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

Hua-ping Huang¹, Bin Chen², Hai-Yan Wang³, and Me He¹

¹Nursing Administration, ²Intensive Care Unit, Mianyang Central Hospital, Mianyang, China

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: CRD42614014973).

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.
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 I² 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 I² 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-
Table 1. The characteristics of included studies

| Study                          | Country    | Study design                        | Setting                | Age, yr       | Intervention protocol                                                                 | Control                          |
|-------------------------------|------------|-------------------------------------|------------------------|---------------|----------------------------------------------------------------------------------------|----------------------------------|
| Bleasdale et al. (2007) [6]   | USA        | RCT                                 | MICU                   | 53 ± 16       | 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)    | 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            | Daily bathing with 2% CHG washcloths                                                   | Daily soap and water bathing     |
| Climo et al. (2013) [12]      | USA        | RCT                                 | Mixed ICUs             | 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            | 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       | Daily bathing with disposable cloths impregnated with 2% CHG                           | Nonmedicated washcloths          |
| Holder et al. (2009) [8]      | USA        | Before and after study              | Mixed ICUs             | 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         | 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            | 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)    | 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            | 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          | 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    | 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)    | Daily bathing with 2% CHG washcloths                                                   | Daily soap and water bathing     |
| Viray et al. (2014) [24]      | USA        | Before and after study              | Mixed ICUs             | 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.
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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.

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

| 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                |

*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

| Study                        | Selection | Outcome |
|------------------------------|-----------|---------|
|                              | Exposed cohort | Non-exposed cohort | Ascertainment of exposure | Outcome of interest | Comparability | Assessment of outcome | Length of follow-up | Adequacy of follow-up | Total score |
| 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) [13]    | *         | *       | *     | *     | -      | *             | -        | -       | -         | 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.

*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.
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 rates were available for eight studies.
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 evaluated 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 hosp-
eral 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 bacteremia 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 healthcare-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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