

Impact of daily bathing with chlorhexidine gluconate on ventilator associated pneumonia in intensive care units: a meta-analysis

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Objective: Ventilator associated pneumonia (VAP) is the most important nosocomial infection in intensive care units (ICUs). Our objective was to assess whether daily bathing with chlorhexidine gluconate (CHG) would significantly result in the reduction of VAP.

Materials and methods: Meta-analysis of randomized controlled trials (RCTs) and quasi-experimental studies were conducted. The setting are medical, surgical, trauma, and combined medical-surgical ICUs. The patients are adult. We searched electronic search engine (PubMed), Embase and the Cochrane Central Register database for all published studies related to the application of daily CHG bathing with VAP risk.

Results: In all, six articles reporting a total of 27,638 ventilator-days met the inclusion criteria; 132 patients in the CHG arm developed a VAP (13,349 ventilator-days), compared with 188 patients in the control arm (14,289 ventilator-days). Daily bathing with CHG was significantly associated with decreased incidence risk of VAP [relative risk (RR): 0.73, 95% confidence interval (CI): 0.57-0.92, $I^2=0\%$]. In the subgroup analysis, we found that daily bathing with 2% CHG impregnated cloths or wipes would reduce the incidence risk of VAP among before-and-after studies (pooled RR: 0.73, 95% CI: 0.57-0.93).

Conclusions: The application of daily bathing with CHG would decrease incidence risk of VAP, which would be an important complementary intervention to barrier precautions.

Keywords: Chlorhexidine; ventilator associated pneumonia (VAP); relative risk (RR)

Submitted Dec 29, 2014. Accepted for publication Mar 26, 2015.

doi: 10.3978/j.issn.2072-1439.2015.04.21

View this article at: <http://dx.doi.org/10.3978/j.issn.2072-1439.2015.04.21>

Introduction

Ventilator associated pneumonia (VAP) represents one of the most important nosocomial infections in critical ill patients with increased longer duration of mechanical ventilation, greater number of intensive care unit (ICU) days, hospital costs, and higher mortality (1,2). Pooled VAP density in adult ICUs in developing countries was 22.9 per 1,000 ventilator-days, at least four times as high as densities reported from the developed countries (3).

“Bundles” are a set of processes of care have been taken to

prevent morbidity of VAP (4), such as semi-recumbent body position (5), hand hygiene, daily sedation vacations (6,7), oral care with chlorhexidine gluconate (CHG) (8,9) and so on. CHG is a classic broad-spectrum antimicrobial activity with a good safety profile against gram-positive and gram-negative bacteria and safety profile (10,11). Recently, there has been a renewed interest in this antiseptic as a crucially complementary measure to prevent acquired central line associated bloodstream infection (CLABSI), surgical site infection (SSI) and antimicrobial-resistant bacteria (12,13) among critical ill patients, suggesting its robust

effects of reducing global but not specific infection rates. Interestingly, Martínez-Reséndez *et al.* revealed the potential role in preventing VAP (14). However, the results remain conflicting rather than conclusive (12,15). Therefore, this meta-analysis was performed to investigate the association between daily bathing with CHG and incidence of VAP.

Materials and methods

The whole procedures of this meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines (16).

Search strategy

An electronic search engine (PubMed), Embase and the Cochrane Central Register database were searched separately up to June 1 2014, for all eligible studies by two different reviewers (W Chen and H Li). An electronic search was performed using the following terms: “chlorhexidine”, “Ventilator associated pneumonia”, “VAP”, “chlorhexidine bath*”, “chlorhexidine washcloth*”. 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 three independent investigators (W Chen, Q Cao and W Zhang) reached consistency on all data sets for this manuscript.

Eligibility criteria

All clinical randomized controlled trials (RCTs), quasi-experimental studies that investigated the efficacy of daily using CHG bathing to prevent the morbidity of VAP among critical ill adult patients in ICU settings were eligible in this study. Studies which have been published in full-articles, and reported the number of intervention and control were included in the latter analysis. CHG bathing which was not applied as the primary part of intervention was excluded (17,18).

Data extraction

Both authors (S Li and H 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.

Quality assessment

A key feature of the Grades of Recommendations Assessment Development and Evaluation (GRADE) method developed by the Cochrane review group was used to assess the quality rather than individual study (19,20). Four categories of quality ratings in GRADE—“high”, “moderate”, “low” and “very low” on the representativeness of risks of bias, inconsistency, indirectness, imprecision and publication bias (*Table 1*) (23). Two authors (W Chen and S Li) assessed the quality of evidence independently following GRADE guidance (19). Disagreement between authors was resolved by discussion and finally judged by the third reviewer (W Zhang).

Statistical analysis

If the between-study heterogeneity was found, a random-effect model was conducted. If I^2 was $\leq 50\%$, 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 (15). Publication bias was evaluated by the linear regression asymmetry test by Egger *et al.* (24). All data were analyzed in Review Manager (v.5.1.6; Oxford, England) and STATA11.0 (Stata-Corp, College Station, Tex).

Results

Figure 1 summarizes the diagram of selection process. From an initial 180 potentially relevant articles, we included six in our final analysis with two RCTs and four quasi-experimental studies (*Figure 1*).

Table 1 shows the methodological quality of included trials following the GRADE method (*Table 1*). All of these available studies were conducted in ICU settings (intervention/control: 13,349 ventilator days/14,289 ventilator days) (14,23-27) (*Table 2*).

We found that daily bathing with CHG would decreased 27% risk of VAP in ICU settings [relative risk (RR): 0.73, 95% confidence interval (CI): 0.59-0.92, $I^2=0\%$] (*Figure 2*). *Figure 2* and *Table 3* summarize the subgroup analysis in this review. We found that daily bathing with CHG would lower incidence risk of VAP especially in subgroup of 2% CHG impregnated cloths or wipes (14,22,25-27) (RR: 0.73, 95% CI: 0.57-0.93) and before-and-after studies (14,25-27) (RR: 0.70, 95% CI: 0.54-0.90) (*Table 3*). Meanwhile, daily bathing with CHG may also decrease the incidence risk of VAP for two RCT studies, although no significant

Table 1 Quality of the evidence for daily bathing with CHG for preventing VAP

No. of studies	Design	Quality assessment					No. of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	RR (95% CI)	Absolute		
4	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Reduced effect for RR >>1 or RR <<1 ¹	92/8,792 (1%)	145/10,253 (1.4%)	RR 0.70 (0.54-0.90)	4 fewer per 1,000 (from 1 fewer to 7 fewer)	Moderate	Critical
2	Randomized trials	Serious ² inconsistency	No serious inconsistency	Serious ³ inconsistency	No serious imprecision	None	40/4,557 (0.9%)	43/4,036 (1.1%)	RR 0.85 (0.55-1.31)	2 fewer per 1,000 (from 5 fewer to 3 more)	Low	Critical

¹, Lacking of standardization in intervention protocol would be a plausible confounding related to the effect; ², just one RCT study used allocation concealment (21); ³, one RCT study selected "SDD + daily CHG bathing" as intervention (21) whereas the other RCT study just chose "daily CHG bathing" (22). CHG, chlorhexidine gluconate; VAP, ventilator associated pneumonia; RR, relative risk; CI, confidence interval; SDD, selective digestive decontamination.

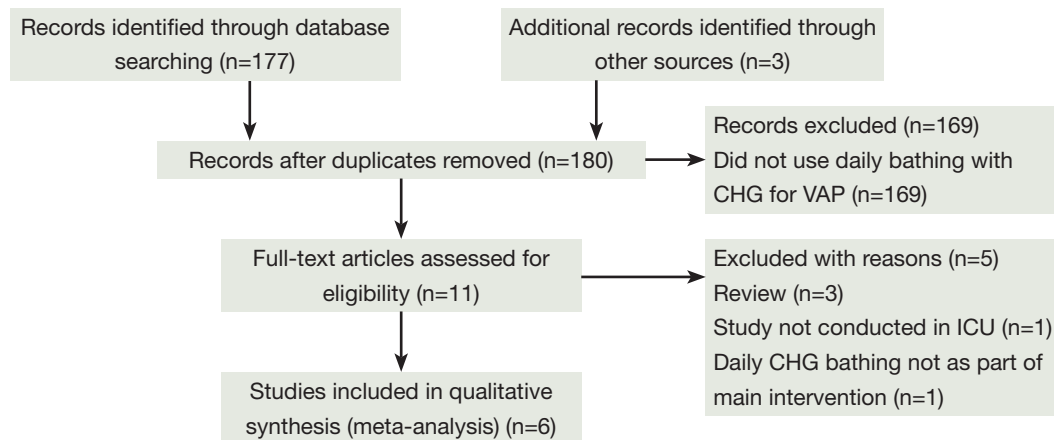


Figure 1 Flow chart of the study selection process: adapted with permission from the PRISMA flow diagram. CHG, chlorhexidine gluconate; VAP, ventilator associated pneumonia; ICU, intensive care unit.

Table 2 Characteristics of included studies in this meta-analysis

Reference	Publication year	Study design	Setting	CHG intervention	Co-interventions or control group	Duration (months)
Camus <i>et al.</i> (21)	2005	RCT	MICU	Nasal mupirocin with 4% CHG body wash daily	Only placebo	30
Bleasdale <i>et al.</i> (22)	2007	Two-arm cross-over trial	MICU	Daily 2% CHG body wash daily with impregnated cloths	Soap and water bathing	12
Popovich <i>et al.</i> (25)	2009	Before-and-after study	MICU	Daily bath with 2% CHG washcloths	Soap and water bathing	24
Popovich <i>et al.</i> (26)	2010	Before-and-after study	SICU	Daily bath with 2% CHG washcloths	Soap and water bathing	24
Evans <i>et al.</i> (27)	2010	Before-and-after study	TICU	Daily bath with 2% CHG washcloths	Disposable washcloths without CHG	12
Martínez-Reséndez <i>et al.</i> (14)	2014	Before-and-after study	MICU and SICU	Daily with 2% CHG-impregnated wipes and hair washed with no-rinse 0.12% CHG foam shampoo	Soap and water bathing	18

CHG, chlorhexidine gluconate; RCT, randomized controlled trial; MICU, medical intensive care unit; SICU, surgical intensive care unit; TICU, trauma intensive care unit.

association was found (21,22) (RR: 0.85, 95% CI: 0.55-1.31) and longer study duration (>20 months) (21,25,26) (RR: 0.80, 95% CI: 0.57-1.11) (Table 3).

A sensitivity analysis by omitting individual study was performed in this meta-analysis to assess the impact of each individual study on the pooled RRs. We found the pooled RRs would not be significantly affected by omitting one multiple-center, placebo-controlled, randomized, double-blind study (21) (RR: 0.73, 95% CI: 0.57-0.93). However, one quasi-experimental study played an important role in

the pooled RRs (Figure 3) (remained RR: 0.81, 95% CI: 0.63-1.05) (14).

The funnel plot is used to investigate the publication bias for VAP. In our meta-analysis the funnel is asymmetric, suggesting existed publication bias (Figure 4).

Discussion

The impact of daily bathing with CHG to prevent health-care associated infection (HAI), such as CLABSI (17),

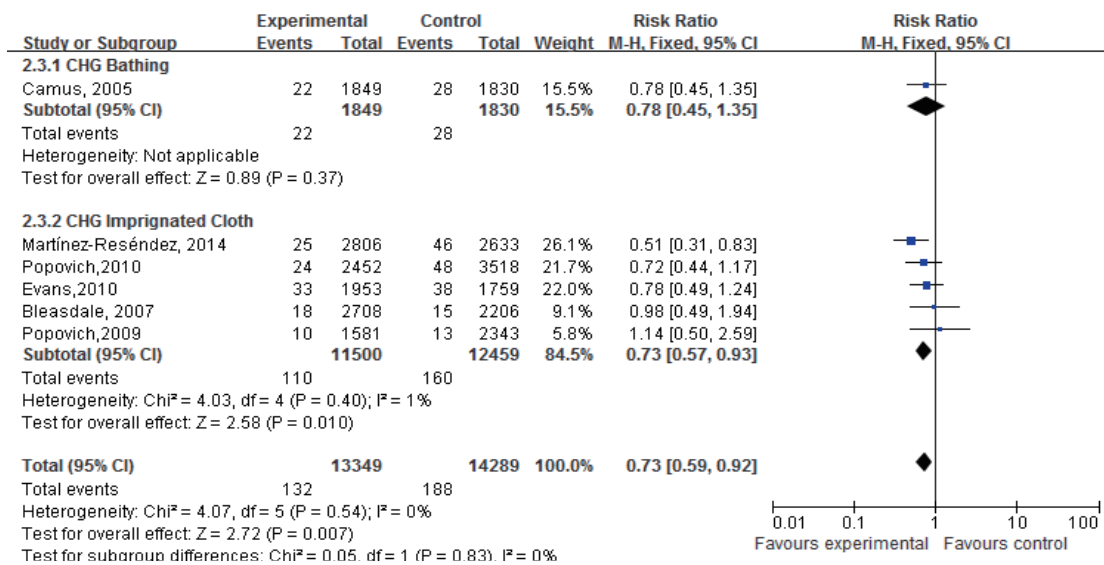


Figure 2 Risk of VAP with CHG bathing and comparator, using ventilator-days in the analysis. VAP, ventilator associated pneumonia; CHG, chlorhexidine gluconate.

Table 3 Subgroup analyses of daily CHG bathing on incidence of VAP

Measurement	No. of study	Intervention		Control		RR (95% CI) ^a
		Events (N=132)	Total ventilator days (N=13,349)	Events (N=188)	Total ventilator days (N=14,289)	
Study design						
Before-and-after study	4	92	8,792	145	10,253	0.70 (0.54-0.90)
RCT	2	40	4,557	43	4,036	0.85 (0.55-1.31)
CHG concentration						
2% impregnated cloths or wipes	5	110	11,500	160	12,459	0.73 (0.57-0.93)
4% liquid	1	22	1,849	28	1,830	0.78 (0.45-1.35)
Study settings						
MICU	3	50	6,138	56	6,379	0.91 (0.62-1.33)
Others	3	82	7,211	132	7,910	0.66 (0.50-0.87)
Duration of study (months)^b						
>20	3	56	5,882	89	7,691	0.80 (0.57-1.11)
≤0	3	76	7,467	99	6,598	0.69 (0.51-0.93)

^a, fixed model; ^b, mean of study duration; $\alpha=0.05$. CHG, chlorhexidine gluconate; VAP, ventilator associated pneumonia; RR, relative risk; CI, confidence interval; RCT, randomized controlled trial; MICU, medical intensive care unit.

SSI (15), multi-drug resistant organisms (MDROs) acquisition (12) and so on, has been well investigated in some clinical trials. However, there were limited studies to explore the association between daily bathing with CHG and incidence risk of VAP among critical ill patients undergoing mechanical ventilation. In this meta-analysis, we reviewed the published epidemiological reports on the

role of daily CHG bathing which would low the incidence risk of VAP (RR: 0.73, 95% CI: 0.59-0.92). Meanwhile, we found that daily bathing with 2% CHG impregnated cloth or wipes would also decrease VAP risk among critical ill patients (RR: 0.73, 95% CI: 0.57-0.93). Our findings suggest that daily bathing with CHG would reduce the risk of VAP in ICU settings.

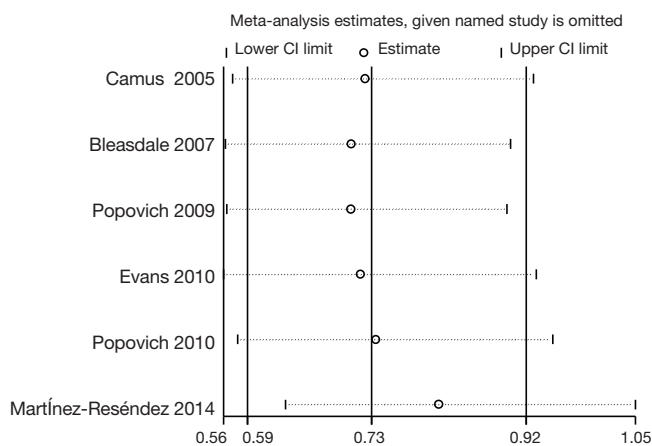


Figure 3 Sensitivity analysis of the association between daily bathing with CHG and VAP. CHG, chlorhexidine gluconate; VAP, ventilator associated pneumonia; CI, confidence interval.

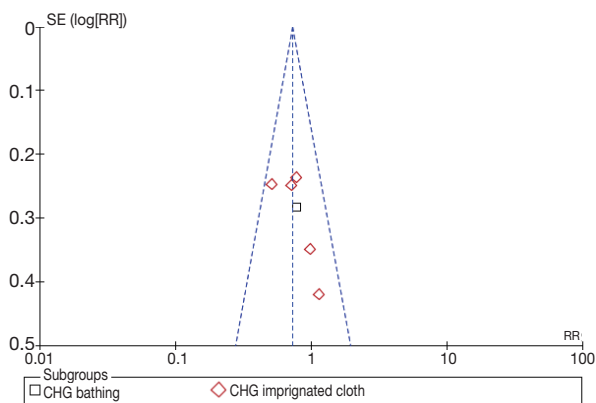


Figure 4 Funnel plot for publication bias of the association between daily bathing with CHG and risk of VAP. CHG, chlorhexidine gluconate; VAP, ventilator associated pneumonia; RR, relative risk.

The precise mechanism to explain the association between daily bathing with CHG and VAP reduction remains unknown. In 2005, Vernon *et al.* (28) performed a prospective single-arm clinical trial in a medical ICU. A total of 1,787 patients were bathed or cleansed and assessed for acquisition of Vancomycin-Resistant Enterococcus (VRE). They found that cleansing patients with chlorhexidine saturated cloths significantly lowered VRE contamination of patients' skin, the environment (RR: 0.3, 95% CI: 0.2-0.5) and health care workers' hands (RR: 0.6, 95% CI: 0.4-0.8) and to decrease patient acquisition of VRE (RR: 0.3, 95% CI: 0.2-0.5) (28), suggesting the great role of daily CHG bathing in decreasing the "colonization pressure" which was a momentous risk factor for HAIs (29),

and in reducing the risk of subsequent infection from manipulation of devices associated with the patient (14), interrupting the cross-infection in ICU settings. Above evidences may account for the potential role of daily CHG bathing in preventing the morbidity of VAP to some extent, which was consistent with the findings of our meta-analysis.

However, some important concerns merit more consideration and caution. First of all, the overall effect was more significant in before-and-after studies compared with the pooled effect from two RCT studies (Table 3). Moreover, one well designed RCT did significantly affect the pooled RRs (21), though the pooled RR would be affected by another quasi-experimental study (14) in sensitivity analysis. Our findings suggested that further well-designed studies should be performed to clarify the benefit of daily bathing with CHG for preventing VAP. In this review, GRADE method was also applied to assess the quality of this study. The benefit between the daily bathing with CHG and acquired VAP was found in observational studies and no significant heterogeneity was tested, the quality of evidence was rated "moderate" according to the GRADE system (Table 1). Two eligible RCT studies (21,22) were pooled in this meta-analysis, and we found that daily bathing with CHG might be associated with lower risk of VAP (RR: 0.85, 95% CI: 0.55-1.31), though the test for overall effect was not significant ($Z=0.73$, $P=0.46$). Recently, although daily bathing with CHG shown some benefits in preventing nosocomial infections regardless of CHG bathing is done using CHG impregnated cloths or a liquid preparation, the standard intervention protocol was still not established. In additional, conceal allocation was not available in one RCT (22). Eventually, we degraded the quality of the evidence and rated "low" according to the GRADE system (Table 1). Nevertheless, the crucial impact of the daily bathing with CHG in preventing VAP should not be neglected by infection preventionists (IPs) or health-care workers (HCWs).

In conclusion, existing data—even if mainly obtained from quasi-experimental studies—support the practice of daily bathing with CHG for reducing VAP for critical ill patients. Additional well-designed large studies were required for the validation of this association.

Acknowledgements

Funding: This study was supported by grants from Jiangsu Province Projects of Preventive Medicine Research (Y2013044) and the Priority Academic Program

Development of Jiangsu Higher Education Institutions (PAPD) and JX10231801.

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Chen W, Cao Q, Li S, Li H, Zhang W. Impact of daily bathing with chlorhexidine gluconate on ventilator associated pneumonia in intensive care units: a meta-analysis. *J Thorac Dis* 2015;7(4):746-753. doi: 10.3978/j.issn.2072-1439.2015.04.21