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The effects of chlorhexidine gluconate bathing on health care–associated infection in intensive care units: A meta-analysis

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ABSTRACT

Purpose: The purpose was to assess the effects of chlorhexidine gluconate (CHG) bathing on health care–associated infections among critically ill patients.
Methods: This meta-analysis evaluated English-language studies from the PubMed, Embase, and Cochrane databases. The Cochrane Collaboration methodology was used to evaluate all publications regarding daily CHG bathing and the risks of acquiring central line–associated bloodstream infection (CLABSI), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE). Risk ratios (RRs) and the ratio of the log RRs (RRR) were estimated with 95% confidence intervals (CIs).
Results: Eighteen studies were included. Compared with conventional care, the RRs (95% CIs) for CLABSI, MRSA, and VRE with CHG bathing were 0.45 (0.37-0.55), 0.67 (0.59-0.77), and 0.60 (0.42-0.85), respectively (all, $P < .05$). For MRSA acquisition, CHG bathing with concomitant nasal antibiotics provided a lower incidence compared with only CHG bathing (RRR: 0.81, 95% CI: 0.66-0.98, $P = .035$). Greater risk reduction was also observed in studies with prolonged interventions (RRR per 1-month extension: −0.02, $P = .027$).
Conclusions: Daily CHG bathing was associated with reduced risks of acquiring CLABSI, MRSA, and VRE. A prolonged intervention period and concomitant nasal antibiotic use were associated with lower risks of MRSA acquisition.

1. Introduction

Health care–associated infections (HAIs) are associated with clinically significant morbidity and mortality among critically ill patients, and the associated costs may not be reimbursed under some health care insurance plans [1]. In addition, infections with multidrug-resistant organisms are considerably more difficult to treat because of the limited number of effective antimicrobial drugs. However, chlorhexidine gluconate (CHG) is effective against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeasts [2]. Furthermore, the use of CHG for skin antisepsis can prevent the transmission of drug-resistant organisms in intensive care units (ICUs), such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and central line–associated bloodstream infection (CLABSI) [3]. Therefore, there has been increasing interest in using daily CHG bathing to reduce HAI among critically ill patients. A number of researchers have reported that daily CHG bathing reduced the acquisition of multidrug-resistant bacteria and decreased the frequencies of bloodstream infections and ventilator-associated pneumonia [3–6]. However, more recent studies have reported contradictory findings that do not support the routine use of CHG bathing to reduce HAI among critically ill patients [7].

After quality management for clinical microbiology was introduced during the 1960s [8], many clinical microbiology laboratories developed standardized biochemical methods to test for antimicrobial susceptibility. Among the various guidelines for quality control, the most widely used guidelines were developed by the Clinical Laboratory Standards Institute [9]. The Clinical Laboratory Standards Institute guidelines include quality control and quality assurance considerations for antibiotic susceptibility testing and culture media to ensure the accuracy, reliability, and reproducibility of the various tests. This quality system has enabled researchers to perform high-quality systematic reviews and meta-analyses of microbiological outcomes from different medical centers.

The present study used meta-analysis to investigate the effects of daily CHG bathing on HAI, compared with the effects of conventional care (eg, soap and water bathing), among critically ill patients.

2. Methods

2.1. Literature search

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses of randomized controlled trials (RCTs)

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[10]. Two independent reviewers (JM Kim and HY Kim) separately searched the PubMed, Embase, and Cochrane Central Register databases for all eligible English-language studies that were published before May 2, 2015. The MeSH search terms were *chlorhexidine, chlorhexidine and nosocomial infection, chlorhexidine and MRSA, chlorhexidine and VRE, chlorhexidine and CLABSI, intensive care unit, and critical illness*. We also searched for *daily showering or whole body washing with chlorhexidine*, which has the same meaning as *daily chlorhexidine bathing*. Additional studies were identified by hand searching the references of the original studies and review articles that were returned by our search. Authors of potentially relevant studies were contacted for further information if relevant data were not published. Case reports, reviews, and abstracts were excluded. The 2 reviewers (JM Kim and HY Kim) selected all data sets for this study via consensus.

2.2. Eligibility criteria

The included studies were prospective trials and interrupted time series (ITS) trials that compared daily CHG bathing with controls (conventional care). The primary outcome measures were the rates for acquisition of CLABSI, MRSA, and VRE among critically ill adult patients in ICU settings. To be included, each study was required to provide microbiology-based rates for CLABSI, MRSA, and VRE acquisition in the intervention and control arms. The definitions and diagnostic criteria for CLABSI, MRSA, and VRE were based on the Centers for Disease Control and Prevention (CDC) definitions [11] (Table 1). Furthermore, to be included, each study was required to report the findings as the number of acquired HAI cases per 1000 central line-days (for CLABSI) or 1000 patient-days in the ICU (for MRSA and VRE). Therefore, 1 study that reported the primary outcomes as weekly incidence rate ratios was excluded from our analysis [12]. Fig. 1 contains a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart for the data selection process.

2.3. Quality assessment

The 2 reviewers assessed the articles and investigated the risk of bias for RCTs using the Risk of Bias (RoB) tool from the Cochrane Collaboration. Quasi-experimental studies were evaluated using the Risk of Bias Assessment tool for Nonrandomized Studies (RoBANS) [13]. Review Manager software (RevMan; version 5.3) was used to evaluate the risk of bias in the included studies.

2.4. Statistical analysis

Meta-analyses were performed to calculate pooled risk ratios (RRs) with 95% confidence intervals (CIs). Based on a conservative approach, we used a random-effects model, which produces wider CIs than a fixed-effect model. Heterogeneity was assessed using 2 methods: Cochrane Q test, which indicates significantly heterogeneity at P values of $< .1$, and I^2 statistics, which indicate significant heterogeneity at values of 30% to 50% [14]. Publication bias was evaluated using Egger regression test and a funnel plot. Among the studies of MRSA acquisition, subgroup analyses were performed using a test of interaction [15] to identify the effects of using concomitant nasal antibiotic ointment. In addition, a meta-regression analysis and a cumulative meta-analysis were performed to identify the influence of treatment duration and the change in effect size due to the accumulation of short-term studies. All statistical analyses were performed using Comprehensive Meta-Analysis software (version 2.0; Biostat Inc, Englewood, NJ).

3. Results

3.1. Identifying eligible studies

The database search retrieved 256 records (93 from PubMed, 175 from Embase, and 92 from the Cochrane Library), and 18 studies (124 ICUs) that were published in English between February 2005 and January 2015 were included in the meta-analysis (Fig. 1). Studies were excluded because they were not clinical trials (eg, reviews and comments on previous studies; n = 78), they were studies regarding CHG bathing that did not involve the whole body (n = 40), only the abstract was available (n = 32), the trial did not evaluate adults (n = 24), the trial evaluated other infections (ie, not CLABSI, MRSA, VRE, or blood contamination; n = 21), the trial examined CHG bathing in non-ICU settings (n = 20), CHG bathing was not performed for all patients in the intervention group (n = 12), and the report was not written in English (n = 3). Studies that did not fulfill the selection criteria (n = 3) [16–18], studies with incomplete outcome data (n = 3) [12,19,20], studies with an unknown study period (n = 1) [21], and studies using a gastric agent with CHG bathing and nasal agents (n = 1) [22] were also excluded. Eleven articles were available regarding CLABSI acquisition [4–7,23–29], 7 articles were available regarding MRSA acquisition [3,25,30–34], and 3 articles were available regarding VRE acquisition [3,25,35].

3.2. Characteristics of the included trials

Eighteen trials were included in this study. One large study accounted for more than half of the patient-days in the MRSA analysis [31]. The characteristics of the 6 RCTs [3,7,23,24,31,32] and 12 ITSs [4–6,25–30,33–35] are summarized in Table 2. The outcomes from each study are summarized in Table 3.

3.3. Quality assessment

The 6 RCTs were evaluated using the RoB tool [3,7,23,24,31,32] (Fig. 2). There was no selection bias or attribution bias in the RCTs, although 4 studies had a high risk of performance bias due to the absence of participant and personnel blinding [3,7,24,31]. Two studies

Table 1
Centers for Disease Control and Prevention definitions [11]

HAI	A localized or systemic condition that results from an adverse reaction to the presence of infectious agent(s) or toxin(s) that (1) occurs in a health care setting (eg, a hospital or outpatient clinic), (2) was not present or incubating at the time of admission unless the infection was related to a previous admission in the same setting, and (3) meets the criteria for a specific infection site if the setting is a hospital.
Colonization	Microorganisms are present on skin, on mucous membranes, in open wounds, or in excretions or secretions, but are not causing adverse clinical signs or symptoms; and inflammation that results from a tissue response to injury or stimulation by noninfectious agents, such as chemicals.
CLABSI	A patient with a central venous catheter in place in whom a recognized pathogen is cultured from 1 or more blood cultures and is not related to an infection at another site. Alternatively, *CLABSI* can be defined as a common skin organism being cultured from 2 or more blood cultures that were drawn on separate occasions (within 2 d of each other), and with at least 1 of the following signs or symptoms (that are not due to infection at another site): fever (38°C), chills, or hypotension. *Acquired CLABSI* is defined as signs and symptoms of infection that were not present at the time of admission, with positive blood culture sample being drawn while the patient was housed in the unit or within 48 h of discharge from the unit.
Colonization with MRSA or VRE	The isolation of MRSA or VRE from a biological material in the absence of any infection signs and symptoms.
Infection with MRSA or VRE	The isolation of MRSA or VRE from normally sterile fluids, or isolation from a normally nonsterile biological material, in the presence of infection symptoms.
Acquisition of MRSA or VRE	An initial negative culture at admission and a follow-up culture that reveals the growth of MRSA or VRE from either a surveillance or clinical specimen that was obtained at >48 h after admission to the ICU.