Effects of daily bathing with chlorhexidine and acquired infection of methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus: a meta-analysis

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ABSTRACT

Objective: Chlorhexidine gluconate (CHG) is a common and safe antimicrobial agent and has been used widely in hand hygiene and skin disinfection; however, whether daily bathing with CHG results in the reduced acquired infection of methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) remains inconclusive.

Methods: We did a meta-analysis searching PubMed, Embase and the Cochrane Central Register database for available studies. Primary outcomes were acquired infection of MRSA, VRE.

Results: In all, twelve articles were available in this review. We found that daily application of chlorhexidine bathing would significantly low the acquired colonization of MRSA [incidence rate ratio (IRR) =0.58, 95% confidence interval (CI): 0.41-0.82] or VRE (IRR =0.51, 95% CI: 0.36-0.73). Remarkably, the using of CHG bathing would significantly reduce the MRSA infection (IRR =0.56, 95% CI: 0.37-0.85), MRSA ventilator associated pneumonia (VAP) (IRR =0.22, 95% CI: 0.07-0.64) and VRE infection (IRR =0.57, 95% CI: 0.33-0.97). No significant publication bias was found in this meta-analysis.

Conclusions: The application of CHG bathing would significantly decrease acquired infection of MRSA or VRE, which may be an important complementary intervention to barrier precautions.

KEY WORDS Chlorhexidine; methicillin-resistant Staphylococcus aureus (MRSA); vancomycin-resistant Enterococcus (VRE)

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Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) are typical drug resistant pathogens in healthcare settings. Critical or immunocompromised patients are at high risk for acquired infection of MRSA or VRE (1). Infection of MRSA and VRE may significantly prolong duration of hospital stay and increase the burden of in-patients. A recent review concluded that the rising morbidity of health care-associated infections (HAIs) caused by MRSA and VRE were serious problems in ICUs (2). It was reported that the prevalence of MRSA is above 60% and the nearly 30% for VRE in ICUs in the United States (3,4). Most common route of MRSA and VRE transmission is cross-transmission via contaminated hands of healthcare workers. Therefore, effective means of interrupting cross-transmission and preventing infection of MRSA and VRE is of great necessity (2).

Application of a skin antisepsis on consecutive days would reduce microbial counts (5). Chlorhexidine gluconate (CHG) has a broad-spectrum antimicrobial activity (6) and has been used widely as a hand wash and skin disinfection with good safety profile (7). Daily bathing with CHG has been reported to eradicate the colonization of high-risk pathogens including MRSA and VRE, thus decreasing the acquired risk for transmission between healthcare workers and patients (8,9). However, it is still inconclusive whether daily application with CHG bathing leads to lower acquisition of MRSA and VRE. Some articles showed that daily chlorhexidine bathing was

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significantly associated with the reduced acquisition of MRSA and VRE (8-10) while some other studies showed inconsistent results (11,12). Therefore, we performed this meta-analysis to investigate the association.

Materials and methods

Search strategy

An electronic search engine (PubMed), Embase and the Cochrane Central Register database were searched separately up to July 1 2013, for all eligible studies by two different reviewers (W Chen and L Li). We used the searching terms which were also MeSH terms, "chlorhexidine", "chlorhexidine and MRSA", "chlorhexidine and VRE". The term "daily showering or whole body washing with chlorhexidine" was the same meaning as "daily chlorhexidine bathing". Additional studies were identified by a hand search of references of original studies or review articles on this topic. No language restrictions were imposed. The two independent investigators (W Chen and L Li) reached consistency on all data sets for this manuscript.

Eligibility criteria

We included all the clinical trials with epidemiological study designs of retrospective surveillance, interrupted time series study, prospective interventional cohort study, before-after intervention study, and random control trial. All the literatures are published to date on the associations between the using of CHG bathing and acquired MRSA or VRE. To be included, studies had to have been published in full-articles, expressed their findings as IRR with 95% confidence interval (CI). The major study outcomes were colonization or infection of MRSA or VRE. Two independent reviewers (W Chen and L Li) examined the literatures to confirm they had fulfilled the defined inclusion criteria. Patients treated with the chlorhexidine-saturated cloth were deemed to have same effects with "daily chlorhexidine bathing". Thus the relevant articles were also included in this review.

Data extraction

Both authors (W Chen and L Li) extracted the data independently using a data extraction form. Disagreement was settled by consensus between all authors. Information on study design, setting, study population, nature of interventions, co-interventions was collected.

Statistical analysis

Q test was used to assess the degree of heterogeneity between studies (13). If the between-study heterogeneity was not found, fixed-effect model was conducted. If I^2 was ≤50%, a fixed effects model was used to calculate a pooled estimate of effect; If the I^2 statistic was >50%, a random effect model was used (14). Publication bias was evaluated by the linear regression asymmetry test by Egger *et al.* (15). All data were analyzed in Review Manager (v.5.1.6; Oxford, England).

Results

In all, twelve studies were available in this review (8-12,16-22). Four articles were available for MRSA colonization (9,10,18,19), seven for MRSA infection (11,12,16-18,21,22), and five for VRE colonization (8-10,21,22), six for VRE infection (9,11,12,16,21,22), two for MRSA ventilator associated pneumonia (VAP) (17,18). Ten studies were interrupted time series study, two cluster-randomized trials (10,19) (Table 1).

MRSA colonization and infection

Four articles investigated the relationship between and acquired colonization of MRSA (intervention: 141,618 patient-days; control: 109,928 patient-days), all of which were performed in interrupted time series study design. As a result, daily using with CHG bathing were significantly associated with reduced colonization risk of MRSA or VRE (MRSA: IRR =0.58, 95% CI: 0.41-0.82) (Figure 1A). Interestingly, as shown in Figure 1B, the application of CHG bathing would significantly decrease acquired infection of MRSA (seven articles, intervention: 70,574 patient-days; control: 69,295 patient-days) (IRR =0.56, 95% CI: 0.37-0.85).

In subgroup analysis, we found that daily bathing with CHG significantly cut down the acquired infection of MRSA VAP (two articles, intervention: 7,290 patient-days, control: 5,736 patient-days) (IRR =0.22, 95% CI: 0.07-0.64, $P_{heterogeneity}$=0.51, I^2 =0%) (Table 2). Moreover, we consistently revealed that CHG bath would decrease the acquired infection of MRSA especially in ICU settings (five articles, intervention: 32,563 patient-days, control: 32,433 patient-days; IRR =0.58, 95% CI: 0.36-0.96).

VRE colonization and infection

Five studies were eligible to assess the impact of CHG bathing and VRE colonization (intervention: 78,733 patient-days; control: 77,370 patient-days). We found that the use of CHG bathing would significantly reduce acquired VRE colonization (IRR =0.51, 95% CI: 0.36-0.73) (Figure 1C). Meanwhile, the intervention also significantly resulted in lower acquired infection of VRE (six articles, intervention: 76,994 patient-days, control: 76,971 patient-days; IRR =0.57, 95% CI: 0.33-0.97) (Figure 1D).

Table 1. Characteristics of included studies in this meta-analysis.

Reference	Publication year	Study design	Setting	CHG Intervention	Co-interventions or control group	Duration of study period
Vernon *et al.*	2006	Interrupted time series	Medical ICU	Bath with 2% CHG washcloths	Soap-and water bathing	Oct 14 2002 to Dec 31 2003
Ridenour *et al.*	2007	Interrupted time series	Medical-coronary ICU	4% CHG bathing	Bathing without CHG	Jan 13 2003 to Aug 14 2004
Climo *et al.*	2009	Interrupted time series	ICUs (mixed)	Bath with 2% CHG washcloths	Soap-and water bathing	Dec 2004 to Jan 2006
Popovich *et al.*	2009	Interrupted time series	Medical ICU	Bath with 2% CHG washcloths	Soap-and water bathing	Sep 2004 to Oct 2006
Popovich *et al.*	2010	Interrupted time series	Surgical ICU	Bath with 2% CHG washcloths	Soap-and water bathing	Sep 2004 to Oct 2006
Fraser *et al.*	2010	Interrupted time series	Medical ICU	Daily chlorhexidine gluconate bath	Surveillance for S. aureus nasal carriage	Jan 1 2006 to Dec 31 2007
Evens *et al.*	2010	Interrupted time series	Trauma ICU	Bath with 2% CHG washcloths	Disposable washcloths without CHG	Nov 2006 to Oct 2007
Kassakian *et al.*	2011	Interrupted time series	General medical units in acute care hospital	Bath with 2% CHG washcloths	Soap-and water bathing	Jan 1 2008 to Mar 31 2010
Bass *et al.*	2012	Interrupted time series	Haematologye oncology ward	Bath with 2% CHG washcloths	Soap-and water bathing	Mar 2010 to Oct 2010
Montecalvo *et al.*	2012	Interrupted time series	Medical ICU, surgical ICU and Respiratory care	Bath with 2% CHG washcloths	Sites A, B, E: nonmedicated bathing cloths;Sites C, D, F:soap and water	Apr 1 2008 to Aug 31 2010
Climo *et al.*	2013	Multicenter, cluster-randomized, crossover trial	ICU (mixed) and denotes bone marrow transplantation unit	No-rinse 2% chlorhexidine-impregnated washcloths	Nonantimicrobial washcloths	Aug 2007 to Feb 2009
Huang *et al.*	2013	Cluster-randomized trial	Adult ICU	Bath with 2% CHG washcloths	MRSA screening and isolation	Jan 1 2009 to Sep 30 2011

MRSA, methicillin resistant Staphylococcus aureus; VRE, vancomycin resistant Enterococci; MICU, medical intensive care unit; TICU, trauma ICU; SICU, Surgical intensive care unit; CHG, Chlorhexidine Gluconate.

Test of heterogeneity and publication bias

The test of heterogeneity related to each analysis was performed in this meta-analysis. For CHG bathing and MRSA or VRE colonization, we found that there were evidence of statistical heterogeneity (I^2 =80.0% for MRSA; 51% for VRE, relatively) and random models were used for pooling of effects. However, for MRSA or VRE infections, there were no significant evidence of heterogeneity and fixed model were selected (I^2 =2% for MRSA; 31% for VRE, relatively). Egger's test was used to evaluate the potential publication bias, which was more pronounced when the higher intercept deviated from zero in linear regression analysis. No significant publication bias was found in this meta-analysis for different comparisons (all P values >0.05).

Discussion

This meta-analysis systematically reviewed the relationship between CHG bathing and the acquisition of MRSA and VRE. We

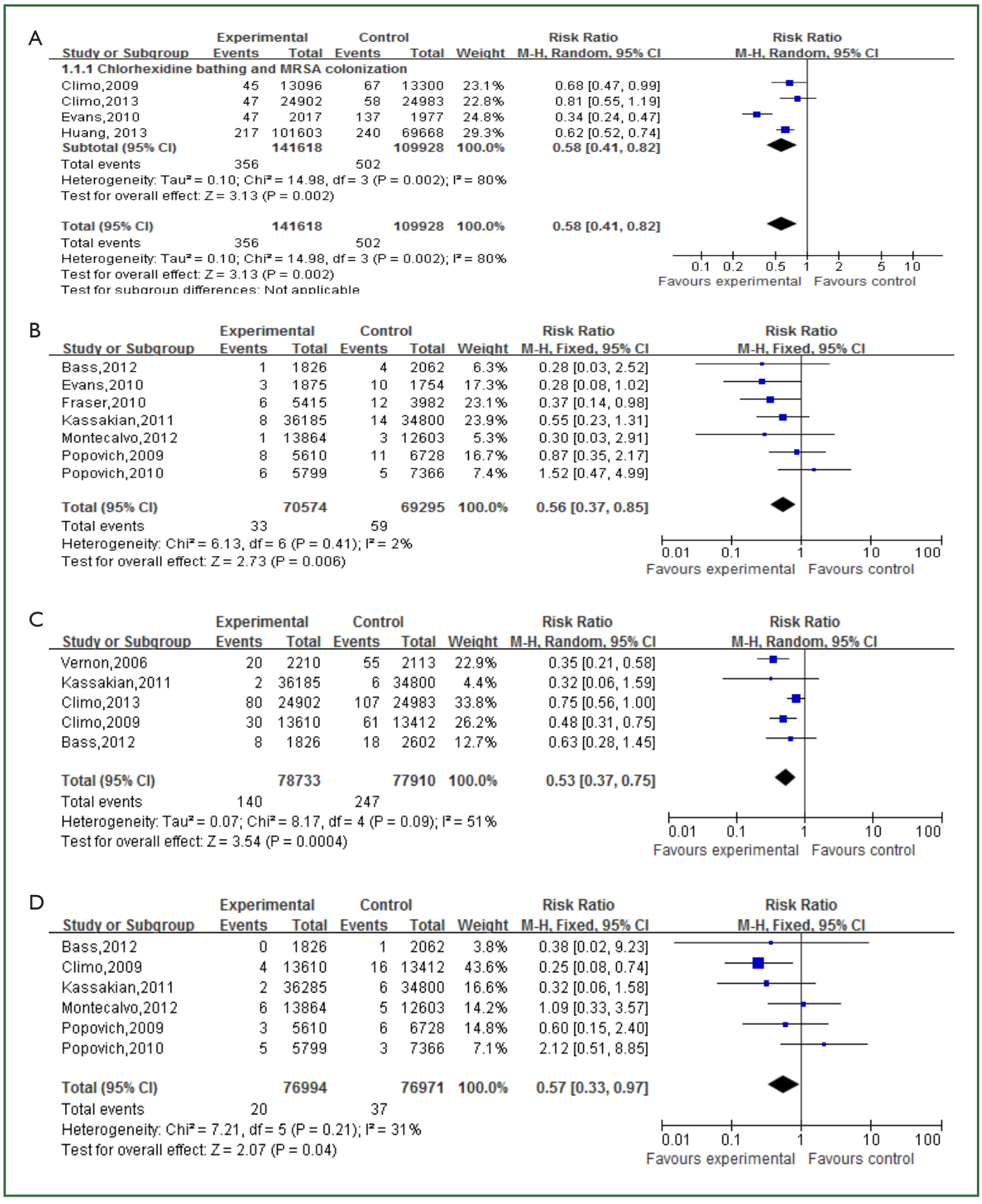

Figure 1. Impact of application with CHG bathing according to relative outcome. A. CHG and MRSA colonization; B. CHG and MRSA infection; C. CHG and VRE colonization; D. CHG and VRE infection.

Table 2. Sub-group analysis of daily using CHG bathing and relative category.

Category	References	Total patient-days		IRR (95% CI)			P	I^2
		Intervention	Control	IRR	Low limit	upper limit		
MRSA VAP	2	7,290	5,736	0.22	0.07	0.64	0.006	0%
MRSA colonization								
ITS*	2	15,113	15,277	0.48	0.24	0.95	0.04	87%
others	2	126,505	94,651	0.65	0.55	0.77	<0.001	36%
MRSA infection								
ICU	5	32,563	32,433	0.58	0.36	0.96	0.03	30%
Non-ICU	2	38,011	36,862	0.49	0.22	1.10	0.58	0%
VRE infection								
ICU	3	25,019	27,506	0.64	0.18	2.21	0.48	64%
Non-ICU	3	51,975	49,465	0.64	0.27	1.54	0.32	0%

*ITS, interrupted time series study.

identified twelve eligible articles including >250,000 patient-days, demonstrating that daily use of CHG bathing was effective in reducing the colonization of nosocomial MRSA, VRE, and significantly decreased the risks of MRSA, VRE infection.

Colonization with MRSA or VRE is a crucial risk factor for healthcare-associated infection. The bacteria can be colonized in multiple sites of the body, such as axillae, anterior naris, inguinal, perineum and so on (23,24). The strategy of decolonization of bacteria limited in single reservoir, such as mupirocin nasal ointment smearing may not enough to eradicate MRSA. Therefore, whole body bathing with CHG may be an important alternative to prevent the multi-sites' colonization (1). Previous studies reported that CHG cleansing resulted in a persistent reduction in density of microbial skin colonization, compared with soap and water bathing (25). Vernon *et al.* found that the daily chlorhexidine cleaning was significantly associated with a decline in the density of VRE on patients' skin, decreases in contamination of healthcare workers' hands and the environment, and a decrease in the incidence of VRE colonization, compared with use of the non-medicated cloths and soap and water (8). Climo *et al.* performed two large multi-center clinical trials (9,10). They consistently revealed that daily chlorhexidine cleaning among ICU patients significantly reduced the acquisition of MRSA and VRE. It is plausible that the lower bacterial densities on the skin of colonized patients by the daily application of CHG bathing may have resulted in decreased rates. In this meta-analysis, we pooled all eligible studies, finding that CHG bathing significantly reduced the acquired MRSA or VRE, strongly suggesting that CHG bathing would result in reduced incidence of MRSA or VRE infection. In this meta-analysis, we proved that CHG bathing was significantly associated with 44% reduced risk of MRSA (Figure 1B) especially for ICU settings (IRR =0.58, 95% CI: 0.36-0.96) (Table 2). Moreover, we also found the incidence of VRE infection would be significantly reduced with the introduction of 2% CHG bathing (Figure 1D). It's plausible that this CHG bathing would reduce whole bacterial burden on patient s' skin that provided a safer environment.

Evens *et al.* performed a retrospective analysis of data collected 6 months before and after institution of CHG bathing protocol, firstly reported that in critically ill trauma patients, who used of the same chlorhexidine washcloths resulted in decreased incidence of VAP (18). Interestingly, in the subgroup analysis, CHG bathing would cut down 78% risk of MRSA VAP (Table 2). And large well-designed random clinical trial was warrant to explore this association.

However, there was no evidence of inducing chlorhexidine resistance in the susceptibility test of bacterial isolates (26). Several previous published articles reported that chlorhexidine resistance was rare among both staphylococci and enterococci with reported minimum inhibitory concentrations (MICs) to chlorhexidine (staphylococci: 0.2-3 mg/L) and (enterococci: 1-6 mg/L) (27-29). There was no any evidence of resistance to chlorhexidine among MRSA and VRE isolates (8,20,30). Remarkably, Batra *et al.* reported that daily chlorhexidine bathing was associated with a highly significant, immediate 70% reduction in acquisition of non-TW MRSA strains (RR =0.3, 95 % CI: 0.19-0.47) whereas shown an increase in acquisition of TW MRSA strains (RR =3.85, 95 % CI: 0.80-18.59). They genotyped the isolations, finding that all TW MRSA strains (sequence type 239) (21 of 21 isolates) and 5% (1 of 21 isolates) of non-TW MRSA strains tested carried the chlorhexidine resistance loci qacA/B. Meanwhile, they also found that in vitro

chlorhexidine minimum bactericidal concentrations (MBC) of TW strains were 3-fold higher than those of non-TW MRSA strains. Both of them could account for the different effects to chlorhexidine between TW MRSA and Non-TW MRSA.

In conclusion, we found that CHG bathing would result in the decreased acquired infection of MRSA or VRE. If this intervention is widely implemented in clinical practice, vigilance for emerging resistance should be required.

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