decontamination with 2% chlorhexidine impregnated washcloths, used after routine bathing, will reduce the incidence of CLASBIs in the HSCT population after discharge for as long as the central line is in place or 14 weeks post discharge, whichever comes first.

Overall Study Design:

This will be single site [University of Chicago (U of C)] prospective, double blinded randomized, controlled clinical trial of daily bathing with no-rinse, 2% CHG-impregnated washcloths (Sage 2% chlorhexidine gluconate cloths; Sage Products Inc., Cary, Illinois) vs placebo chlorhexidine washcloths. The main study outcomes will be primary BSI and clinical (culture-negative) sepsis. Catheter insertion policy for the U of C HSCT program mandates interventional radiology insertion of central venous catheters on the day of admission for HSCT conditioning using sterile technique, full barrier drapes, and insertion site disinfection with 2% CHG. Antiseptic- or antibiotic-coated catheters are not used. While hospitalized, patients follow routine daily 2% CHG baths. Routine catheter care with CHG-Alcohol (Chloraprep) dressing changes and a CHG-biopatch at the insertion site will be done weekly, per standard of care, while inpatient and will continue in the outpatient setting. Prior to discharge, enrolled subjects will be randomized to 2% CHG vs placebo washcloths (supplied as a blinded product) which the patient will continue until end of study. No other catheter-associated BSI infection control interventions will be implemented during the study.

Setting and Participants:

Approximately 200 HSCTs are done annually at the U of C. On admission for transplant, HSCT patients commence use of daily 2% chlorhexidine applied by impregnated washcloths after routine daily washing. This is done as part of standard care in an effort to prevent inpatient CLASBIs. Once patients have demonstrated engraftment of neutrophils (absolute neutrophil count >500 cells/mm3 for 48 hours) routine home bathing instructions are given by the nursing staff in preparation for discharge. These instructions include educating the patient specifically not to allow the central line insertion site to become wet (i.e.: no showers or baths), technique for scrubbing the catheter hub(s), and sterile technique for accessing the line in those who will be performing home IV administration.

The incidence of inpatient hospital acquired (HA) and outpatient present on admission (POA) CLASBIs as evaluated here at the U of C (see table below) has been previously determined and the outpatient data will be used as our initial data control group:

**Number of CLABSI by Nursing Unit September 2007 to August 2008**

| Unit | Number of HA-CLABSI | Number of POA-CLABSI |
|---|---|---|
| T6NW | 32 | 18 |
| T6NE | 1 | 30 |
| T6SW | 3 | 28 |
| **TOTAL** | **36** | **76** |

Methods:
Approval of the study protocol will be obtained from the University of Chicago Institutional Review Board.

Subjects:
Approximately 200 HSCT subjects will be enrolled

Inclusion Criteria:
Each patient admitted to the U of C HSCT unit aged ≥18 years during the study periods will be approached regarding the study.

Exclusion Criteria:
Patients who have already experienced an allergy or rash related to use of chlorhexidine washcloths or other CHG products will be excluded.

Patients with extensive open wounds will be excluded from the study.

Study Procedures:
Prior to discharge, eligible subjects will be approached for study participation. Those who agree to participate and complete the consent process will be randomized to the active or placebo study arms.

Study Washcloth (2% CHG and placebo) :
Subjects will receive an instruction sheet that illustrates where to use the washcloths. Use of the washcloths will be done in the following sequential order to rinse all body surfaces, with the exception of the mucous membranes of the eyes and mouth.
First: neck, shoulders and chest; Second: axillae, arms and hands; Third: abdomen then groin and then perineum; Fourth: right leg and foot; Fifth left leg and foot and the Sixth:back of the neck back and buttocks.

Subjects received education on using chlorhexidine washcloths throughout the hospitalization for their HSCT and prior to discharge from the inpatient hospitalization, therefore oversight of the trial will not include direct observation of bathing. There will be no washout period in the transition from the inpatient setting.

The dates of catheter placement will be recorded and used to calculate length of catheter days in place. The discharge date and discharge setting will be recorded. Data will be recorded in RedCap.

Data on all positive blood cultures will be collected for bacterial/fungal pathogens. Incident bacteremia (or fungemia) will include only the first episode of bacteremia / fungemia and will not include duplicate organisms or subsequent infections as the primary aim of the study is to prevent the incident CLABSI. A bacteremia / fungemia will constitute treatment failure. Subjects will stop study product and be followed for 4 weeks for safety assessment (incident of adverse event associated with study product). Hospital admissions will be recorded. Association with study product will be determined. Cost of hospitalizations related to CLASBI will be determined.

A study diary will be used by subjects to confirm compliance with daily bathing. The study staff will ensure the subject is using the proper bathing technique at each weekly visit. This document will be reviewed and collected weekly when the subject comes for routine outpatient central line catheter care. The study diary will also capture compliance with the outpatient central line accessing protocol. As the subject will access their line using the standard practice (sterile technique with chlorhexidine-alcohol preps) the study will collect the data on this process. Additionally subjects will be asked to save all packaging from washcloths used each week and bring this packaging to the weekly outpatient visit. This will allow study staff to note compliance with washing and to ensure subjects have an adequate supply of washcloth packages. The study staff will enter the total quantity of washcloth packages used during the week on a compliance monitoring worksheet.

Length of Study Participation:
Participation will begin at the time of consent prior to discharge. Subjects will use the study washcloths while the central line remains in place or until 14 weeks post HSCT discharge, whichever comes first.

Stopping Rules:
Subjects that are diagnosed with a bacteremia or fungemia will stop use of product after a positive result.

Payment:
Subjects will not receive any payment for participation in the study

Statistical Plan and Considerations:
The plan is to accrue up to 200 subjects, however, after the first 100 subjects complete the study, the data set will be locked and unblinded and the incidence of CLABSIs in each group will be determined. If the difference between the groups is highly statistically significant, ($P < 0.001$), the study will be halted. A 'Student's' t Test will be used to determine difference in outcome (bacteremia or no bacteremia) between the two groups.

Assuming that the outpatient setting would have a higher incidence of CLABSI given the previous Infection Control snapshot, recalculating with an ~50% higher outpatient rate, the estimated number of patients would be calculated as:

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. sampsi 0.12 0.0485, power(0.8)
Estimated sample size for two-sample comparison of proportions
Test Ho: p1 = p2, where p1 is the proportion in population 1
                and p2 is the proportion in population 2
Assumptions:
        alpha =   0.0500  (two-sided)
        power =   0.8000
           p1 =   0.1200
           p2 =   0.0485
        n2/n1 =   1.00

Estimated required sample sizes:
           n1 =      263
           n2 =      263
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For our evaluation we based the numbers of patients on the number of HSC transplants performed annually with a reasonable period of time to enroll subjects. Interim analyses will be performed early on to see if a significant difference exists in making it appropriate or not appropriate to continue

Risks and Benefits:

This clinical research involves minimal risk to the patients involved since it involves only the use of two FDA approved bathing products. Potential recognized risks of bathing with chlorhexidine include local skin irritation, allergic reaction and irritation of mucous membranes. The FDA has waved requirement for an IND.

Data Handling and Record Keeping

All data collection files will be password protected and stored on computers belonging to study investigators. Data collected will be entered into the password protected Access database.Personal health information will be maintained with the database during study period, microbiology data, and medical record review. All patients will be assigned a unique study identification number. This number will be accessible only to study investigators and study staff. Any hard copies of datasets will be stored in a locked filing cabinet in the Infectious Diseases Clinical Trials office. After all data are collected, analyzed, and published, linkage between patients and their unique identifier will be destroyed, with the exception of data collected through Infection Control Departments as part of hospital operations. Identified datasets related to infection control activities will be maintained at the primary institution according to hospital operations policy.

References:


1. Centers for Disease Control and Prevention. Guidelines for the prevention of intravascular catheter-related infections. *MMWR Morb Mortal Wkly Rep*. 2002; 51 (No. RR-10): 1-29.
2. Liang SY and Marschall J.Update on Emerging Infections: News from the Centers for Disease Control and Prevention. Ann Emerg Med. 2011; 58: 447-450.
3. Umscheid CA, Mitchell MD, et al. Estimating the proportion of reasonably preventable hospital-acquired infections and associated mortality and costs. Infect Control Hosp Epidemiol. 2011 Feb;32(2):101-114.
4. Agency for Healthcare Research and Quality. *Tools for Reducing Central Line-Associated Blood Stream Infections*. Rockville, MD: Agency for Healthcare Research and Quality; 2014. http://www.ahrq.gov/professionals/ education/curriculum-tools/clabsitools/index.html.
5. Agency for Healthcare Research and Quality. Appendix 2. Central line-associated bloodstream infections fact sheet. http://www.ahrq.gov/ professionals/education/curriculum-tools/clabsitools/ clabsitoolsap2.html. Published 2015.
6. (Eliminating CLABSI, A National Patient Safety Imperative: Final Report. http://www.ahrq.gov/ professionals/quality-patient-safety/cusp/clabsi-final/index.html)
7. Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: Data summary for 2006 through 2008, issued December 2009. Am J Infect Control 2009; 37: 783–805.
8. Simon A, Fleischhack G, Hasan C, et al. Surveillance for nosocomial and central line-related infections among pediatric hematology-oncology patients. Infect Control Hosp Epidemiol 2000; 21: 592–596

9. Dudeck MA, Horan TC, Peterson KD, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2010, device-associated module. Am J Infect Control 2011;39:798–816.
10. Mermel LA. Infections caused by intravascular devices. In: Pfeiffer JA, ed. *APIC Text of Infection Control and Epidemiology*. 2nd ed. St. Louis: Mosby, 2000:30–38.
11. Almuneef MA, Memish ZA, Balkhy HH, Hijazi O, Cunningham G, Francis C. Rate, risk factors and outcomes of catheter-related bloodstream infection in a paediatric intensive care unit in Saudi Arabia. *J Hosp Infect* 2006; 62(2):207–213. 22.
12. Alonso-Echanove J, Edwards JR, Richards MJ, et al. Effect of nurse staffing and antimicrobial-impregnated central venous catheters on the risk for bloodstream infections in intensive care units. *Infect Control Hosp Epidemiol* 2003; 24(12): 916–925.
13. Lorente L, Henry C, Martin MM, Jimenez A, Mora ML. Central venous catheter–related infection in a prospective and observational study of 2,595 catheters. *Crit Care* 2005; 9(6): R631– R635.
14. Rey C, Alvarez F, De-La-Rua V, et al. Intervention to reduce catheter-related bloodstream infections in a pediatric intensive care unit. *Intensive Care Med* 2011; 37(4):678–685.
15. Lorente L, Jimenez A, Naranjo C, et al. Higher incidence of catheter-related bacteremia in jugular site with tracheostomy than in femoral site. *Infect Control Hosp Epidemiol* 2010; 31(3): 311–313
16. Climo MW, Yokoe DS, Warren DK, Perl TM, Bolon M, Herwaldt LA, Weinstein RA, Sepkowitz KA, Jernigan JA, Sanogo K, Wong ES. Effect of daily chlorhexidine bathing on hospital acquired infection. New Engl J Med 2013; 368, 6: 533-542.
17. Metzger KE, Rucker Y, Callaghan M, Churchill M, Jovanovic BD, Zembower TR Bolton MK. The burden of Mucosal Barrier Injury Laboratory –Confirmed Bloodstream Infection among Hematology, Oncology and Stem Cell Transplant Patients. Infect Control Hosp Epidemiol 2015; 36, 2: 119-124
18. Pongruangporn M, Ajenjo MC, Russo AJ, McMullen KM, Robinson C, Williams RC, Warren DK. Patient- and Device-Specific Risk Factors for Peripherally Inserted Central Venous Catheter-Related Bloodstream Infections. Infect Control Hosp Epidemiol 2013; 34, 2: 184-189.
19. Rosenberg A, Alatary SD, Peterson AF. Safety and efficacy of the antiseptic chlorhexidine gluconate. Surg Gynecol Obstet 1976; 143: 789-92.
20. Edmiston CE Jr, Seabrook GR, Johnson CP, Paulson DS, Beausoleil CM. Comparative of a new and innovative 2% chlorhexidine gluconate-impregnated cloth with 4% chlorhexidine gluconate as topical antiseptic for preparation of the skin prior to surgery. Am J Infect Control 2007; 35: 89-96.
21. Dixon JM, Carver RL. Daily chlorohexidine gluconate bathing with impregnated cloths results in statistically significant reduction in central line-associated bloodstream infections. Am J Infect Control 2010; 38: 817-21.

22. Evans HL, Dellit TH, Chan J, Nathens AB, Maier RV, Cuschieri J. Effect of chlorhexidine whole-body bathing on hospital-acquired infections among trauma patients. Arch Surg 2010; 145: 240-6.
23. Huang SS, Datta R, Platt R. Risk of acquiring antibiotic-resistant bacteria from prior room occupants. Arch Intern Med 2006; 166: 1945-51.
24. Datta R, Platt R, Yokoe DS, Huang SS. Environmental cleaning intervention and risk of acquiring multidrug-resistant organisms from prior room occupants. Arch Intern Med 2011; 171: 491-4.
25. Byers KE, Anglim AM, Anneski CJ, Germanson TP, Gold HS, Durbin LJ, et al. A hospital epidemic of vancomycin-resistant Enterococcus: risk factors and control. Infect Control Hosp Epidemiol 2001; 22: 140-7.

26. Martinez JA, Ruthazer R, Hansjosten K, Barefoot L, Snydman DR. Role of environmental contamination as a risk factor for acquisition of vancomycin resistant enterococci in patients treated in a medical intensive care unit. Arch Intern Med 2003; 163: 1905-12.
27. Zhou Q, Moore C, Eden S, Tong A, McGeer A. Factors associated with acquisition of vancomycin-resistant enterococci (VRE) in roommate contacts of patients colonized or infected with VRE in a tertiary care hospital. Infect Control Hosp Epidemiol 2008; 29: 398-403.
28. Kassakian SZ, Mermel LA, Jefferson JA, Parenteau SL, Machan JT. Impact of chlorhexidine bathing on hospital-acquired infections among general medical patients. Infect Control Hosp Epidemiol 2011; 32: 238-43.
29. Bleasdale SC, Trick WE, Gonzalez IM, Lyles RD, Hayden MK, Weinstein RA. Effectiveness of chlorhexidine bathing to reduce catheter-associated bloodstream infections in medical intensive care unit patients. Arch Intern Med 2007; 167: 2073-9