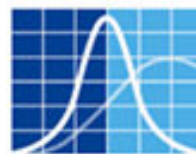




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The Efficacy of Daily Bathing with Chlorhexidine for Reducing Healthcare-Associated Bloodstream Infections: A Meta-analysis

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Reviewed work(s):

Source: *Infection Control and Hospital Epidemiology*, Vol. 33, No. 3 (March 2012), pp. 257-267

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ORIGINAL ARTICLE

The Efficacy of Daily Bathing with Chlorhexidine for Reducing Healthcare-Associated Bloodstream Infections: A Meta-analysis

John C. O'Horo, MD;¹ Germana L. M. Silva, MD;² L. Silvia Munoz-Price, MD;³ Nasia Safdar, MD, PhD⁴

DESIGN. Systematic review and meta-analysis of randomized controlled trials and quasi-experimental studies to assess the efficacy of daily bathing with chlorhexidine (CHG) for prevention of healthcare-associated bloodstream infections (BSIs).

SETTING. Medical, surgical, trauma, and combined medical-surgical intensive care units (ICUs) and long-term acute care hospitals.

PARTICIPANTS. Inpatients.

METHODS. Data on patient population, diagnostic criteria for BSIs, form and concentration of topical CHG, incidence of BSIs, and study design were extracted.

RESULTS. One randomized controlled trial and 11 nonrandomized controlled trials reporting a total of 137,392 patient-days met the inclusion criteria; 291 patients in the CHG arm developed a BSI over 67,775 patient-days, compared with 557 patients in the control arm over 69,617 catheter-days. CHG bathing resulted in a reduced incidence of BSIs: the pooled odds ratio using a random-effects model was 0.44 (95% confidence interval, 0.33–0.59; $P < .00001$). Statistical heterogeneity was moderate, with an I^2 of 58%. For the subgroup of studies that examined central line-associated BSIs, the odds ratio was 0.40 (95% confidence interval, 0.27–0.59).

CONCLUSIONS. Daily bathing with CHG reduced the incidence of BSIs, including central line-associated BSIs, among patients in the medical ICU. Further studies are recommended to determine the optimal frequency, method of application, and concentration of CHG as well as the comparative effectiveness of this strategy relative to other preventive measures available for reducing BSIs. Future studies should also examine the efficacy of daily CHG bathing in non-ICU populations at risk for BSI.

Infect Control Hosp Epidemiol 2012;33(3):257–267

Healthcare-associated bloodstream infections (BSIs), which are most associated with central lines, account for significant morbidity and mortality among intensive care unit (ICU) patients. Although recent years have seen a decline in central line-associated BSIs (CLABSIs) occurring in ICUs in the United States, recent data from the Centers for Disease Control and Prevention (CDC) indicate that 12,000–18,000 CLABSIs occurred in US ICUs in 2009. CLABSIs cost the healthcare system approximately \$16,550 per episode, with an attributable mortality of 15%–25% per episode.¹

The major mechanism of CLABSIs with short-term devices, generally defined as those in place for 10 days or fewer, is the extraluminal route, where skin microorganisms invade the percutaneous tract.² Recognition of this pathogenetic mechanism has led to several preventive strategies targeting cutaneous antisepsis,³ such as the use of chlorhexidine (CHG) rather than povidone-iodine at the time of catheter insertion^{4,5} and a CHG-impregnated sponge dressing placed at the site of insertion.^{6,7} In contrast, fewer efforts have been directed

toward reducing healthcare-associated BSIs other than CLABSIs. One beneficial approach to reducing healthcare-associated BSIs, including CLABSIs, is the use of CHG bathing to reduce cutaneous microbial bioburden. The premise that CHG bathing will reduce healthcare-associated infections is biologically plausible because heavy skin bacterial colonization on patients facilitates transmission by healthcare workers to other susceptible patients and reducing bacterial skin bioburden would be expected to interrupt or minimize healthcare-associated transmission. Moreover, CHG bathing may also reduce contamination of the hands of healthcare workers, thus further limiting the likelihood of transmission.^{8,9} CHG acts by disrupting cytoplasmic membranes and remains active hours after application with a broad spectrum of activity.¹⁰ Daily bathing of ICU patients with CHG has been shown to reduce healthcare-associated BSIs, including CLABSIs, in some but not all recent studies.^{8,9,11–17} A systematic assessment of the magnitude of the effect on BSIs, including CLABSIs; the process of implementation; and poten-

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Received August 9, 2011; accepted October 31, 2011; electronically published January 25, 2012.

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tial adverse effects of daily bathing of patients with CHG is lacking. We undertook a meta-analysis to determine the efficacy of daily bathing of patients with CHG with respect to decreasing healthcare-associated BSIs, including CLABSIs. Secondary objectives included assessment of costs and mortality.

METHODS

Eligibility Criteria

Individual or cluster randomized controlled trials and quasi-experimental studies, both published and unpublished, that evaluated the efficacy of daily bathing with CHG versus soap and water or standard of care to prevent healthcare-associated BSIs in ICUs and non-ICUs among men, women, or children were included. Trials using CHG bathing perioperatively for the purposes of reducing surgical site infections were excluded.

Search Strategy

Bibliographic databases searched until May 23, 2011, included BioMed CENTRAL, PubMed, CINAHL Plus, Web of Knowledge, and Google Scholar. Other resources used included databases, such as OpenSIGLE at INIST (Institut de l'Information Scientifique et Technique) and the National Technical Information Service (<http://www.ntis.gov>); relevant conference proceedings; clinical trials registers (<http://www.clinicaltrials.gov>); and manual searching of relevant references of retrieved articles. There was no restriction by language or date of publication.

Study Selection

Studies were selected independently by 3 authors (G.L.M.S., J.C.O., and N.S.), applying the eligibility criteria described above. Disagreements among abstracters regarding inclusion and exclusion of any particular study were resolved by discussion among the authors. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram was used to present the study selection process through its different phases.¹⁸

Data Extraction

Data were extracted independently by 3 authors (G.L.M.S., J.C.O., and N.S.) from published reports and from the original researchers by means of an electronic data-collection form (see Box 1). When necessary, authors were contacted for additional data or confirmation of results. Studies were classified by their design as a controlled interrupted times series if there were measurements before and after the intervention, as a cluster nonrandomized trial when treatment was allocated by unit or other cluster, and as a randomized controlled trial for studies using true random allocation.

Box 1: Information Abstracted from Each Study

- Location
- Setting
- Duration
- Mean age of subjects
- Gender ratio
- Intervention
- Comparator
- Events in intervention arm
- Events in comparator group
- Other infections
- Compliance assessment
- Diagnostic criteria
- Source of funding
- Group and individual allocation
- Comparison groups
- Randomization technique
- Assessment of confounders
- Baseline assessment of outcome variables
- Study design

Quality of Studies and Risk of Bias

Randomized controlled trials and nonrandomized studies were assessed for risk of bias. Sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias were noted for the included studies. Risk of publication bias across studies was assessed using a funnel plot and Egger's test. Sensitivity analyses were performed to assess the impact of each individual study on study results and heterogeneity.

Data Synthesis

Data analysis was performed using the Mantel-Haenszel random-effects model for dichotomous data and inverse variance random effects for continuous data.¹⁹ Heterogeneity was assessed with an I^2 statistic, where 0% indicates no heterogeneity and 100% indicates the highest level of heterogeneity.²⁰ Data analysis was performed using Cochrane Database's Review Manager 5.1.0 software.

RESULTS

Study Selection

Our search criteria identified 133 studies; 117 were excluded for using CHG for a purpose other than bathing, 1 for being a case report, 1 for not using CHG as part of the main intervention,²¹ and 3 for being review articles. This search strategy is described in Figure 1. Ultimately, 12 studies met the criteria, with 1 being a randomized controlled trial and the remaining 11 being quasi-experimental studies. A total of 137,392 patient-days were reported across the studies, with 67,775 participants bathing daily with CHG and 69,617

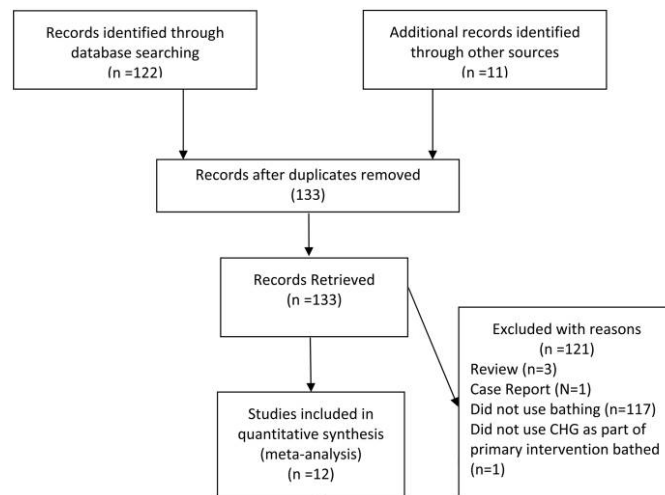


FIGURE 1. Study selection flow diagram: adapted with permission from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 2009 flow diagram.¹⁸ CHG, chlorhexidine.

patient-days during which daily soap-and-water baths were received.

Study Characteristics

All studies were conducted between 2005 and 2010 in the United States, except for one in France¹¹ and another in southern Israel.¹² The setting of 10 studies was ICUs, including medical,^{9,11,12,22,23} surgical,¹⁶ mixed medical-surgical^{8,13,24} and trauma¹⁷ ICUs, in addition to coronary⁸ and respiratory care²⁴ units. Munoz-Price et al¹⁵ performed their study at a long-term acute care hospital, which included a high proportion of patients requiring mechanical ventilation and central vascular catheters. All studies were performed among adults. Study characteristics are detailed in Table 1.

Bathing protocols. Daily CHG baths were used in all but 1 study,¹¹ which used twice-daily bathing. Seven studies used 2% CHG-impregnated cloths (Sage Products), the equivalent of 500 mg of CHG per cloth.^{9,14,16,17,22-24} In the study by Munoz-Price et al,¹⁵ a 1 : 2 dilution with bulk 4% CHG (Betasept; Purdue Pharma) and tap water was used to create a 2% solution that was used up to the jawline, using 3 clean washcloths. Emphasis was placed on not using additional water, and the solution was allowed to dry without rinsing. Climo et al⁸ reported that nurses mixed the contents of a 4-oz bottle of 4% CHG with warm water in a 6-qt basin at the bedside. Three other studies used a 4% CHG solution to bathe the patients.^{9,12,13} In the study by Camus et al,¹¹ the participants were bathed every 12 hours with 15 mL of a 4% solution of CHG (Hibiscrub; AstraZeneca). In the study by Borer et al,¹² 4% CHG (Septal Scrub; Teva Medical) was poured onto a sponge previously moistened with warm water to bathe the patients excluding the face and scalp. The solution remained on the patients' skin for at least 2 minutes before being re-

moved with warm tap water. Finally, the study by Gould et al¹³ reported using Hibiscrub cleansing solution (4% CHG gluconate; SSL International).

Additional infection control interventions. In 2 studies, the authors stated that no additional infection control interventions were used at the time of the study.^{9,15} It was part of the trial by Borer et al¹² to screen all patients admitted to the medical ICU (MICU) for *Acinetobacter baumannii* within 2 hours after admission and then periodically until discharge during the CHG period. During the preintervention period, patients with *A. baumannii* infections were identified only by clinical cultures, isolated, and placed under contact isolation. Camus et al¹¹ combined intranasal 2% mupirocin every 8 hours for 5 consecutive days with CHG bathing in the treatment group; in addition, intensified attention to hand hygiene measures, isolation precautions, and active surveillance measures were in place. Hand hygiene and active surveillance cultures were also emphasized in the study by Climo et al.⁸ Evans et al¹⁷ performed active surveillance for *A. baumannii* and methicillin-resistant *Staphylococcus aureus* (MRSA) by means of serial cultures; in addition, CHG was used for skin preparation before catheter insertion, in CHG and silver sulfadiazine-coated catheters, and in mouthwash during oral care for ventilated patients. In the trial by Gould et al,¹³ only patients with MRSA infections identified by clinical culture were placed in contact isolation before the intervention. During the intervention, surveillance cultures were done and all MRSA-positive patients were placed under contact isolation. In addition, all patients received topical nasal anti-MRSA preparations (2% fusidic acid, 3% oxytetracycline, and 0.5% neomycin sulphate combined with 0.1% CHG hydrochloride) every 6 hours for the duration of their stay during the intervention period. Finally, 2% CHG was used for skin dis-

TABLE 1. Characteristics of Included Studies

Reference	Location	Setting	Duration	Mean age, years ^a	Female sex	Intervention	Comparator	Other ICI	CA	Diagnostic criteria for BSI	Source of funding
Bleasdale et al, ⁹ 2007	Single center, USA	Two 11-bed MICUs	Jun 8–Dec 20, 2005, and Jan 5–Jun 21, 2006	T: 53 ± 16 C: 52 ± 15	T: 157 C: 179	Daily 2% CHG baths with impregnated cloth product	Daily soap-and-water bath	No	NR	CDC definition of primary BSI ^b	Sage Products and CDC
Borer et al, ¹² 2007	Single center, southern Israel	8-bed MICU	Feb 2001–Feb 2002 and Mar 2002–Dec 2003	NR	NR	Daily 4% CHG baths with liquid uid preparation	Daily soap-and-water bath	Yes	NR	Catheter-related BSI	None
Camus et al, ¹¹ 2005	Multicenter, France	12-, 21-, and 19-bed MICUs	Apr 1996–Oct 1998	T: 65 (21–86) C: 67 (19–84)	T: 44 C: 44	Twice-daily 4% CHG baths with liquid preparation	Twice-daily soap-and-water bath	Yes	NR	CDC definition of CVC-related BSI ^b	PHRC and GSK; some study drugs were provided by AstraZeneca
Climo et al, ⁸ 2009	Multicenter, USA	6 ICUs (coronary care units, surgical, cardiac surgery, mixed)	Dec 2004–Jan 2006	NR	NR	Daily CHG baths with liquid preparation	Daily bed baths with nonmedicated soap and water	Yes	Yes	MRSA or VRE bacteremia	Cooperative program award from CDC
Dixon and Carver, ²² 2010	Single center, USA	9 surgical ICU beds	Jan 2007–Sep 2009	NR	NR	Daily CHG baths with impregnated cloth product	Daily bed baths with nonmedicated soap and water	Yes	Yes	CDC definition	Sage Products unrestricted educational
Evans et al, ¹⁷ 2010	Single center, USA	12-bed trauma ICU	Nov 2006–Apr 2007 and May–Oct 2007	T: 39 ± 16 C: 40 ± 15	T: 75 C: 79	Daily 2% CHG baths with impregnated cloth product	Daily bathing with a disposable cloth bath product	Yes	No	CDC definition of CRBSI ^b	Dr Nathens is supported through a CRC
Gould et al, ¹³ 2007	Single center, USA	16-bed mixed medical-surgical ICU	May 1999–Apr 2001 and May 2001–Apr 2003	T: 58.5 ± 18.48 C: 56.8 ± 19.39	T: 762 C: 548	Daily 4% CHG baths with liquid uid preparation	Daily soap-and-water baths	Yes	No	Any patient with a blood culture positive for MRSA	Chief Scientists Office of the Scottish Executive Health Department

Holder and Zellingner, ¹⁴ 2009	Single center, USA	Medical and cardiovascular ICUs	Oct 2007–Mar 2008 and Apr 2008–Sep 2008	NR	NR	Daily 2% CHG baths with impregnated cloth product	No preexisting protocol	No	Yes	Presence of bacteremia	NR
Montecalvo et al, ²⁴ 2010	Multicenter, USA	1 MICU, 1 respiratory care unit, 4 mixed medical-surgical ICUs	Apr 2008–Sep 2009	NR	NR	Daily 2% CHG baths with impregnated cloth product	No preexisting protocol	No	Yes	Presence of bacteremia	NR
Munoz-Price et al, ¹⁵ 2009	Single center, USA	70-bed LTACH	Feb 2006–Feb 2008	NR	NR	Daily 2% CHG baths with liquid preparation	Daily soap-and-water baths	No	Yes	NR	NR
Popovich et al, ¹⁶ 2009	Single center, USA	21-bed MICU	Sep 2004–Oct 2005 and Nov 2005–Oct 2006	T: 59.3 C: 59.5	NR	Daily 2% CHG baths with impregnated cloth product	Daily soap-and-water baths	Yes	NR	CDC definitions ^b	Prevention Epicenter grant from CDC
Popovich et al, ²³ 2010	Single center, USA	30-bed surgical ICU	Sep 2004–Oct 2005 and Nov 2005–Oct 2006	T: 59.2 ± 1.8 C: 58.4 ± 1.84	NR	Daily 2% CHG baths with impregnated cloth product	Daily soap-and-water baths	Yes	No	CLABSI ^c	Study funded in part by CDC

NOTE. BSI, bloodstream infection; C, control group; CA, compliance assessment; CDC, Centers for Disease Control and Prevention; CHG, chlorhexidine; CLABSI, central line-associated BSI; CRBSI, catheter-related BSI; CRC, Canada Research Chair; CVC, central venous catheter; GSK, GlaxoSmithKline; ICI, infection control intervention; ICU, intensive care unit; LTACH, long-term acute care hospital; MICU, medical ICU; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported; PHRC, Programme Hospitalier de Recherche Clinique; T, treatment group; VRE, vancomycin-resistant enterococci.

^a Data are the mean, the mean ± standard deviation, or the mean (range) for the treatment or control group.

^b See Garner et al.²⁵

^c See O'Grady et al.²⁸

TABLE 2. Study Design (Adapted with Permission from the *Cochrane Handbook for Systematic Reviews of Interventions*⁹⁾)

	Bleasdale et al, ⁹ 2007	Borer et al, ¹² 2007	Camus et al, ¹¹ 2005	Climo et al, ⁸ 2009	Dixon and Carver, ²² 2010	Evans et al, ¹⁷ 2010	Gould et al, ¹³ 2007	Holder and Zellinger, ¹⁴ 2009	Montecalvo et al, ²⁴ 2010	Munoz-Price et al, ¹⁵ 2009	Popovich et al, ¹⁶ 2009	Popovich et al, ²³ 2010
Allocation												
Was the allocation at the group level?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the allocation at the individual level?	N	N	Y	N	N	N	N	N	N	N	N	N
Was there a comparison												
Between 2 or more groups of participants/ clusters receiving different interventions?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Within the same group of participants/clusters over time?	N	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y
Were participants/clusters allocated to groups by												
Concealed randomization?	N	N	Y	N	N	N	N	N	N	N	N	N
Quasi-randomization?	N	N	N	N	N	N	N	N	N	N	N	N
By other action of researchers?	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y
Time differences?	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Location differences?	Y	N	N	N	N	N	N	N	N	N	N	N
Treatment decisions?	N	N	N	N	N	N	N	N	N	N	N	N
Participants' preference?	N	N	N	N	N	N	N	N	N	N	N	N
On the basis of outcome?	N	N	N	N	N	N	N	N	N	N	N	N
Some other process?												
Which parts of the study were prospective?												
Identification of participants	Y	Y ^a	Y	Y	Y	N	Y ^a	Y ^a	Y	Y ^a	N	N
Assessment of baseline and allocation to intervention												
Assessment of outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Generation of hypotheses	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
On what variables was comparability between groups assessed?												
Potential confounders	Y	N	Y	N	N	Y	Y	N	N	N	N	N
Baseline assessment of outcome variables	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Study design	CINRT	CITS	RCT	CITS	CITS	CITS	CITS	CITS	CITS	CITS	CITS	CITS

NOTE. CITS, control interrupted time series; CINRT, cluster nonrandomized controlled trial; N, no; RCT, randomized controlled trial; Y, yes.

^a Yes for 1 group.

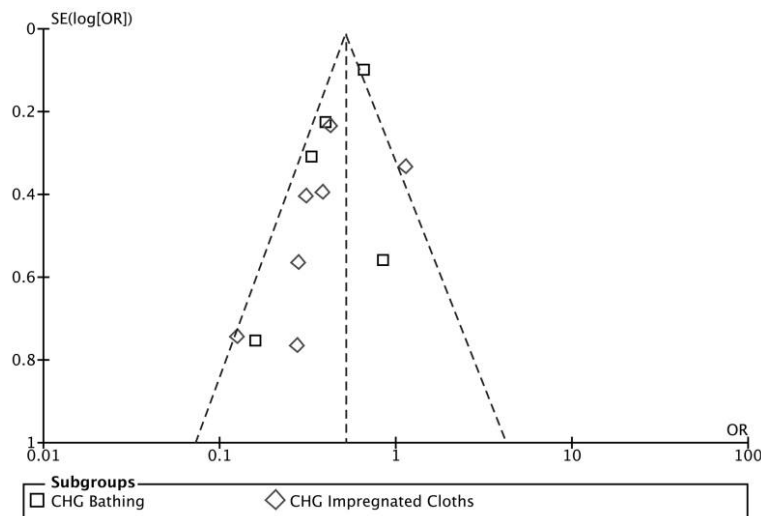


FIGURE 2. Assessment of publication bias using a funnel plot, where effect size is measured against study size. Larger studies should trend toward the mean, and smaller studies show predictable larger variance within the bounds of the funnel. As studies lay outside the funnel, publication bias is present. CHG, chlorhexidine; OR, odds ratio; SE, standard error.

infection before central line insertion during both periods in the studies by Popovich et al.^{16,23}

Assessment of fidelity to the intervention. Compliance with the CHG bathing schedule was not assessed in 3 studies.^{13,17,22} Climo et al⁸ estimated compliance weekly by monitoring the inventory of CHG bottles supplied to the study unit. At least 30 patient-days were monitored monthly during the first 6 months, and compliance rose from 40% to 98% within the first 3 months.¹⁴ Munoz-Price et al¹⁵ monitored directly observed compliance through the first 2 months of the intervention. Dixon and Carver²² evaluated compliance via a daily log tracking bathing activities.

Definition of study outcomes. Seven studies^{9,12,14–16,22–24} used CLABSI as the primary end point. Four used all healthcare-associated BSI rather than just CLABSI as the primary end point,^{8,11,13,17} finding significant decreases in both. One looked at rates of *A. baumannii* bacterial colonization as the primary end point,¹² demonstrating significant skin decolonization with CHG bathing.

Studies reporting definitions for CLABSI were largely consistent with the CDC definitions or modifications of that definition.²⁵ Bleasdale et al⁹ determined MICU-related infections by performing a medical record review when a positive clinical culture was detected at any site or a new order for antibiotic was given. In addition, CDC definitions were used to classify MICU-related infections as primary healthcare-associated BSI, clinical sepsis, and secondary BSI. In the study by Borer et al,¹² an episode of catheter-related BSI was defined as a patient with an intravascular catheter in place with at least 1 *A. baumannii*-positive blood culture obtained from a peripheral vein, clinical manifestation of infection, no other apparent source for the BSI, and positive semiquantitative (more than 15 colony-forming units per catheter segment)

A. baumannii culture from the catheter tip, which differed significantly from the CDC definition used in the majority of studies. Camus et al¹¹ employed the CDC definition of CLABSI. Climo et al⁸ considered the first positive blood culture obtained more than 48 hours after ICU admission showing growth of MRSA or vancomycin-resistant enterococci as a healthcare-associated BSI. Similarly, the definition of MRSA bacteremia used in the study by Gould et al¹³ was the presence of MRSA on blood culture confirmed by polymerase chain reaction. Evans et al¹⁷ classified bloodstream infections as CLABSI or secondary BSI according to CDC definitions. In addition, all infections occurred in the ICU and were identified by retrospective review of microbiological data and corroboration with medical record review. Nosocomial infection rates were determined by reviews of infection control practitioner logs and patient medical charts in the 2009 study by Popovich et al.¹⁶ Clinical culture results were obtained from a microbiologic database, and ICU-acquired infections were defined as recommended by the CDC.¹⁶ In a second study by Popovich et al,²³ data were also extracted from administrative, infection control practitioner, patient chart, and microbiology databases. The definition of CLABSI was consistent with CDC recommendations.^{3,22} Four included studies did not provide their operational definition of BSI.^{14,15,22,24}

Risk of Bias within Studies and across Studies

Assessment of study quality is shown in Table 2. Except for 1 study, all were quasi-experimental, with limited to no assessment of potential confounding factors. Only 1 study used allocation concealment,¹¹ which raises the concern of observer bias. While outcome ascertainment was done at baseline and during the study period, only 4 studies evaluated compara-

TABLE 3. Summary of Healthcare-Associated Bloodstream Infection (BSI) Incidence with Chlorhexidine and Comparator

Reference	No. of patients		No. of patient-days (or catheter-days for studies evaluating only CLABSI)		No. of healthcare- associated BSIs or CLABSIs	
	Treatment	Control	Treatment	Control	Treatment	Control
Bleasdale et al, ⁹ 2007 ^a	391	445	2,210	2,119	9	22
Borer et al, ¹² 2007 ^a	320	329	1,600	1,923	2	15
Camus et al, ¹¹ 2005	130	127	1,991	1,961	6	7
Climo et al, ⁸ 2009	2,650	2,670	15,423	15,993	14	41
Dixon and Carver, ²² 2010 ^a	NR	NR	3,148	3,346	8	27
Evans et al, ¹⁷ 2010	286	253	1,785	1,904	4	15
Gould et al, ¹³ 2007	1,421	1,232	6,664	6,899	171	264
Holder and Zellinger, ¹⁴ 2009 ^a	NR	NR	20,000	3,333	2	12
Montecalvo et al, ²⁴ 2010 ^a	1,832	1,808	13,864	12,603	2	12
Munoz-Price et al, ¹⁵ 2009 ^a	405	340	7,632	6,210	29	59
Popovich et al, ¹⁶ 2009 ^a	1,951	2,163	5,610	6,728	2	19
Popovich et al, ²³ 2010 ^a	1,387	1,938	5,799	7,366	17	19

NOTE. CLABSI, central line-associated BSI; NR, not recorded.

^a Studies that used CLABSI as their only end point.

bility between control and treatment groups. A funnel plot is shown in Figure 2; some degree of publication bias was shown by Egger's test, which was significant ($P = .01$).

Main Outcome

The primary outcome was healthcare-associated BSI as defined by the individual studies; 291 patients in the CHG arm developed a BSI over 67,775 patient-days, compared with 557 patients in the control arm over 69,617 catheter-days. A random-effects model resulted in an odds ratio (OR) of 0.44 (95% confidence interval [CI], 0.32–0.59; $P < .00001$). Table 3 and Figure 3 summarize the main outcome.

Subgroup Analysis

CHG is available either as a liquid or as an impregnated cloth wipe. To compare the efficacy of these modes of administration, a subgroup analysis was performed with healthcare-associated BSI as the outcome. CHG bathing was similarly efficacious regardless of whether cloth or liquid was used (OR with CHG wipes, 0.41 [95% CI, 0.25–0.65]; OR with all other studies, 0.47 [95% CI, 0.31–0.71]).

Analyzing study end points as part of the sensitivity analysis failed to detect a significant difference when studies used CLABSI (OR, 0.40 [95% CI, 0.27–0.59]) or all healthcare-associated BSI (OR, 0.46 [95% CI, 0.31–0.69]) as an end point.

To determine whether a single large study had a disproportionate impact on the meta-analysis, we undertook sensitivity analyses by sequentially omitting each study. We did not find any individual study or subgroup to have a material impact on the results of the meta-analysis.

Assessment of Heterogeneity

Our analysis found high clinical heterogeneity, likely stemming from variations across study designs, choice of outcome, variability in application of CHG, and choice of pathogen under study. Statistical heterogeneity was moderate. When we performed subgroup analyses by type of CHG formulation and choice of outcome definition, we found that the degree of statistical heterogeneity did not change. The limited number of studies overall precluded additional subgroup analyses by patient population or location.

Secondary Outcomes

Adverse effects. Six studies evaluated adverse effects of CHG.^{9,11,12,15,17,24} Five of them were nonrandomized trials and had no information on adverse effects in the control group. Bleasdale et al⁹ reported that 3 participants were excluded from the CHG arm after developing rashes ultimately determined not to be due to CHG. Two (0.6%) of 320 patients developed a localized CHG-related skin rash in the trial by Borer et al.¹² Evans et al¹⁷ witnessed 2 rashes during the CHG period that prevented continued use of the product, both of which were attributed to antibiotic therapy and resolved without intervention. Adverse events in the study by Montecalvo et al²⁴ were 1 rash possibly related to CHG. Munoz-Price et al¹⁵ stated that 3 of 405 patients had to discontinue the liquid CHG applications because of generalized redness or itching. In addition, the wound care team observed that approximately 1% of patients had increased dryness of the skin. However, the liquid preparation used in that study contains a small concentration of isopropyl alcohol. Finally, a skin allergy occurred in 6 patients (4.6%) who received CHG and

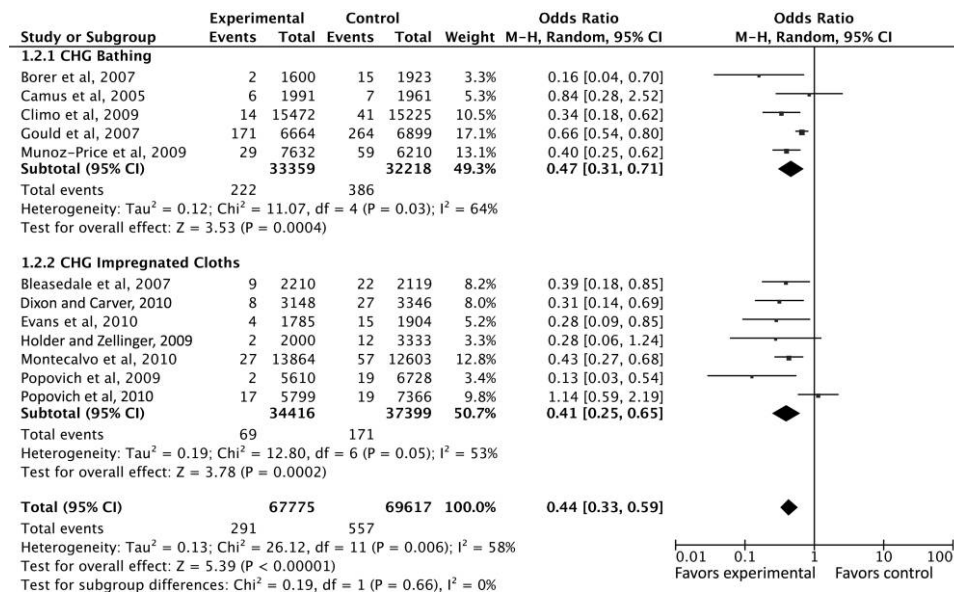


FIGURE 3. Risk of healthcare-associated bloodstream infection (BSI) with chlorhexidine (CHG) bathing and comparator, using patient-days in the analysis. “Events” refers to the study end point of central line-associated BSI or BSI, as defined in Table 1. Studies using a CHG-impregnated cloth are listed in the lower subgroup (1.2.2); all other studies are listed on top (1.2.1). CI, confidence interval; M-H, Mantel-Haenszel.

in 6 patients (4.8%) who received nonantimicrobial liquid soap in the randomized trial by Camus et al.¹¹

Cost. Four studies presented data on CHG cost.^{13–15,17} Evans et al¹⁷ estimated the cost of CHG cloths to be \$5.52 per bath at the time of the trial, as opposed to \$1.23 per bath for a disposable bathing product that does not contain CHG. Another study invested £4.44 per patient for a week’s supply of nasal ointment and CHG body wash, not including the nursing time needed to administer the decontamination agent, and reported savings predominantly owing to reduced length of stay.¹³ Holder and Zellinger¹⁴ stated that savings were seen in staff time, despite an increase in the cost per bath (\$5.50 vs \$1.46 per patient). They also calculated a projected cost savings of \$1.56 million per year if CHG baths were used in all 4 hospital ICUs, based on a 75% reduction in BSIs over 6 months. Finally, Munoz-Price et al¹⁵ considered CHG to be inexpensive (\$1–\$5 per day, depending on the preparation) and about the same cost of soap-and-water baths. No formal cost-effectiveness analysis was undertaken in any study.

Mortality. Two studies reported data on crude mortality.^{11,17} Mortality was 87 (15.9%) of 545 reported patients in the CHG arm and 101 (19.8%) of 509 patients in the control arm, yielding a nonsignificant difference with a fixed-effects model (OR, 0.78 [95% CI, 0.56–1.09]; $P = .15$).

DISCUSSION

We found that, among ICU patients, daily CHG bathing reduces the risk of healthcare-associated BSI, including CLABSI. Similar benefit is obtained regardless of whether CHG bathing

is done using CHG cloths or a liquid preparation. All included studies were conducted in the adult population; thus, our results are not generalizable to the pediatric population. The evidence is strongest for MICU patients; a trial conducted solely in a surgical ICU did not find a benefit with CHG bathing. While no formal cost-effectiveness analysis was done, the low cost of CHG compared with the high cost of even a single healthcare-associated BSI suggests that CHG bathing likely saves costs.

These overall conclusions, however, are tempered by several issues that merit consideration and caution in interpreting these findings. First, even though most of the included studies favored the use of CHG bathing, study design considerations deserve attention. Only a single randomized controlled trial met our inclusion criteria. The remainder of the studies were quasi-experimental, with little to no assessment of or adjustment for confounding variables. One study did not find a benefit with CHG bathing; it was the only study to use surgical patients exclusively, and the authors hypothesized that their finding may have resulted from the fact that wound infections from abdominal and thoracic surgeries cause bacterial translocation and contamination that would not have been effectively stemmed by the use of daily bathing. These authors also noted that the study design was quasi-experimental and did not adequately control for other risk factors that may have biased this study toward the null.²² Conversely, similar limitations may have biased the results to support a beneficial effect of CHG bathing in those studies that found a difference.

Second, there was considerable variability in the choice of

study outcome and definition of study outcome, ranging from healthcare-associated BSI to only CLABSI defined by various modifications of the CDC definitions. Interinstitutional variability in definitions, especially for CLABSI surveillance, and its impact on CLABSI rates has been well described recently.²⁶ We attempted to mitigate this factor in our analysis by undertaking subgroup analyses stratifying by choice and definition of outcome, and we did not find any difference in our overall results. Third, the widespread application of these results is limited because of variability in implementation of the intervention, lack of standardization in protocol, and lack of assessment of fidelity to the intervention in many of the studies that employed CHG bathing. This may be particularly relevant in the decision to rinse off the CHG after bathing or to leave the antiseptic on the skin for the studies that used liquid CHG preparations. Given the prolonged activity of CHG, we believe it would be more desirable to leave the solution on the skin rather than rinse it off. Fourth, our analysis found evidence of publication bias. We performed a comprehensive, exhaustive search to identify all available data; however, it is plausible that studies showing a lack of benefit of CHG would be less likely to be published.

Evidence for the use of CHG bathing outside of the MICU environment is lacking; only 1 study specifically investigated a dedicated surgical ICU,²³ and the rest were either medical-surgical ICUs or exclusively MICUs. The single study that evaluated CHG bathing in a long-term acute care hospital also found a benefit to CHG bathing.

As CLABSIs and healthcare-associated BSIs are becoming increasingly more prominent outside the ICU,²⁷ the use of CHG bathing should also be examined in the non-ICU setting. Additional considerations in this noncritical population should include a careful assessment of adverse effects, such as patient report of skin dryness and irritation. Studies included in our analysis were limited to ICU patients, for whom patient self-report is often not feasible. Adverse effects of CHG bathing were not consistently evaluated in these studies, but when reported they were rare, with rash being the most common and in one study occurring at a rate identical to that in the liquid soap arm.¹¹

In conclusion, existing data—largely obtained, however, from nonrandomized controlled trials—support the practice of daily bathing with CHG for decreasing healthcare-associated BSIs and CLABSIs. This is most convincingly demonstrated in the MICU population, where most of the studies were undertaken.

Further research is needed to determine whether this strategy has a role in other intensive care environments or non-intensive care environments. The comparative effectiveness of CHG bathing relative to other measures shown to reduce CLABSIs, such as CHG-impregnated dressings and antiseptic-impregnated catheters, needs to be assessed. Future studies should provide data on the characteristics of the patient populations to assess the comparability of treatment and control groups. Although use of CHG-impregnated cloth is

promising in that standardization of the amount and CHG concentration is easier to achieve, the available data provide equal support for CHG solution and CHG-impregnated cloth.

ACKNOWLEDGMENTS

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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