ORIGINAL ARTICLE

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The efficacy of daily chlorhexidine bathing for preventing healthcare-associated infections in adult intensive care units

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Background/Aims: Healthcare-associated infections (HAIs) in critically ill patients with prolonged length of hospital stay and increased medical costs. The aim of this study is to assess whether daily chlorhexidine gluconate (CHG) bathing will significantly reduce the rates of HAIs in adult intensive care units (ICUs).
Methods: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were systematically searched until December 31, 2014 to identify relevant studies. Two authors independently reviewed and extracted data from included studies. All data was analyzed by Review Manager version 5.3.
Results: Fifteen studies including three randomized controlled trials and 12 quasi-experimental studies were available in this study. The outcomes showed that daily CHG bathing were associated with significant reduction in the rates of primary outcomes: catheter-related bloodstream infection (risk ratio [RR], 0.44; 95% confidence interval [CI], 0.32 to 0.63; $p < 0.00001$), catheter-associated urinary tract infection (RR, 0.68; 95% CI, 0.52 to 0.88; $p = 0.004$), ventilator-associated pneumonia (RR, 0.73; 95% CI, 0.57 to 0.93; $p = 0.01$), acquisition of methicillin-resistant *Staphylococcus aureus* (RR, 0.78; 95% CI, 0.68 to 0.91; $p = 0.001$) and vancomycin-resistant *Enterococcus* (RR, 0.56; 95% CI, 0.31 to 0.99; $p = 0.05$).
Conclusions: Our study suggests that the use of daily CHG bathing can significantly prevent HAIs in ICUs. However, more well-designed studies are needed to confirm these findings.

Keywords: Chlorhexidine gluconate; Bathing; Infection; Intensive care units

INTRODUCTION

Healthcare-associated infections (HAIs) are the most common cause of morbidity and mortality among hospitalized patients. In 2011, approximately 648,000 patients experienced 721,800 HAIs in United States acute care hospitals [1]. Critically ill patients in intensive care units (ICUs) are at high risk for infection as a result of underlying immunodeficiency; comorbidity; and placement of invasive devices, such as endotracheal tubes and

intravascular devices [2]. Infections are strongly associated with prolonged length of stay (LOS) and increased medical charges [3].

Healthcare professionals have proposed several strategies for preventing HAIs, including compliance with hand hygiene, aseptic technique, and contact isolation precautions for patients, but these strategies can be difficult to maintain. Chlorhexidine gluconate (CHG) is a widely used antiseptic agent that has excellent antimicrobial activity and rapidity of action [4]. Furthermore,

in contrast with other antiseptic agents, the residual antimicrobial activity of CHG is not affected by the presence of body fluids and blood [5]. Some previous studies have demonstrated that daily CHG body bathing can effectively prevent HAIs, such as catheter-related bloodstream infections (CRBSIs) [6-12], surgical site infections [13], and the colonization of multidrug-resistant organisms (MDROs) [10,12,14]. However, the findings from a recent single-center, cluster-randomized controlled trial (RCT) challenged this approach [15], reporting that daily CHG bathing did not reduce rates of infection-related primary outcomes when compared with routine care (rate difference, –0.04; 95% confidence interval [CI], –1.10 to 1.01; p = 0.95). To solve this ongoing issue, we performed this systematic review and meta-analysis to assess whether daily CHG bathing, compared with usual care, significantly decreases the rates of HAIs in adult ICUs.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement to report this systematic review and meta-analysis [16]. The protocol of this study was registered on PROSPERO (the international register of systematic reviews; registration number: CRD42014014973).

Search strategy

The searches of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were performed from their inception to December 31, 2014. The searches were restricted to English publications and human subjects. The following search terms were used: chlorhexidine, body wash, bathing, showering, hospital-acquired infection, methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant *Enterococcus* (VRE) colonization/acquisition, ICU, and critically ill patients. The reference lists of the original and related reviews were also manually searched to identify any additional relevant studies. The latest search was performed on March 31, 2015.

Study selection

All included studies had to meet the following criteria:

(1) participants: adult patients in ICUs; (2) intervention: use of daily CHG bathing. If patients were treated with CHG washcloths, we defined it as daily CHG bathing; (3) comparison: soap and water or other routine care; (4) outcomes: at least one of the quantitative outcomes mentioned in the next section of this article was reported; and (5) study design: RCTs, interrupted time series studies, and before and after studies. Studies were excluded if they combined CHG bathing with oral or topical decontamination; if participants were in pediatric ICUs, general wards, cancer wards, or nursing homes; or if they were protocols, unpublished or duplicated studies, editorials, or review articles.

Data extraction

Two of the authors (HPH and BC) independently extracted and summarized the data from each included study. Any disagreement was resolved by discussion and consensus. The following characteristics of the studies were extracted: the first author, year of publication, country, study design, setting, patient characteristics, intervention protocols, and outcomes.

The primary outcomes included CRBSI, catheter-associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP), and acquisition of MRSA and VRE. The secondary outcomes were LOS, overall hospital mortality, and adverse events.

Quality assessment

Two of the authors (HPH and HYW) independently used the Cochrane Risk of Bias Tool to assign a judgment of low, unclear, or high risk of bias for RCTs according to the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data, selective reporting, and other bias [17]. The Newcastle-Ottawa Quality Assessment Scale was used to assess the methodological quality of non-randomized studies, which consist of three items: selection, comparability, and outcome assessment [18]. A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. A score of 6 or more indicates a study with high quality.

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Statistical analysis

Review Manager Software version 5.3 (Cochrane Collaboration, Oxford, United Kingdom) was used to pool data. Differences between the two groups were presented as a weighted mean difference (WMD) with a 95% CI for continuous outcomes and risk ratio (RR) with a 95% CI for dichotomous outcomes. Cochrane's Q test and the I^2 statistic were used to assess heterogeneity between studies, which was defined as a p value for Cochran's Q test of < 0.1 and an I^2 value of > 50% [19]. If there was significant heterogeneity, the random effects model was used to combine the data; otherwise, the fixed-effects model was used. A p < 0.05 was judged as statistically significant.

RESULTS

Study selection

Fig. 1 shows a diagram of the study selection process. Three hundred and thirty-nine relevant publications were identified during the initial search. Fifteen studies, including three RCTs [6,12,15] and 12 quasi-experimental studies [7-11,14,20-25], met the criteria and were included in the final meta-analysis.

Characteristics of included studies

Table 1 presents the characteristics of each included study. All included studies were conducted after 2005 in the United States, except one study in France [25] and one in Mexico [22]. Seven studies occurred in mixed ICUs [7,8,12,15,21,22,24], four in medical ICUs [6,11,14,25], two in surgical ICUs [9,20], one in a general ICU [23], and one in a trauma ICU [10]. For the intervention protocol of the included studies, all studies used 2% CHG-impregnated cloths for bathing except for one that used 4% CHG-based soap [24].

Methodological quality assessment

The risk of bias assessment summaries of the included studies are presented in Tables 2 and 3. For RCTs, only one study adequately reported the sequence generation method [15]. No studies provided the details about allocation concealment or the blinding methods. All of the studies used the intention-to-treat analysis to handle the missing data. Overall, all of the included RCTs were judged as having a high risk of bias. The risk of bias as-
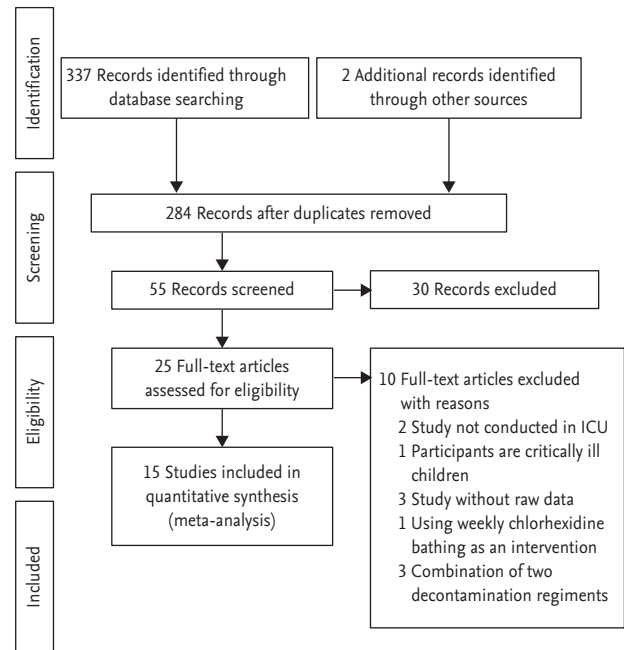
Figure 1. The process for studies selection. ICU, intensive care unit.

sessment for non-RCTs showed that the majority of the studies were rated with a score of more than 6, except for two studies [8,23].

Primary outcomes

CRBSI

Eleven studies [6-12,15,20-22] provided data on CHG bathing and CRBSI rates. Pooled results showed a significant difference between the CHG bathing arm and control arm on CRBSI rates (RR, 0.50; 95% CI, 0.36 to 0.71; p < 0.0001) and there was a moderate heterogeneity (I^2 = 69%; p = 0.0004) (Fig. 2).

CAUTI

Data on CAUTI rates were extracted from seven of the included studies [6,10,11,15,20,22,25]. The results revealed that there was a significant difference between the two groups on CAUTI rates (RR, 0.68; 95% CI, 0.52 to 0.88; p = 0.004) and there was a low heterogeneity (I^2 = 43%; p = 0.10) (Fig. 3).
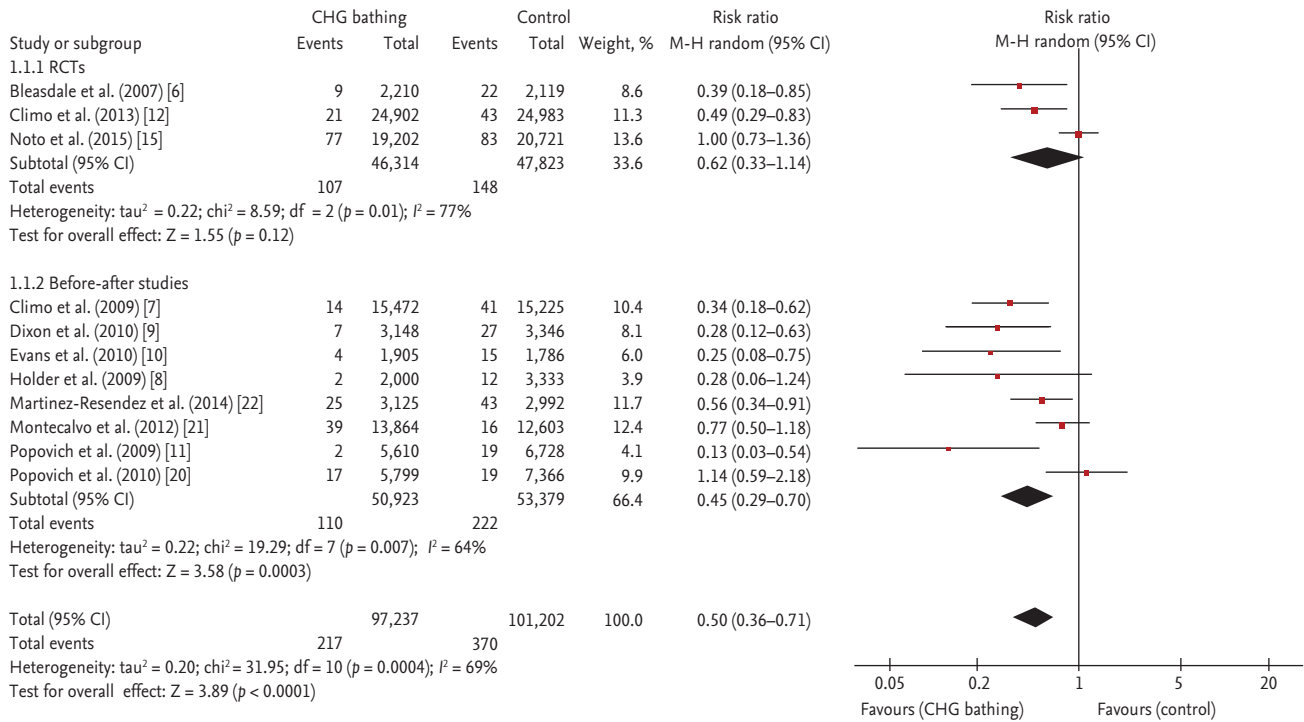
VAP

Six studies [6,10,11,15,20,22] assessed the effect of CHG bathing on reducing the incidence of VAP. The pooled

Table 1. The characteristics of included studies

Study	Country	Study design	Setting	Age, yr CHG	Age, yr Control	Intervention protocol	Control
Bleasdale et al. (2007) [6]	USA	RCT	MICU	53 ± 16	52 ± 15	Daily bath with 2% CHG-impregnated washcloths	Daily bath with soap and water
Cassir et al. (2015) [25]	France	Before and after study	MICU	58 (46–68)	61 (48–73)	Daily skin cleansing with disposable cloths saturated with 2% CHG	Daily bathing with soap and water
Climo et al. (2009) [7]	USA	Before and after study	Mixed ICUs	NR	NR	Daily bathing with 2% CHG washcloths	Daily soap and water bathing
Climo et al. (2013) [12]	USA	RCT	Mixed ICUs	NR	NR	Daily bath with washcloths impregnated with 2% CHG	Daily bathing with nonantimicrobial washcloths
Dixon et al. (2010) [9]	USA	Before and after study	SICU	NR	NR	Daily bath with disposable 2% CHG impregnated cloths	Daily soap and water bathing
Evans et al. (2010) [10]	USA	Before and after study	TICU	39 ± 16	40 ± 15	Daily bathing with disposable cloths impregnated with 2% CHG	Nonmedicated washcloths
Holder et al. (2009) [8]	USA	Before and after study	Mixed ICUs	NR	NR	Daily bath with 2% CHG washcloths	Standard body cleansing
Martinez-Resendez et al. (2014) [22]	Mexico	Before and after study	Mixed ICUs	49.74	47.47	Daily bathing with 2% CHG impregnated wipes	Daily bath with soap and water
Montecalvo et al. (2012) [21]	USA	Before and after study	Mixed ICUs	NR	NR	Daily bathing with 2% CHG washcloths	Daily bath with soap and water or nonmedicated cloths
Noto et al. (2015) [15]	USA	RCT	Mixed ICUs	56 (42–68)	57 (42–68)	Daily bathing of with cloths impregnated with 2% CHG	Daily bathing with disposable nonantimicrobial cloths
Petlin et al. (2014) [23]	USA	Before and after study	ICU	NR	NR	Daily bathing with 2% CHG washcloths	Daily bath with soap and water
Popovich et al. (2009) [11]	USA	Before and after study	MICU	59.3	59.5	Daily skin cleaning with 2% CHG impregnated cloths	Daily bathing with soap and water
Popovich et al. (2010) [20]	USA	Before and after study	SICU	59.2 ± 1.8	58.4 ± 1.8	Daily skin cleansing with 2% CHG impregnated cloths	Daily soap and water bathing
Vernon et al. (2006) [14]	USA	Before and after study	MICU	61 (30–94)	68 (27–79)	Daily bathing with 2% CHG washcloths	Daily soap and water bathing
Viray et al. (2014) [24]	USA	Before and after study	Mixed ICUs	NR	NR	Daily bathing with 4% CHG-based soap	Daily bathing with standard method

Values are presented as mean ± SD, median (interquartile range) or mean.
CHG, chlorhexidine gluconate; RCT, randomized clinical trial; MICU, medical intensive care unit; ICU, intensive care unit; NR, not report; SICU, surgical intensive care unit; TICU, trauma intensive care unit.

Study or subgroup	CHG bathing Events	Total	Control Events	Total	Weight, %	Risk ratio M-H random (95% CI)	Risk ratio M-H random (95% CI)
1.1.1 RCTs							
Bleasdale et al. (2007) [6]	9	2,210	22	2,119	8.6	0.39 (0.18–0.85)	
Climo et al. (2013) [12]	21	24,902	43	24,983	11.3	0.49 (0.29–0.83)	
Noto et al. (2015) [15]	77	19,202	83	20,721	13.6	1.00 (0.73–1.36)	
Subtotal (95% CI)		46,314		47,823	33.6	0.62 (0.33–1.14)	
Total events	107		148				
Heterogeneity: tau² = 0.22; chi² = 8.59; df = 2 (p = 0.01); I² = 77%							
Test for overall effect: Z = 1.55 (p = 0.12)							
1.1.2 Before-after studies							
Climo et al. (2009) [7]	14	15,472	41	15,225	10.4	0.34 (0.18–0.62)	
Dixon et al. (2010) [9]	7	3,148	27	3,346	8.1	0.28 (0.12–0.63)	
Evans et al. (2010) [10]	4	1,905	15	1,786	6.0	0.25 (0.08–0.75)	
Holder et al. (2009) [8]	2	2,000	12	3,333	3.9	0.28 (0.06–1.24)	
Martinez-Resendez et al. (2014) [22]	25	3,125	43	2,992	11.7	0.56 (0.34–0.91)	
Montecalvo et al. (2012) [21]	39	13,864	16	12,603	12.4	0.77 (0.50–1.18)	
Popovich et al. (2009) [11]	2	5,610	19	6,728	4.1	0.13 (0.03–0.54)	
Popovich et al. (2010) [20]	17	5,799	19	7,366	9.9	1.14 (0.59–2.18)	
Subtotal (95% CI)		50,923		53,379	66.4	0.45 (0.29–0.70)	
Total events	110		222				
Heterogeneity: tau² = 0.22; chi² = 19.29; df = 7 (p = 0.007); I² = 64%							
Test for overall effect: Z = 3.58 (p = 0.0003)							
Total (95% CI)		97,237		101,202	100.0	0.50 (0.36–0.71)	
Total events	217		370				
Heterogeneity: tau² = 0.20; chi² = 31.95; df = 10 (p = 0.0004); I² = 69%							
Test for overall effect: Z = 3.89 (p < 0.0001)							

Figure 2. The effects of daily chlorhexidine gluconate (CHG) bathing in reducing catheter-related bloodstream infection. CI, confidence interval; RCT, randomized clinical trial; df, degrees of freedom; M-H, Mantel-Haenszel.

Study or subgroup	CHG bathing Events	Total	Control Events	Total	Weight, %	Risk ratio M-H random (95% CI)	Risk Ratio M-H random (95% CI)
2.1.1 RCTs							
Bleasdale et al. (2007) [6]	13	2,210	17	2,119	10.1	0.73 (0.36–1.51)	
Noto et al. (2015) [15]	384	19,202	663	20,721	35.1	0.63 (0.55–0.71)	
Subtotal (95% CI)		21,412		22,840	45.3	0.63 (0.56–0.71)	
Total events	397		680				
Heterogeneity: tau² = 0.00; chi² = 0.18; df = 1 (p = 0.67); I² = 0%							
Test for overall effect: Z = 7.46 (p < 0.00001)							
2.1.2 Before-after studies							
Cassir et al. (2015) [25]	4	1,344	17	1,546	5.2	0.27 (0.09–0.08)	
Evans et al. (2010) [10]	12	1,846	14	1,972	9.2	0.92 (0.42–1.97)	
Martinez-Resendez et al. (2014) [22]	25	3,125	54	3,237	17.4	0.48 (0.30–0.77)	
Popovich et al. (2009) [11]	13	5,610	20	6,728	10.6	0.78 (0.39–1.57)	
Popovich et al. (2010) [20]	20	5,799	19	7,366	12.3	1.34 (0.71–2.50)	
Subtotal (95% CI)		17,724		20,849	54.7	0.70 (0.43–1.14)	
Total events	74		124				
Heterogeneity: tau² = 0.18; chi² = 10.08; df = 4 (p = 0.04); I² = 60%							
Test for overall effect: Z = 1.45 (p = 0.15)							
Total (95% CI)		39,136		43,689	100.0	0.68 (0.52–0.88)	
Total events	471		804				
Heterogeneity: tau² = 0.05; chi² = 10.57; df = 6 (p = 0.10); I² = 43%							
Test for overall effect: Z = 2.87 (p = 0.004)							

Figure 3. The effects of daily chlorhexidine gluconate (CHG) bathing in reducing catheter-associated urinary tract infection. CI, confidence interval; RCT, randomized clinical trial; df, degrees of freedom; M-H, Mantel-Haenszel.

Table 2. Risk-of-bias assessment of randomized clinical trial[a]

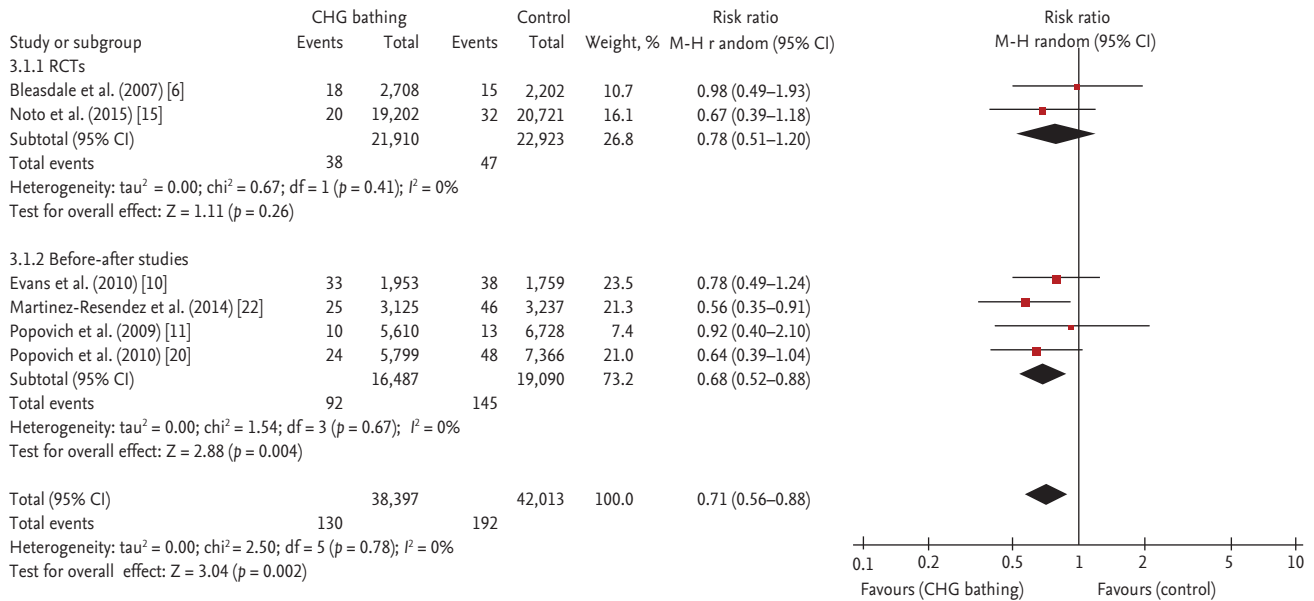| Study	Adequate sequence generation	Allocation concealment	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall risk of bias
Bleasdale et al. (2007) [6]	Unclear	Unclear	High	Low	Low	Low	Low	High
Climo et al. (2013) [12]	Unclear	Unclear	High	Unclear	Low	Low	Low	High
Noto et al. (2015) [15]	Low	Unclear	High	Low	Low	Low	Low	High

[a]Risk of bias was evaluated by using the Cochrane risk-of-bias tool.

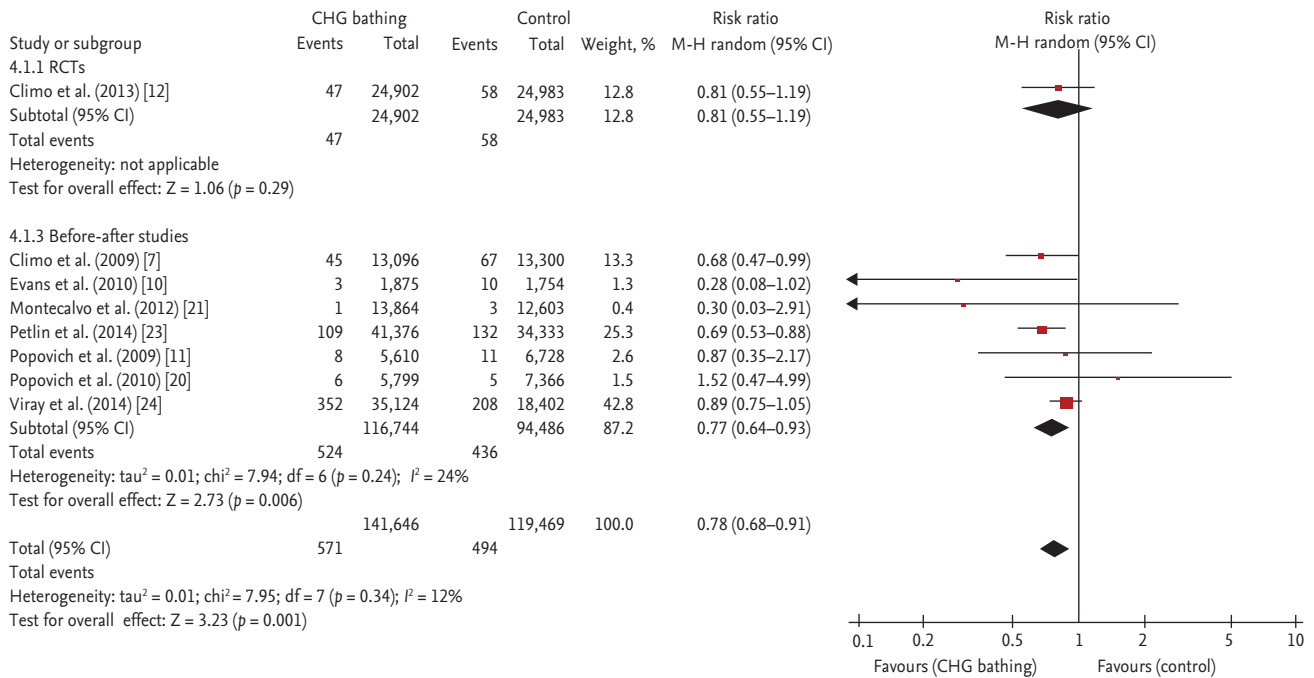**Table 3. Risk-of-bias assessment of the before and after studies[a]**

Study	Selection				Comparability	Outcome			Total score
	Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Cassir et al. (2015) [25]	*	*	*	*	**	*	-	*	8
Climo et al. (2009) [7]	*	*	*	*	**	*	*	*	9
Dixon et al. (2010) [9]	*	*	*	*	*	*	*	-	7
Evans et al. (2010) [10]	*	*	*	*	**	*	*	-	8
Holder et al. (2009) [8]	*	*	*	-	-	*	-	-	4
Martinez-Resendez et al. (2014) [22]	*	*	*	*	**	*	-	-	6
Montecalvo et al. (2012) [21]	*	*	*	-	**	*	*	-	7
Petlin et al. (2014) [23]	*	*	*	*	-	*	-	-	5
Popovich et al. (2009) [11]	*	*	*	*	*	*	*	-	7
Popovich et al. (2010) [20]	*	*	*	*	*	*	*	-	7
Vernon et al. (2006) [14]	*	*	*	*	**	*	*	-	8
Viray et al. (2014) [24]	*	*	*	*	-	*	*	-	6

A study can be awarded a maximum of "*" for each numbered item within the selection and outcome categories. A maximum of "**" can be given for comparability. "*" means good representation.

[a]Risk of bias was assessed with use of the Newcastle-Ottawa Quality Assessment Scale. A score of 6 or more indicates a low risk of bias.

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	CHG bathing		Control			Risk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight, %	M-H random (95% CI)	M-H random (95% CI)
3.1.1 RCTs							
Bleasdale et al. (2007) [6]	18	2,708	15	2,202	10.7	0.98 (0.49–1.93)	
Noto et al. (2015) [15]	20	19,202	32	20,721	16.1	0.67 (0.39–1.18)	
Subtotal (95% CI)		21,910		22,923	26.8	0.78 (0.51–1.20)	
Total events	38		47				
Heterogeneity: tau^2 = 0.00; chi^2 = 0.67; df = 1 (p = 0.41); I^2 = 0%							
Test for overall effect: Z = 1.11 (p = 0.26)							
3.1.2 Before-after studies							
Evans et al. (2010) [10]	33	1,953	38	1,759	23.5	0.78 (0.49–1.24)	
Martinez-Resendez et al. (2014) [22]	25	3,125	46	3,237	21.3	0.56 (0.35–0.91)	
Popovich et al. (2009) [11]	10	5,610	13	6,728	7.4	0.92 (0.40–2.10)	
Popovich et al. (2010) [20]	24	5,799	48	7,366	21.0	0.64 (0.39–1.04)	
Subtotal (95% CI)		16,487		19,090	73.2	0.68 (0.52–0.88)	
Total events	92		145				
Heterogeneity: tau^2 = 0.00; chi^2 = 1.54; df = 3 (p = 0.67); I^2 = 0%							
Test for overall effect: Z = 2.88 (p = 0.004)							
Total (95% CI)		38,397		42,013	100.0	0.71 (0.56–0.88)	
Total events	130		192				
Heterogeneity: tau^2 = 0.00; chi^2 = 2.50; df = 5 (p = 0.78); I^2 = 0%							
Test for overall effect: Z = 3.04 (p = 0.002)							

0.1 0.2 0.5 1 2 5 10
Favours (CHG bathing)   Favours (control)

Figure 4. The effects of daily chlorhexidine gluconate (CHG) bathing in reducing ventilator-associated pneumonia. CI, confidence interval; RCT, randomized clinical trial; df, degrees of freedom; M-H, Mantel-Haenszel.

	CHG bathing		Control			Risk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight, %	M-H random (95% CI)	M-H random (95% CI)
4.1.1 RCTs							
Climo et al. (2013) [12]	47	24,902	58	24,983	12.8	0.81 (0.55–1.19)	
Subtotal (95% CI)		24,902		24,983	12.8	0.81 (0.55–1.19)	
Total events	47		58				
Heterogeneity: not applicable							
Test for overall effect: Z = 1.06 (p = 0.29)							
4.1.3 Before-after studies							
Climo et al. (2009) [7]	45	13,096	67	13,300	13.3	0.68 (0.47–0.99)	
Evans et al. (2010) [10]	3	1,875	10	1,754	1.3	0.28 (0.08–1.02)	
Montecalvo et al. (2012) [21]	1	13,864	3	12,603	0.4	0.30 (0.03–2.91)	
Petlin et al. (2014) [23]	109	41,376	132	34,333	25.3	0.69 (0.53–0.88)	
Popovich et al. (2009) [11]	8	5,610	11	6,728	2.6	0.87 (0.35–2.17)	
Popovich et al. (2010) [20]	6	5,799	5	7,366	1.5	1.52 (0.47–4.99)	
Viray et al. (2014) [24]	352	35,124	208	18,402	42.8	0.89 (0.75–1.05)	
Subtotal (95% CI)		116,744		94,486	87.2	0.77 (0.64–0.93)	
Total events	524		436				
Heterogeneity: tau^2 = 0.01; chi^2 = 7.94; df = 6 (p = 0.24); I^2 = 24%							
Test for overall effect: Z = 2.73 (p = 0.006)							
		141,646		119,469	100.0	0.78 (0.68–0.91)	
Total (95% CI)							
Total events	571		494				
Heterogeneity: tau^2 = 0.01; chi^2 = 7.95; df = 7 (p = 0.34); I^2 = 12%							
Test for overall effect: Z = 3.23 (p = 0.001)							

0.1 0.2 0.5 1 2 5 10
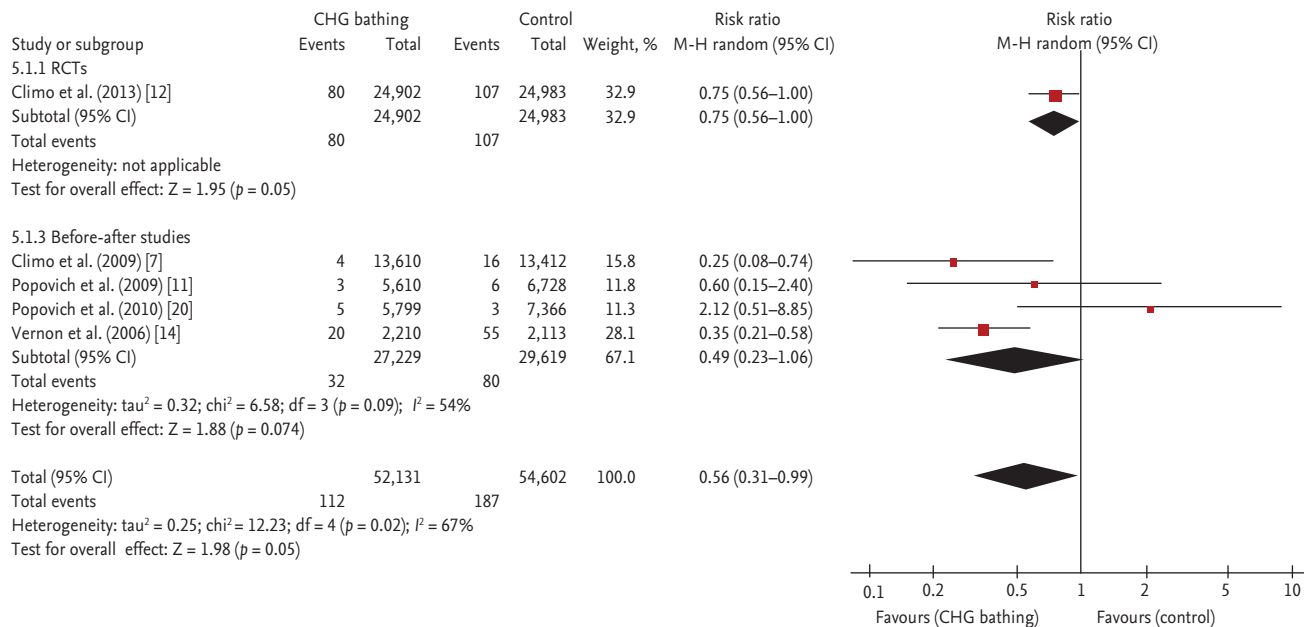Favours (CHG bathing)   Favours (control)

Figure 5. The effects of daily chlorhexidine gluconate (CHG) bathing in reducing methicillin-resistant *Staphylococcus aureus* acquisition. CI, confidence interval; RCT, randomized clinical trial; df, degrees of freedom; M-H, Mantel-Haenszel.

results showed that CHG bathing was strongly associated with a lower risk of VAP when compared with soap and water or other controls (RR, 0.71; 95% CI, 0.56 to 0.88; p = 0.002) and there was no heterogeneity (I^2 = 0%;

p = 0.78) (Fig. 4).

MRSA acquisition

MRSA acquisition rates were available for eight stud-

	CHG bathing		Control			Risk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight, %	M-H random (95% CI)	M-H random (95% CI)
5.1.1 RCTs							
Climo et al. (2013) [12]	80	24,902	107	24,983	32.9	0.75 (0.56–1.00)	
Subtotal (95% CI)		24,902		24,983	32.9	0.75 (0.56–1.00)	
Total events	80		107				
Heterogeneity: not applicable							
Test for overall effect: Z = 1.95 (p = 0.05)							
5.1.3 Before-after studies							
Climo et al. (2009) [7]	4	13,610	16	13,412	15.8	0.25 (0.08–0.74)	
Popovich et al. (2009) [11]	3	5,610	6	6,728	11.8	0.60 (0.15–2.40)	
Popovich et al. (2010) [20]	5	5,799	3	7,366	11.3	2.12 (0.51–8.85)	
Vernon et al. (2006) [14]	20	2,210	55	2,113	28.1	0.35 (0.21–0.58)	
Subtotal (95% CI)		27,229		29,619	67.1	0.49 (0.23–1.06)	
Total events	32		80				
Heterogeneity: tau^2 = 0.32; chi^2 = 6.58; df = 3 (p = 0.09); I^2 = 54%							
Test for overall effect: Z = 1.88 (p = 0.074)							
Total (95% CI)		52,131		54,602	100.0	0.56 (0.31–0.99)	
Total events	112		187				
Heterogeneity: tau^2 = 0.25; chi^2 = 12.23; df = 4 (p = 0.02); I^2 = 67%							
Test for overall effect: Z = 1.98 (p = 0.05)							

0.1 0.2 0.5 1 2 5 10
Favours (CHG bathing)   Favours (control)

Figure 6. The effects of daily chlorhexidine gluconate (CHG) bathing in reducing vancomycin-resistant *Enterococcus* acquisition. CI, confidence interval; RCT, randomized clinical trial; df, degrees of freedom; M-H, Mantel-Haenszel.

ies, including one RCT [11] and seven before and after studies [7,10,11,20,21,23,24], which showed a significant reduction in the risks of MRSA acquisition in the CHG bathing group (RR, 0.78; 95% CI, 0.68 to 0.91; p = 0.001) with a low heterogeneity (I^2 = 12%; p = 0.34) (Fig. 5).

VRE acquisition
Five studies [7,11,12,14,20] provided data on daily CHG bathing and VRE acquisition. The outcomes showed that daily CHG bathing was associated with decreased VRE acquisition (RR, 0.56; 95% CI, 0.31 to 0.99; p = 0.05) and there was a moderate heterogeneity (I^2 = 67%) (Fig. 6).

Secondary outcomes

LOS
Hospital LOS was reported in eight studies. However, four of studies did not provide the standard deviation of the outcome [7,11,12,15]. Pooled results revealed that there was no significant differences between the two groups on LOS (WMD, –0.27; 95% CI, –0.68 to 0.14; p = 0.20) using the random-effects model (I^2 = 44%).

Overall hospital mortality
Four studies [10,15,22,25] involving 10,882 patients evalu-

ated the effects of daily CHG bathing on overall hospital mortality. Outcomes showed that daily CHG bathing was associated with less hospital mortality (10.16% vs. 11.45%; RR, 0.88; 95% CI, 0.79 to 0.97; p = 0.01).

Adverse events
Only three studies evaluated adverse effects during the CHG bathing period. Bleasdale et al. [6] reported that three subjects were excluded from the CHG arm after developing rashes; however, it was ultimately determined not to be due to CHG. Evans et al. [10] witnessed two rashes that prevented continued use of CHG, both of which were caused by antibiotic therapy and resolved without intervention. Petlin et al. [23] did not find patient reports of skin irritation during the study.

DISCUSSION

This further meta-analysis demonstrated that daily CHG bathing had an overwhelming effect on decreasing the rates of the composite primary outcomes, including CRBSI, CAUTI, VAP, and acquisition of MRSA and VRE. However, there was no sufficient evidence to support that the use of daily CHG bathing can reduce hospi-

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tal LOS. In this meta-analysis, only studies conducted in adult ICUs were included; therefore, the results are not generalizable to hospitalized children. Fortunately, one well-designed trial can be a useful supplement for this specific population [26]. In this cluster-randomized, crossover study, the authors found that the incidence of bacterium was 36% lower among patients receiving daily CHG bathing compared with patients receiving standard bathing practices (3.28 vs. 4.93 per 1,000 days; adjusted incidence rate ratio, 0.64; 95% CI, 0.42 to 0.98) and there were no significant differences in the incidence of adverse events.

We found that there was a significant reduction CRBSI rates and the acquisition of MDROs when either 2% CHG-impregnated washcloths or CHG bathing were used, which is in accordance with previous systematic reviews [27,28]. To date, CHG bathing has been mainly employed in critical care settings; a limited number of studies were conducted in hospital-wide settings. One study conducted in a long-term acute care hospital reported that daily CHG baths can result in a net reduction of 99% in central venous CRBSI rates [29]. Another study performed in a general medical hospital provided strong evidence that daily bathing with CHG was associated with a 64% reduced risk of developing MRSA and VRE HAIs (hazard ratio, 0.36; 95% CI, 0.2 to 0.8; p = 0.01) [30].

To our knowledge, this is the first study to evaluate the efficacy of daily CHG bathing on preventing VAP and CAUTI. Our findings suggest that daily CHG bathing will reduce the risk of VAP (RR, 0.71; 95% CI, 0.56 to 0.88) and CAUTI (RR, 0.68; 95% CI, 0.52 to 0.88) in ICU settings. VAP is one of the most common HAIs in ICUs and occurs in 8% to 28% of patients receiving mechanical ventilation [31]. Aspiration of oropharyngeal pathogens into the lower respiratory tract is considered the major mechanism for the development of VAP [32]. Therefore, many strategies have been used to reduce bacteria in the oral cavity of patients who are mechanically ventilated [33]. Routine oral care with CHG has become the standard of care for patients receiving mechanical ventilation in most hospitals [34]. However, a recent meta-analysis [35] involving 16 studies showed that oral care with CHG did not decrease VAP risk in non-cardiac surgery patients and provided no additional benefits for patient-centered outcomes in either cardiac surgery or non-cardiac surgery patients. The relevant guidelines or

recommendations about this practice may need to be re-evaluated. In contrast, our study demonstrated that daily CHG bathing can significantly decrease the risk of VAP development. Several aspects probably contribute to this difference. First is the different methods of prevention (oral care vs. bathing) employed in both studies. Second is that the mean duration of mechanical ventilation in this study was shorter than in the study conducted by Klompas et al. [35], which may lead to an underestimation of VAP incidence.

Multiple guidelines to prevent CAUTI have been released [36,37]. Similar to CRBSI, many CAUTI prevention strategies have been bundled into a composite of several interventions, such as inserting catheters using aseptic technique and sterile equipment, hand hygiene, standard precautions, and so on. However, evidence for daily CHG bathing as routine care for preventing CAUTI is scant. Findings from our study provide more support for healthcare providers to use this approach. Previous culture-based analyses showed that hospitalized patients had a higher risk of skin colonization with gram-negative bacteria, particularly in the perineal area [38]. In the ICU, *Escherichia coli* accounts for approximately 18% to 26% of CAUTIs [39]. Recently, a study assessed the effect of daily CHG bathing on skin microbiota [40]. The results showed that daily CHG bathing is associated with a reduction in gram-negative bacteria colonization together with substantial skin microbiota shifts. These findings may be a possible explanation for why daily CHG bathing can prevent CAUTI in our study.

Although this meta-analysis provides some evidence that daily CHG bathing can effectively prevent HAIs, some limitations should also be concerned. One is that only three eligible RCTs were included in this study. Therefore, the conclusions must be interpreted with caution. Second is that the overall quality of the included studies was low. None of the included RCTs used the double-blinding method, which may result in performance bias and detection bias. Third is that the included studies did not adequately evaluate the long-term effects of CHG bathing on overall mortality and adverse events, which are important outcomes for critically ill patients in ICUs.

In conclusion, this meta-analysis suggests that daily CHG bathing is significantly associated with lower risk of CRBSI, CAUTI, VAP, and acquisition of MRSA and

VRE in ICU. However, more large sample size studies with long-term follow-up are needed to confirm and update these findings.

KEY MESSAGE

1. Daily chlorhexidine gluconate (CHG) bathing can significantly decrease the risk of health-care-associated infections development in intensive care units, when compared with standard care.
2. Daily CHG bathing can reduce the overall hospital mortality. However, there is no influential on hospital length of stay.
3. Majority studies included in this meta-analysis were quasi-experimental studies, more well-designed randomized controlled trials are needed to confirm these findings.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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