Chlorhexidine-based body washing for colonization and infection of methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus: an updated meta-analysis

Guibao Xiao1,∗
Zhu Chen2,∗
Xiaojue Lv1
1Center of Infectious Diseases, West China Hospital of Sichuan University, Chengdu, Sichuan Province, People’s Republic of China; 2Public Health Clinic Center of Chengdu, Chengdu, Sichuan Province, People’s Republic of China
∗These authors contributed equally to this work

Background: The effects of chlorhexidine-based body washing (CHW) on health care-associated infections have been reported in numerous studies, while their findings remain conflicting. This study aims to update the evidence for the effects of CHW on the risk of colonization or infection with hospital-acquired methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE).

Methods: Two independent authors searched PubMed, Embase, and Cochrane Library from inception through February 2018. We selected all observational studies or clinical trials for the effect of CHW on the risk of colonization and infection with hospital-acquired MRSA or VRE. Random-effects models were applied to calculate summary incidence rate ratios (IRRs) for the related associations.

Results: Of 140 records identified, we obtained data from 17 relevant articles for meta-analysis. Compared with patients without antiseptic bathing, patients with CHW had a significantly lower risk of MRSA colonization (IRR 0.61, 95% CI 0.48–0.77) and VRE colonization (IRR 0.58, 95% CI 0.42–0.80). Similarly, we also noted that patients with CHW had a significantly lower risk of MRSA infection (IRR 0.65, 95% CI 0.52–0.81). However, no significantly lower risk of VRE infection (IRR 0.61, 95% CI 0.30–1.25) was noted in patients with CHW. Sensitivity analyses or trim-and-fill method confirmed the robustness of the findings.

Conclusion: Current evidence supports that patients with CHW had a significantly lower risk of MRSA or VRE colonization and a lower risk of MRSA infection. More evidence should be accumulated to reinforce these findings, especially on the effect of CHW on the risk of VRE infection.

Keywords: chlorhexidine, methicillin-resistant Staphylococcus aureus, MRSA, vancomycin-resistant Enterococcus, VRE, bathing, meta-analysis

Introduction
Over the past few decades, methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) have become two of the commonest causes of health care-associated infections (HAIs), occurring mostly among individuals with diagnosed health care-associated status such as hospitalization, surgical interventions (eg, central venous catheters), and dialysis. It is estimated that more than 100,000 HAIs occur in USA annually.1 These two kinds of infections frequently lead to increased length of hospital stay, patient morbidity and mortality, and substantial cost burden to the health care system.2
Chlorhexidine gluconate (CHG) has a broad-spectrum antibacterial activity, especially for Gram-positive bacteria such as MRSA and VRE. It has been reported that CHG can reduce the overall bioburden of multidrug-resistant Gram-positive organisms, thus reducing the incidence of HAIs and transmissions.\(^3\)\(^\text{4}\)\(^\text{5}\) Several epidemiological studies showed that daily use of CHG could reduce the rate of MRSA or VRE acquisition and bloodstream infections associated with these organisms in the intensive care units (ICUs) and general medicine units.\(^9\) However, several other studies have reported neutral findings that do not support using daily CHG bathing.\(^10\)\(^\text{11}\) There is also a lack of randomized clinical trials to provide direct evidence for the effect of CHG bathing on the risk of MRSA and VRE colonization or infection. With these dubious results, we aimed to reevaluate the existing uncertain evidence regarding this issue by updating the systematic review and meta-analysis of all published data.

**Methods**

**Literature search**

This meta-analysis was conducted under the guidance of a 27-item checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). We searched PubMed, Embase, and the Cochrane Library on February 1, 2018. The following words were searched as keywords and text words: (shower* OR bath* OR wash* OR cleans*) AND (chlorhexidine OR chlorohex* OR eludril* OR cordoryl* OR Periochip* OR CHX OR nolvasan* OR sebidin* OR tubulicid* OR Cervitec* OR Chlorzin* OR hibitane*) AND ("methicillin-resistant* OR meticillin-resistant* OR MRSA OR EMRSA OR MDRO" OR “vancomycin resistant enterococcus* OR VRE”). We did not restrict language or publication type. Gray literature including abstracts was also included. The bibliographies of relevant articles were manually searched for additional references that may have been missed in the database searches. The search strategies for the three databases are given in the “Supplementary materials”.

**Study selection and eligibility criteria**

Eligible studies were included if they satisfied the following inclusion criteria: 1) studies investigating the associations between the use of chlorhexidine-based body washing (CHW) and the risk of colonization or infection with hospital-acquired MRSA or VRE; 2) cluster-randomized trial, before-and-after study, quasi-experimental study, interrupted time series study, and sequential group single-arm clinical trial were applied as study designs; and 3) studies or trials reported incidence rate ratios (IRRs) and their 95% CIs or related data for the calculation of their IRRs. Studies were excluded if they did not satisfy the inclusion criteria. Two investigators (G.X. and Z.C.) independently conducted literature search and selection. We selected the largest studies with the most comprehensive data or analyses when overlapping studies were included.

**Data extraction**

Data extraction was carried out by two investigators (G.X. and Z.C.), independently using a Microsoft excel spreadsheet (2010 professional edition; Microsoft Corporation, Redmond, WA, USA). The extracted data were then cross-checked and determined by a senior investigator (X.L.). Data extracted included first author, publication year, study design, patient selection, study setting, major intervention, and control intervention. The corresponding authors of original studies were consulted for missing information if necessary.

**Study bias assessment**

Two authors (G.X. and Z.C.) independently assessed study bias using the Cochrane Risk of Bias Tool. The study was scored as low, unclear, or high risk of bias for randomized controlled trials based on random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete data, selective reporting, and others.\(^12\) For nonrandomized studies, we used the Newcastle–Ottawa Scale (NOS) to assess the methodological bias, encompassing participant selection, comparability, and outcome assessment.\(^13\) A total of nine stars were assigned for each study with a score of ≥6 representing high quality.

**Statistical analyses**

IRR was set as the effect size measure. The summary effect size was pooled using a random-effects model because we considered that the different patients included in different regions during different periods with different study designs were very likely to have substantial heterogeneity. The Q test was applied to assess the existence of heterogeneity and F statistic to quantify the percentage of between-study heterogeneity, with a value being <0.10 considered as statistically significant.\(^14\) Funnel plot, Begg’s test, and Egger’s test were used to judge for publication bias.\(^15\)\(^\text{16}\) Furthermore, we also used the Duvall and Tweedle trim-and-fill model to adjust risk estimates,\(^17\) which imputes effect sizes until the error distribution closely approximates normality; such a procedure provides a more unbiased estimate of the effect size than does the observed estimate. All meta-analyses were conducted and figures were generated using Stata version 12.0 (StataCorp LP, College Station, TX, USA).
Results

Literature search

The database literature search yielded a total of 146 citations, and after removal of duplicates, 132 individual citations remained. After screening by title or abstract, 31 articles were identified for full text review. Finally, a total of 17 articles met the inclusion criteria. A manual reference search of included articles yielded no additional article that met inclusion criteria (Figure 1). Four articles identified in the original search were excluded because the data were insufficient for meta-analysis. We contacted the corresponding authors to request the original data; however, none of the primary data were available for meta-analysis.

Seventeen individual articles (four cluster-randomized trials, four quasi-experimental studies, three before–after interventional studies and six nonrandomized controlled trials or observational studies) were included in this systematic review and meta-analysis. In total, 467,484 participants were analyzed, of whom 247,605 received intervention with CHW and 219,879 were not exposed to CHW intervention. Eight studies reported data from ICUs, and the others provided data from patients in mixed departments. Ten studies were conducted in multicentered institutions, and seven studies were carried out on single hospital sites. Details of the included studies are presented in Table 1. Generally, most of the nonrandomized trials had a low risk of bias with the NOS score ranging from 7 to 9, while most of the randomized trials have a high risk of bias, especially in the aspects of blinding method of participants and outcome assessment (refer the “Supplementary materials”).

Results of meta-analyses and publication bias assessment

CHW and MRSA colonization

Nine studies investigated the association between CHW and MRSA colonization, which included 438 events in the

Figure 1 Flow diagram of articles selected for inclusion in the meta-analysis.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>Patient selection</th>
<th>Study setting</th>
<th>Major intervention</th>
<th>Control intervention</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowe et al[18]</td>
<td>2017</td>
<td>Prospective crossover study</td>
<td>Patients from four inpatient medical units (25 beds each) from May 1, 2014 to August 10, 2015</td>
<td>Four medical inpatient units in an urban, academic Canadian hospital</td>
<td>Daily CHW over a 7-month period, including a 1-month wash-in phase</td>
<td>Daily bathing with nonmedicated soap and water</td>
<td>Rates of hospital-associated MRSA and VRE colonization or infection</td>
</tr>
<tr>
<td>Amirov et al[19]</td>
<td>2017</td>
<td>Cluster-randomized, open-label, controlled trial</td>
<td>Chronic care patients</td>
<td>Three hospital units</td>
<td>Daily CHW</td>
<td>Daily nonantiseptic bathing</td>
<td>MRSA incidence</td>
</tr>
<tr>
<td>Kim et al[20]</td>
<td>2016</td>
<td>Interrupted time series study</td>
<td>Patients admitted to the ICU for &gt;48 hours</td>
<td>A 829-bed tertiary care hospital in Hallym University Sacred Heart Hospital</td>
<td>16-month CHW between August 2013 and November 2014</td>
<td>14-month without bathing with chlorhexidine between June 2012 and July 2013</td>
<td>Rates for MRSA acquisition</td>
</tr>
<tr>
<td>Millar et al[21]</td>
<td>2015</td>
<td>Three-group, field-based, cluster-randomized trial</td>
<td>US Army soldiers 17 to 42 years of age, ethnically diverse, and in generally good physical condition</td>
<td>A US army soldier hospital</td>
<td>CHW with a wash cloth after using their personal soap during an additional once-weekly shower</td>
<td>Standard, enhanced standard body wash without using chlorhexidine</td>
<td>MRSA skin and soft-tissue infections' colonization prevalence</td>
</tr>
<tr>
<td>Colling et al[22]</td>
<td>2015</td>
<td>Multicenter, retrospective, controlled study</td>
<td>Patients undergoing hip and knee arthroplasties at two affiliated hospitals in the Fairview Hospital System between January 2010 and June 2012</td>
<td>An 874-bed hospital and a community hospital</td>
<td>Having preoperative CHG shower or bath policy in place</td>
<td>Having no antiseptic shower or bath</td>
<td>Rate of S. aureus and MRSA surgical site infections</td>
</tr>
<tr>
<td>Climo et al[6]</td>
<td>2013</td>
<td>A multicenter, cluster-randomized, nonblinded crossover trial</td>
<td>Patients in nine ICUs and bone marrow transplantation units in six hospitals</td>
<td>Nine ICUs and bone marrow transplantation units in six hospitals in USA</td>
<td>CHW-impregnated washcloths for a 6-month period, exchanged for the alternate product during the subsequent 6 months</td>
<td>Bathing with non- antimicrobial washcloths for a 6-month period, exchanged for the alternate product during the subsequent 6 months</td>
<td>The incidence rates of acquisition of hospital-acquired BSIs and acquisition of multidrug-resistant organisms</td>
</tr>
<tr>
<td>Huang et al[23]</td>
<td>2013</td>
<td>Three-group, cluster-randomized trial</td>
<td>Patients in adult ICUs in Hospital Corporation of America hospitals</td>
<td>45 hospitals in 16 states with a total of 74 adult ICUs</td>
<td>Bathing with 2% CHG washcloths</td>
<td>Bathing without 2% CHG washcloths</td>
<td>MRSA BSI</td>
</tr>
<tr>
<td>Bass et al[11]</td>
<td>2013</td>
<td>Before-and-after study</td>
<td>Hematology/oncology patients at the Alfred Hospital</td>
<td>A 34-bed major tertiary teaching hospital in Melbourne, Australia</td>
<td>Bathing with 2% CHG-impregnated washcloths</td>
<td>Bathing with routine soap and water</td>
<td>Incidence rate of VRE colonization</td>
</tr>
<tr>
<td>Montecalvo et al.24</td>
<td>2012</td>
<td>Prospective, three-phase, multiple-hospital, non-randomized trial</td>
<td>Patients from a tertiary care hospital and four community hospitals in Westchester County, New York</td>
<td>A medical ICU and the respiratory care unit of a tertiary care hospital and the medical-surgical ICUs of 4 community hospitals</td>
<td>Intervention phase: patients were bathed with 2% CHG cloths, with the number of baths administered and skin tolerability assessed. Postintervention phase: CHG bathing was continued but without oversight by research personnel.</td>
<td>Preintervention phase: patients were bathed with soap and water or nonmedicated bathing cloths</td>
<td>Hospital-acquired CVC-associated BSI rates</td>
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<td>-------------------------------------------------</td>
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<tr>
<td>Kassakian et al.9</td>
<td>2011</td>
<td>Quasi-experimental study</td>
<td>Patients at four general medicine units, with a total of 94 beds, at a 719-bed academic tertiary care facility in Providence, RI</td>
<td>Four general medicine units at a 719-bed academic tertiary care center</td>
<td>Daily bathing with chlorhexidine-impregnated cloths</td>
<td>Daily bathing with soap and water</td>
<td>Incidence of MRSA and VRE HAIs</td>
</tr>
<tr>
<td>Evans et al.26</td>
<td>2010</td>
<td>Retrospective before-and-after study design</td>
<td>Severely injured patients in a 413-bed level I trauma center that serves patients from four states</td>
<td>Daily chlorhexidine bathing during the 6-month intervention</td>
<td>Bathed without chlorhexidine prior to the intervention</td>
<td>HAIs and the rate of isolation of multidrug-resistant organisms</td>
<td></td>
</tr>
<tr>
<td>Fraser et al.25</td>
<td>2010</td>
<td>Retrospective quasi-experimental study</td>
<td>Patients in the medical ICU</td>
<td>Daily CHG baths</td>
<td>Daily body wash without CHG</td>
<td>The incidence of hospital-acquired BSI, the incidence of ventilator-associated pneumonia</td>
<td></td>
</tr>
<tr>
<td>Popovich et al.10</td>
<td>2010</td>
<td>Quasi-experimental, pre–post study</td>
<td>Patients in the 30-bed surgical ICU at Rush University Medical Center, a 720-bed tertiary care teaching hospital in Chicago</td>
<td>A medical ICU at Rush University Medical Center and a tertiary care teaching hospital in Cleveland, Ohio</td>
<td>Substituted skin cleansing with no rinse, 2% CHG-impregnated cloths</td>
<td>Soap and water bathing</td>
<td>ICU-acquired CLABSI; blood culture contamination and other ICU-acquired nosocomial infection</td>
</tr>
<tr>
<td>Climo et al.28</td>
<td>2009</td>
<td>Multicenter, before–after interventional study</td>
<td>Patients from six ICUs at four academic centers</td>
<td>Six ICUs at four major tertiary care referral hospitals in USA</td>
<td>Daily bathing with a chlorhexidine-containing solution</td>
<td>Soap and water bathing</td>
<td>Incidence of MRSA and VRE colonization and BSI</td>
</tr>
<tr>
<td>Popovich et al.27</td>
<td>2009</td>
<td>Quasi-experimental, pre–post study</td>
<td>Patients in the 21-bed medical ICU at Rush University Medical Center, a 720-bed tertiary care teaching hospital in Chicago</td>
<td>A medical ICU at Rush University Medical Center and a tertiary care teaching hospital in Chicago</td>
<td>Substituted skin cleansing with no rinse, 2% CHG-impregnated cloths</td>
<td>Skin cleansing with soap and water</td>
<td>Medical ICU-acquired CVC-associated BSI, blood culture contamination, and other medical ICU-acquired nosocomial infection</td>
</tr>
<tr>
<td>Ridenour et al.29</td>
<td>2007</td>
<td>Interrupted time series study</td>
<td>Patients in a 427-bed tertiary care Veterans Affairs hospital</td>
<td>A medical-coronary ICU</td>
<td>Chlorhexidine bathing</td>
<td>Bathing without chlorhexidine</td>
<td>The incidence of MRSA colonization and infection</td>
</tr>
<tr>
<td>Vernon et al.30</td>
<td>2006</td>
<td>Prospective, sequential group, single-arm clinical trial</td>
<td>Patients in a 21-bed medical ICU at a 720-bed hospital in Chicago</td>
<td>A medical ICU at a 720-bed hospital in Chicago</td>
<td>Bath with 2% CHG washcloths</td>
<td>Soap and water bathing</td>
<td>Incidence of VRE acquisition</td>
</tr>
</tbody>
</table>

Abbreviations: BSI, bloodstream infections; CHG, chlorhexidine; CHw, chlorhexidine-based body washing; CLABSI, central line-associated bloodstream infections; CVC, central venous catheter; HAIs, health care-associated infections; ICU, intensive care unit; MRSA, methicillin-resistant Staphylococcus aureus; S. aureus, Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus.
intervention group and 660 events in the control group among 322,053 participants. Meta-analysis showed that the summary IRR was 0.61 (95% CI 0.48–0.77, P=60.9%, P<0.001 for heterogeneity; Figure 2A). There was no evidence of publication bias using the Begg’s (P=0.917) or Egger’s test (P=0.817). The results did not change after using the trim-and-fill method when no missing studies were added (Table 2).

### CHW and MRSA infection

Ten studies investigated the association between CHW and MRSA infection, which included 137 events in the intervention group and 193 events in the control group among 370,422 participants. Summary estimates showed that the pooled IRR was 0.65 (95% CI 0.52–0.81, P=0%, P=0.723 for heterogeneity; Figure 2B). There was no evidence of

#### Table 2 Results of meta-analysis for the effects of CHW on the risk of MRSA colonization or infection and VRE colonization or infection; analyses of the publication bias with different models

<table>
<thead>
<tr>
<th>Variable</th>
<th>No of studies</th>
<th>IRR (95% CI)</th>
<th>P</th>
<th>I2, Phet</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHW and MRSA colonization</td>
<td>9</td>
<td>0.61 (0.48–0.77)</td>
<td>&lt;0.001</td>
<td>60.9, 0.009</td>
</tr>
<tr>
<td>CHW and MRSA infection</td>
<td>10</td>
<td>0.65 (0.52–0.81)</td>
<td>&lt;0.001</td>
<td>0.0, 0.723</td>
</tr>
<tr>
<td>CHW and VRE colonization</td>
<td>8</td>
<td>0.58 (0.42–0.80)</td>
<td>0.001</td>
<td>53.8, 0.034</td>
</tr>
<tr>
<td>CHW and VRE infection</td>
<td>6</td>
<td>0.61 (0.30–1.25)</td>
<td>0.176</td>
<td>30.6, 0.206</td>
</tr>
</tbody>
</table>

**Notes:** Fill, number of studies added by trim-and-fill method; het, heterogeneity; T&F, result of trimmed and filled analysis, using assumption of random effects.

**Abbreviations:** CHW, chlorhexidine-based body washing; het, heterogeneity; IRR, incidence rate ratio; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus.

**Figure 2** Forest plots comparing the effects of CHW on the risk of (A) VRE colonization, (B) MRSA infection, (C) VRE colonization, and (D) VRE infection with those of the routine intervention.

**Note:** Weights are from random-effects analysis.

**Abbreviations:** CHW, chlorhexidine-based body washing; IRR, incidence rate ratio; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus.
publication bias using the Begg’s test \( (P=0.592) \) or Egger’s test \( (P=0.896) \). The results did not change after using the trim-and-fill method when no missing studies were added (Table 2).

CHW and VRE colonization

Eight studies investigated the association between CHW and VRE colonization, which involved 195 events in the intervention group and 296 events in the control group among 201,556 participants. Meta-analysis showed that the pooled IRR was 0.58 (95% CI 0.42–0.80, \( F=53.8\% \), \( P=0.034 \) for heterogeneity; Figure 2C). There was no evidence of publication bias using the Begg’s test \( (P=1.000) \) or Egger’s test \( (P=0.617) \). The results did not change after using the trim-and-fill method when no missing studies were added (Table 2).

CHW and VRE infection

Six studies investigated the association between CHW and VRE infection, which included 20 events in the intervention group and 37 events in the control group among 153,965 participants. Summary estimates showed that the pooled IRR was 0.61 (95% CI 0.30–1.25, \( I^2=30.6\% \), \( P=0.206 \) for heterogeneity; Figure 2D). There was no evidence of publication bias using the Begg’s test \( (P=0.707) \) or Egger’s test \( (P=0.983) \). The results did not change after using the trim-and-fill method when no missing studies were added (Table 2).

Sensitivity analyses

Sensitivity analyses by excluding one study at a time from each analysis indicated that all the four meta-analysis results seemed to be robust to the influence of individual studies (Figure 3). The results were also not substantially altered when combining studies with the same study design (data not shown).

Discussion

In this meta-analysis of nonrandomized controlled studies, moderate to strong decreases in the risk of IRR of MRSA colonization, VRE colonization, and MRSA infection for individuals with CHW were observed. Although the result for VRE infection was not significant in the meta-analysis, the association appeared to have similar trend with MRSA infection.

Our findings are consistent with five previous meta-analyses of CHW and risk of HAIs\(^{31-35} \) but included a much larger sample size, more focused analyses on the two HAIs including MRSA and VRE, sensitivity and trim-and-fill method analyses, and analyses of incidence rate ratios. To our knowledge, this is the largest meta-analysis to comprehensively summarize results for the relationship between CHW and MRSA and VRE infections, not just focused on ICU patients. The null association for VRE infection might be because of the few studies involved in this outcome subset with a limited sample size, which should be further investigated.

Figure 3 Sensitivity analyses for the effects of CHW on the risk of (A) MRSA colonization, (B) MRSA infection, (C) VRE colonization, (D) VRE infection.

Abbreviations: CHW, chlorhexidine-based body washing; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus.
This meta-analysis has several strengths. First, it is strengthened by applying a comprehensive search strategy, making literature screening and eligibility criteria rigorous, and reporting the findings transparently. Second, the three major databases were thoroughly searched without language or publication date limits, making the risk of missing publications less possible, which could minimize publication bias. Third, at least two authors selected studies and cross-checked and identified the final included studies. In order to perform the meta-analysis more objectively and minimize the selection bias to the greatest extent, all the authors jointly developed a data abstract form through discussion.

There are some limitations for this meta-analysis. First, most of the studies have difference in study design such as cluster-randomized trials, quasi-experimental studies, and before–after interventional studies, which is one source of inter-study heterogeneity. In fact, most of the studies were observational and retrospective, with some having limited capacity for adjustment, and thus were at a high risk of selection bias and residual confounding. Second, since there were a small number of studies in each outcome subset, we had to interpret the results with caution, although no evidence of publication bias in the analysis of all four outcome subsets was noted. Third, heterogeneity was rather high in two of the four analyses (I² > 50%), but this appeared to partly attribute to differences in the size of the risk estimates between studies rather than a lack of association. Fourth, study patients had wide variation in baseline features, and were from different kinds of units such as ICUs,5,10,20,23,25,27,28,30 general medicine units,24,29 and inpatient medical units,19 potentially leading to significant heterogeneity in outcomes, which limited the capacity for pooled analyses.

**Conclusion**

Current evidence to some extent supports the hypothesis that patients with application of CHW had significantly lower MRSA colonization and infection, as well as VRE colonization. More evidence should be accumulated to reinforce these findings, especially on the effect of CHW on VRE infection.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


