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State of the Science Review

# Risks and benefits of using chlorhexidine gluconate in handwashing: A systematic literature review

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*Key Words:*
Hand hygiene
Health care personnel
Resistance
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Integrity of the skin

***Background:*** Antimicrobial soaps containing chlorhexidine gluconate (CHG) are indicated for hand hygiene (HH) in specific situations. This study aimed to identify whether the continuous use of CHG for HH affects the reduction of healthcare-associated infections (HAI), the selection of microorganisms resistant to CHG, or hands skin damage.

***Methods:*** Systematic review was performed using the protocol of the Joanna Briggs Institute, including clinical trials and observational comparative studies. Search was conducted via PubMed, Medline, CINAHL, LILACS, Embase, Cochrane Library, Scopus, Web of Science, ProQuest, Google Scholar, and gray literature. To evaluate outcomes, 3 independent reviews were conducted: HAI rates, presence of resistance genes or higher minimum inhibitory or bactericidal concentration, and damage to skin integrity.

***Results:*** Studies showed no significant difference in HAI rates when using CHG for HH. Among 13 studies, 10 suggested an association with use of and tolerance to CHG. The use of CHG was associated with skin reaction events.

***Conclusions:*** Strong evidence regarding the risks and benefits of CHG for HH is still lacking. Due to potential risk of selecting mutants carrying genes for cross-resistance to CHG and antibiotics, it is advisable to reserve the use of CHG for purposes other than HH.



There is a lack of consensus regarding the indication of antimicrobial soap for hand hygiene (HH). According to the Centers for Disease Control and Prevention[1] and the World Health Organization,[2] there is a lack of evidence demonstrating the clinical benefits—that is, reduction of infection rates—regarding the use of soap with or without an antimicrobial. Chlorhexidine gluconate (CHG) is 1 of the main antiseptic agents present in antimicrobial soaps. Its broad spectrum activity, acceptable tolerability, and good safety margin make CHG 1 of the most widely used biocides.[3]

When it comes to the use of germicides, there is concern regarding the issue of microbial resistance. This is of particular relevance in the face of global awareness concerning the cautious use of antimicrobials. So far, the molecular mechanism of bacterial resistance to antiseptics is still poorly understood.[4,5] Decreased susceptibility to CHG has been found to be mediated by certain genes, including *qac*A, *qac*B, *smr*, *nor*A, and *ebr*.[6] The term *resistance* itself should be used with caution because cutoff points are not yet known and product concentrations used on the market are usually higher than those required for the inhibition of microorganisms.[4] In addition, in the literature, there are reports of skin reactions as the antiseptic concentration increases.[4] CHG is widely used in health care settings for a variety of purposes.[7-9] Therefore, a synthesis of evidence regarding the benefits and risks of CHG for HH will be helpful in driving the rational use of soap containing this antimicrobial. The objective of this work was to analyze the effects of continuous use of CHG for HH through a systematic literature review focused on 3 outcomes: reduction of infections related to health care–associated infections (HAIs), selection of microorganisms resistant to CHG, and occurrence of skin damage.

## METHODS

To answer the proposed question (Q), we performed 3 independent systematic reviews by addressing the following: Q1—is the use of soap containing CHG for HH associated with a reduction in HAI transmission? Q2—is the use of CHG associated with the selection of microorganisms resistant to this antiseptic agent? Q3—is the use of soap with CHG associated with the occurrence of damage to skin integrity?

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These reviews were finished in April 2017 and updated in September 2018. The method design followed the protocol recommended by the Joanna Briggs Institute,[10] which was applied to the checklist proposed by the Systematic Review and Meta-Analysis Protocols 2015.[11]

*Data sources*

We performed a systematized search of indexed descriptors and key words using PubMed, Medline, CINAHL, LILACS, Embase, Cochrane Library, Scopus, Web of Science, ProQuest Dissertations and Theses, Google Scholar, and gray literature, with no language restrictions. The search protocol included publications from 1985 based on delivery of the first recommendation guide for HH.[12] An overview of the search strategy is described in Table 1; details are provided as a supplementary file.

The first phase of study selection occurred via an independent reading by 2 reviewers (M.M.B. and J.R.G.) of titles and abstracts for inclusion of preselected articles; after preselection was complete, the articles were read in full. The consensual decision making process for the inclusion of articles took place in a meeting between reviewers. Disagreements were discussed with a third reviewer (M.C.P.). Cross-references were obtained using selected publications.

*Study eligibility criteria*

We included nonrandomized and randomized clinical trials and observational studies that evaluated the following outcomes: Q1—HAI rates; Q2—presence of resistance genes or higher minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC); Q3—evaluation of skin integrity of health professionals.

*Study appraisal and risk of bias*

Each study was assessed according to the Joanna Briggs Levels of Evidence. The risk of bias was assessed by using the Critical Appraisal Tools from the Joanna Briggs Institute. Papers were evaluated according the type of study (13 items for randomized controlled trials, 9 items for quasi-experimental studies, 8 items for cross sectional studies).[10] The authors adopted a minimum of 5 and 6 affirmative answers in the checklist respectively, for the cross-sectional or quasi-experimental studies, and randomized controlled trials as the threshold for a paper to be included in this review.

## RESULTS

The search strategy resulted in 1,908 articles. After applying the inclusion and exclusion criteria, followed by a quality evaluation of the studies, the final sample consisted of 4 studies for Q1, 13 studies for Q2, and 7 studies for Q3. A summary of the research process is depicted in Figure 1. It was not possible to conduct a meta-analysis for each research question because of the large amount of heterogeneity among studies.

**Table 1**
Overview of PICO search strategy for literature review (April 2017, updated in September 2018)

| | |
|---|---|
| Problem | ("hand hygiene" [MeSH Major Topic]) |
| Intervention | ("chlorhexidine gluconate" [Other Term]) |
| Comparison (Q1) | ("1-propanol" [MeSH Major Topic] OR "ethanol" [MeSH Major Topic]) OR ("soaps" [MeSH Major Topic]) |
| Outcome (Q1) | ("disease transmission, infectious" [MeSH Major Topic]) OR ("disease transmission" [Other Term]) |
| Outcome (Q2) | ("microbial sensitivity tests" [MeSH Major Topic] OR "qace" [Other Term]) OR ("qnrb" [Other Term]) OR ("multidrug-resistant" [Other Term]) OR ("mdr genes" [Other Term]) |
| Outcome (Q3) | ("skin diseases" [MeSH Major Topic] OR "hand dermatoses" [MeSH Major Topic]) OR ("dermatitis, irritant" [MeSH Major Topic]) |

MeSH, Medical Subject Heading; qrnb, plasmid-mediated quinolone resistance gene; *PICO*, problem, intervention, comparison, outcome; *Q*, question.

*Q1: Is the use of soap containing CHG for HH associated with a reduction in HAI transmission?*

Among the 4 studies included, 3 were carried out in teaching hospitals, and all of them involved the care team. The 4 articles were published between 1991 and 2005. The findings that respond to Q1 are shown in Table 2.

P01[13] mentions the possibility of a change in the behavior of professionals as they were being observed. However, results also showed that nonantimicrobial soap was used more than soap containing CHG. Despite the trend in reduction in HAI rates when using CHG, there was no statistically significant difference between soaps. The isolated microorganisms were mainly coagulase-negative *Staphylococcus*, *Staphylococcus aureus, Enterobacteriaceae, Corynebacterium* spp, and *Micrococcus* spp (in order of frequency), microorganisms considered normal for the microbiota of the skin.

P02[14] points out that, despite decreasing the number of infections, there was no statistical significance in favor of CHG.

P03[15] analyzed variables that could interfere with the outcome, such as weight of the neonates, study site, and follow up time, and concluded there were no significant differences in infection risk during the period of CHG use and the period of use of the alcohol-based product for any type of infection.

P04[16] showed that, with the use of triclosan, the mean weekly rate of new methicillin-resistant *Staphylococcus aureus* (MRSA) cases was reduced from 3.4%-0.14% ($P > .0001$) in the experimental ward, without significant changes in rates in the control unit, which continued using CHG. Therefore, there was no association between the use of CHG and the reduction of HAI rates in the evaluated units.

*Q2: Is the use of CHG associated with the selection of microorganisms resistant to this antiseptic agent?*

To answer this question, 13 articles that met the inclusion criteria were analyzed. They employed a variety of study designs. The findings that correspond to the second question are described in Table 3.

In P01,[17] authors defined CHG resistance based on MRSA isolates possessing *qac*A/B genes. This study was performed as a community-based cluster randomized controlled trial investigating skin and soft tissue infection prevention. The study group (which received CHG 4% for weekly 10-minute shower) was comprised by 10,030 soldiers from an outpatient ambulatory. In this study, 720 MRSA isolates were identified. Only 10 (1.6%) of 615 isolates were resistant to CHG, including 3 from the CHG group and 7 from the non-CHG group ($P > .99$). Therefore, an association between use of and resistance to CHG was not shown. However, among its limitations, the study did not assess adherence levels of the study group, which could create bias.

P02[7] showed no association between the use of CHG and the presence of the *qacA/B* genes in *Staphylococcus epidermidis* isolates or increased MICs or MBCs for CHG. The highest exposure of scrub nurses to CHG was not associated with higher MIC or MBC. This study did not identify the presence of *qac* genes in a collection sample from the 1960s. The authors offered the hypothesis that introduction of *qac* genes might be associated with the more recent scaled use of CHG or related compounds.

P03[8] defined *resistance* as MIC ≥4 μg/mL. They identified this level of resistance to CHG in 72 of 206 MRSA isolates from a national collection initiated in 1998 in Taiwan. However, all strains did not harbor *qacA/B* genes. Most of the strains were ST239 and ST59, but the later strains had no detected resistance to CHG.

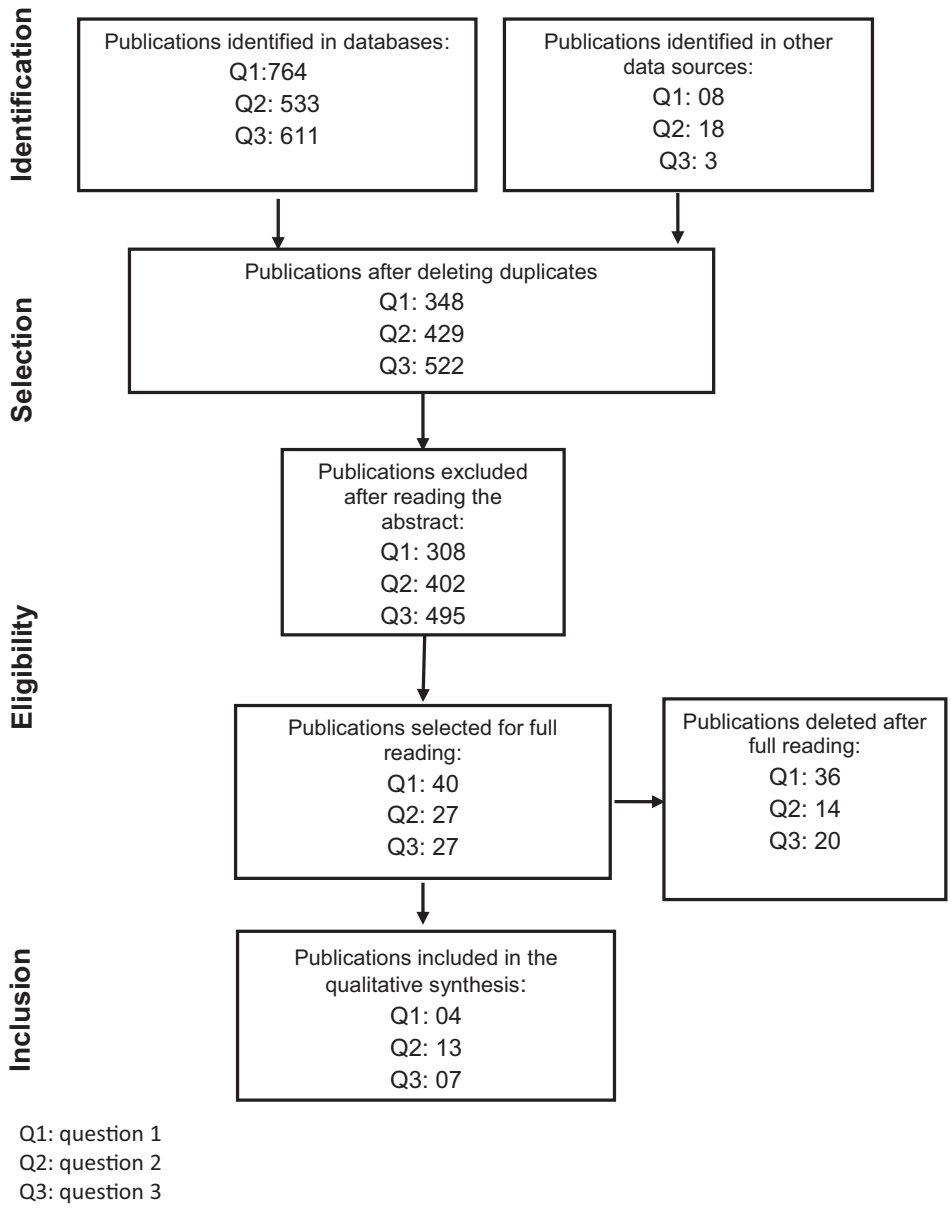


**Fig 1.** Summary of study selection used to compose article samples inserted in review of questions 1, 2, and 3 (Q1, Q2, and Q3).

P04[18] studied MRSA strains collected in 4 different years. They identified that *qacA/B* genes were absent in 1990, but were identified in the following years and ranged from 26.7%-35%. Regarding the MRSA strains without *qacA/B* genes, MIC ≥4 μg/mL was identified in 20.2% (37 of 183). This study demonstrated an increase in the proportion of tested MRSA isolates with high CHG MICs in an environment with long-term use of CHG. They observed an increasing presence of ST239 harboring *qacA/B* genes, which could represent an advantage in clonal spread.

P05[19] identified 11.8% (72) of 608 *S aureus* isolates with *qacA/B* genes. Most of these strains were MRSA ST239 and ST5, which were the most prevalent in units with high routine use of CHG as a decolonization agent. However, this study did not evaluate the amount of CHG used, making a comparison between the prevalence of resistance genes and CHG impossible.

P06[4] evaluated the impact of the intervention of a daily bath with CHG to prevent colonization and infection in patients in a bone marrow transplantation unit. The primary outcome of interest in the study was infection or colonization owing to vancomycin-resistant enterococcus, but there was also interest in other gram-negative bacteria. There was a significant decrease in the incidence of colonization and infection caused by vancomycin-resistant enterococcus during the intervention period; in contrast, the infection rates of multidrug-resistant gram-negative organisms increased. Of note, years after the intervention, there was an outbreak caused by *Pseudomonas aeruginosa.* The authors suggested that the molecular mechanisms of resistance to CHG were probably closely linked to the presence of an efflux pump. They also observed a shift in *P aeruginosa* from polyclonal before to clonal after the intervention, suggesting this was owing to extensive use of CHG in the unit.

P07[20] was based on the rationale that if exposure to CHG exerts an effect on the selection of CHG resistance, this effect would be different according to the extent of CHG use. For this, they created a usage index of liters consumed per beds per year. In this study, no organism had an MIC exceeding 128 mg/L. Interestingly, this study did not observe an association between CHG index of exposure and MIC or zone diameters for individual species. However, when all studied organisms were analysed together, they observed

**Table 2**
Synthesis of review study characteristics that answer Q1: Is the use of soap containing CHG for HH associated with the reduction of HAI transmission? (Brazil, 2017-2018)

| Publication/level of evidence* (Critical Appraisal†) | Study design | Scenario and aim | Duration | Product evaluated | Comparison | Sample | Results |
|---|---|---|---|---|---|---|---|
| P01<br>Marena et al, 2002[13]<br>-<br>2.c<br>(6/9) | Nonrandomized, prospective, crossover | Scenario: 2 surgical wards (1 vascular and 1 neurologic) of an Italian teaching hospital with 1,200 beds<br>Aim: "to improve the motivation and awareness of the importance of HH practices, to assess the effectiveness of a new chemical system in checking HH compliance, and to evaluate the efficacy and tolerability of 2 soap solutions used during regular working hours" | 4 mo | CHG 4% | Nonantimicrobial soap | 74 professionals (46% medical staff, 43% nurses, 8% nursing technicians)/patients hospitalized during study | There was a trend in reduction of infection rates but no significant statistical difference |
| P02<br>Doebbeling et al, 1992[14]<br>-<br>2.c<br>(5/9) | Nonrandomized, prospective, crossover | Scenario: ICU of a US university hospital with 46 beds (23 surgical, 12 medical-surgical, 11 cardiovascular)<br>Aim: "to compare the effects of 2 agents on nosocomial infection rates in the ICU" | 8 mo | CHG 4% | Nonantimicrobial soap, followed by isopropyl alcohol 60% | 1,352 patients in the CHG group × 542 soap + isopropyl under the care of 577 professionals | Although the number of infections decreased, there was no statistical relevance in favor of CHG |
| P03<br>Larson et al, 2005[15]<br>-<br>2.c<br>(8/13) | Prospective clinical trial, crossover | Scenario: 2 neonatal ICUs from a North American hospital (43- and 50-bed units)<br>Aim: "to compare the effect of 2 hand hygiene regimens on infection rates and skin condition and microbial counts of nurses' hands in neonatal intensive care units" | 2 y | Antiseptic detergent containing CHG 2% | Alcohol product with 61% ethanol and emollients | 2,932 patients (1,692 used CHG and 1,240 used ethanol) under the care of 119 nurses | There were no significant differences in infection rates between the 2 ICUs |
| P04<br>Webster, 1991[16]<br>-<br>2.d<br>(6/9) | Prospective and retrospective | Scenario: all neonates in the neonatal ICU and wards of largest Australian metropolitan hospital<br>Aim: "to evaluate the effects of triclosan on the methicillin-resistant *Staphylococcus aureus* (MRSA) rates in a neonatal intensive care nursery and to measure the amount of skin damage caused by handwashing with triclosan" | 10 mo‡ | CHG 4% (Hibiclens™) | Triclosan 1% (Novaderm™) | 46 prospectively admitted newborns | The mean weekly MRSA rate of new cases was reduced from 3.4%-0.14% ($P > .0001$) in the experimental area (triclosan) |

*CHG, chlorhexidine* gluconate; *HAI,* health care–associated infection; *HH*, hand hygiene; *ICU*, intensive care unit; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *Q,* question.
*Levels of evidence classified according to the Joanna Briggs Institute Levels of Evidence, indicated by number and letter (ie 2 c).
†The Critical Appraisal Tool from Joanna Briggs Institute tool was applied specifically for each type of study design. The numerator indicates the number of affirmative answers and the denominator the total number of checklist questions ex: 6/9.
‡(Retrospective) + 7 wk (prospective).

**Table 3**
Synthesis of review study characteristics that answer Q2: Is the use of CHG associated with the selection of microorganisms resistant to this antiseptic agent? (Brazil, 2017-2018)

| Publication/level of evidence* (MAStARI†) | Study design | Scenario and aim | Product evaluated | Microorganism | Technique used | Results |
|---|---|---|---|---|---|---|
| P01<br>Schlett et al, 2014[17]<br>-<br>1.c<br>(9/12) | Randomized clinical trial | Scenario: community-based cluster randomized controlled trial for skin and soft tissue infection prevention in outpatient unit for medical clinic infantry trainees using 3 study groups—(1) standard group: educational briefing; (2) enhanced standard group: educational briefing + supplemental education + weekly additional 10-minute shower; (3) CHG group: weekly 10-minute shower with CHG 4%<br>Clinical cultures and swabs from anterior nares collected<br>Aim: "to determine the prevalence of CHG resistance in clinical and colonizing MRSA isolates" | CHG 4% (Hibiclens) | MRSA | ATCC 700699 used as a control strain<br>Breakpoints adopted<br>Susceptible: ≤ 4 μg/mL; low-level resistance: 8-64 μg/mL; high-level resistance: 512 μg/mL<br>Detection of presence of gene (*qac*A/B) by PCR | No difference in the prevalence of presence of genes between study groups |
| P02<br>Skovgaard et al, 2013[7]<br>-<br>3.d<br>(7/9) | Cross-sectional | Scenario: isolates from 8 surgical nurses exposed to CHG (high-level exposure) and 10 patients before and after orthopedic surgery; isolates of blood sample collections dated 1965-1966<br>Aim: "evaluate if exposure to chlorhexidine selects CHG-tolerant *S epidermidis* and the consequences of long-term exposure to CHG" | CHG 85% ethanol, 0.5% CHG/0.5% glycerol (Iduscrub)<br>CHG 4% (Hibiscrub)<br>CHG 20%<br>CHG 20% + 96% ethanol | *S epidermidis* | MIC and MBC using broth microdilutions<br>Gene *qac* detection by PCR<br>ATCC 12228 as control | MIC and MBC were similar among patients and scrub nurses.<br>Highest measured MBC was 15 mg/L; isolate harbored *qac* genes<br>5/26 isolates from patients before hospitalization harbored *qac* genes<br>MIC and MBC values had no significant differences among *qac*-positive or negative strains.<br>*qac* genes were not present in isolates from 1965-1966 |
| P03<br>Sheng et al, 2009[8]<br>-<br>4.c<br>(8/9) | Cross-sectional | Scenario: 206 MRSA isolates randomly selected from a collection of clinical samples from inpatients and outpatients from different health care settings<br>Aim: "to determine the susceptibility of MRSA isolates to CHG and the prevalence of MRSA isolated with *qac*A/B and *smr* genes; to determine clonal spread of MRSA strains resistant to CHG" | CHG 4% (Hibiscrub) | MRSA | MIC by agar dilution<br>Detection of *qac*A/B and *smr* genes by multiplex PCR<br>Definition of resistance to CHG: MIC ≥ 4 μg/mL<br>Typing of strains by MLST and SCCmec | 72/206 (35%) of MRSA isolates showed MIC ≥ 4 μg/mL; among them, 67 (93.1%) carried *qacA/B* genes<br>No isolate harbored the *smr* gene<br>MRSA majority were ST59 SCCmec IV or V and ST239 SCCmec III (48.0% resistant to CHG) |
| P04<br>Wang et al, 2008[18]<br>-<br>4.c<br>(7/9) | Descriptive longitudinal | Scenario: university hospital with high prevalence of MRSA and long-term CHG use; MRSA isolates (240) causing bloodstream infections and other clinical specimens collected in 1990, 1995, 2000, and 2005<br>Aim: "understand changes in susceptibility to CHG as well as the proportion of MRSA isolates carrying qacA/B gene" | CHG 4% | MRSA | MIC by agar dilution method<br>Detection of *qac*A/B genes by PCR<br>Definition of resistance to CHG: MIC ≥ 4 μg/mL<br>Typing of strains by MLST | 83/240 (34.6%) showed MIC ≥ 4 μg/mL<br>Proportion of isolates with MIC ≥ 4 μg/mL increased from 1.7% in 1990 to 50% in 1995 and remained 46.7% in 2005<br>46/57 (80.7%) of MRSA with *qac*A/B genes expressed MIC ≥ 4 μg/mL |

(*continued on next page*)

**Table 3** (*Continued*)

| Publication/level of evidence* (MAStARI†) | Study design | Scenario and aim | Product evaluated | Microorganism | Technique used | Results |
|---|---|---|---|---|---|---|
| P05<br>Li et al, 2013[19]<br>-<br>4.c<br>(7/9) | Cross-sectional | Scenario: 608 *S aureus* samples of clinical specimens collected at a teaching hospital, 414 MRSA and 194 MSSA; CHG was used as a decolonization agent in the ICU and surgical ward<br>Aim: "to determine the prevalence, molecular characteristics, and genotype-phenotype correlation of hospital-acquired *S aureus* infections" | - | *S aureus* | Detection of *qac*A/B genes by PCR<br>Typing of strains by MLST and SCCmec | Genes *qacA/B* were found in 11.8% (72/608) of isolates<br>Majority of strains harboring *qacA/B* genes were ST239 and ST5; among them, MRSA ST239 SCCmec III was predominant |
| P06<br>Mendes et al, 2016[4]<br>-<br>1.d<br>(8/9) | Quasi-experimental | Scenario: 1,393 patients and 127 isolates from a stem cell and hematopoietic stem cell transplantation unit. Intervention: daily bath with CHG 2%<br>Aim: "to evaluate the impact of CHG bathing on colonization and infection by MDR bacteria; to assess the CHG MIC and presence of efflux pump genes before and after the implementation of daily bathing with CHG" | CHG 2% | *P aeruginosa, K pneumoniae, A baumannii, E faecium* | MIC by agar dilution with CHG ATCC13883 and ATCC25922 used as controls<br>Assessment of MIC of CHG in the presence of efflux pump inhibitors CCCP: MIC reduction at least 4-fold in the presence of CCCP<br>Detection of genes of resistance by PCR<br>Evaluation of clonality by PFGE | CCCP response was higher in the intervention period for all tested microorganisms Gene *cep*A found in *P aeruginosa* (44.5%, preintervention), *K pneumoniae* (62,9%), *A baumannii* (42.4%)<br>Changes in clonal pattern of *P aeruginosa* after intervention |
| P07<br>Block et al, 2002[20]<br>-<br>4.d<br>(7/9) | Cross-sectional | Scenario: clinical isolates (blood, urine, respiratory tract, wounds, and others) from an acute and tertiary care hospital with adult and pediatric patients; hospital use of CHG in aqueous (0.5%), alcohol 70% (0.5%), and surgical scrub (4%) formulation<br>Aim: "to evaluate the relationship between the use of CHG and the susceptibility of isolated microorganisms in patients of a general hospital" | CHG 20% solution from the hospital pharmacy | MRSA, *S aureus, S coagulase negative, K pneumoniae, P aeruginosa, A baumannii, Candida albicans* | MIC in agar dilution of CHG diluted from 0.5-256 mg/L<br>MIC in disk diffusion containing 50 μg of CHG<br>Index of intensity of CHG usage (L/bed/year) categorized as low, intermediate, and high | No significant association between exposure indices of CHG and MICs or zone diameters for individual species<br>All organisms together with significant correlation between both MIC and zone of inhibition |
| P08<br>Vali et al, 2017[9]<br>-<br>2.c<br>(8/9) | Cross-sectional | Scenario: isolates of MRSA (121) and MSSA (56) from clinical specimens<br>Aim: "identify the lineages of MRSA and MSSA with reduced susceptibility to CHG" | CHG | MRSA<br>MSSA | MIC-CHG 100 mg/mL in water with broth microdilution<br>MBC by subculturing 10 μl from each well with no grow<br>Use of ECOFF = MIC ≥ 4 mg/L, MBC ≥ 30 mg/L<br>No attempt to compare use and resistance to CHG | Genes *qac*A-C identified in 12.3% of MRSA and *qac*A in 5.4% of MSSA<br>Reduced susceptibility observed to CHG (MBC ≥ 30 mg/L) in MSSA isolates in non-*qac* strains |
| P09<br>McNeil et al, 2015[5]<br>-<br>2.c<br>(7/9) | Longitudinal | Scenario: 247 patients and isolates selected from *S aureus* surveillance study, children's hospital, and nosocomial infections from 2007-2013. CHG highly used since 2002 for different purposes<br>Aim: "to examine all *S aureus* isolates from nosocomial infections for the presence of *qacA/B* and *smr* and to correlate with clinical findings" | CHG | *S aureus* | MIC and MBC using broth macrodilution ATCC 29213 used as control<br>Detection of *smr* and *qacA/B* genes by PCR<br>PFGE and MLST typing | 111/247 (44.9%) isolates with 1 or both genes, more frequent *smr* (33.1%)<br>Among 98 MRSA strains, 44 were *smr* and 26 *qacA/B*<br>$MIC_{90}$ >256 was observed in strains *smr* and *qua*A/B-positive<br>Significant differences in $MBC_{90}$ among isolates with both genes |
| | Cross-sectional | | CHG | MRSA, MSSA | | |

(*continued on next page*)

**Table 3** (*Continued*)

| Publication/level of evidence* (MAStARI†) | Study design | Scenario and aim | Product evaluated | Microorganism | Technique used | Results |
|---|---|---|---|---|---|---|
| P10<br>Hughes et al, 2017[6]<br>-<br>2.c<br>(6/9) | | Scenario: 188 isolates from several clinical sample collections from an 800-bed tertiary hospital. Use of CHG for HH, surgical scrubs, and skin antisepsis<br>Aim: "to detect the prevalence of phenotypic tolerance to triclosan and CHG in clinical *S aureus* isolates; to compare the prevalence of MIC to CHG or triclosan and whether raised MIC was related to clonal spread of MRSA" | | | MIC by agar dilution method<br>ATCC 25923 used as control<br>Definition of MIC for CHG: ≥ 4 mg/L; triclosan: ≥ 1 mg/L<br>MLST, SCC*mec*, and spa type by PCR | Isolates with *qac*A exhibited raised MIC to CHG<br>ST22 and ST239 exhibited MIC for CHG: ≥ 4 mg/L<br>ST22 exhibited MIC for triclosan: > 1 mg/L<br>MIC for MSSA 0.5-4 mg/L<br>MIC for MRSA 1-8 mg/L |
| P11<br>Bhardwaj et al, 2017[21]<br>-<br>2.c<br>(7/9) | Laboratory-based, experimental | Scenario: selected strains or plasmids from laboratory collection, serial passage experiments<br>Aim: "to test the hypothesis that serial exposure to sub-MIC CHG selects for VRE *faecium* mutants with reduced susceptibility to CHG and other membrane and cell wall–targeting antimicrobials, with particular focus on daptomycin" | CHG 4% (Hibiclens) | *E faecium* | MIC for CHG by broth microdilution<br>MIC for daptomycin by Etest<br>Genome sequencing analysis<br>RT-qPCR<br>Phosphate assay, lipidomic analysis<br>Gene deletion and agar CHG susceptibility assay | After serial passages, reduced CHG emerged (4-fold shift in CHG MIC)<br>Subpopulations with reduced daptomycin susceptibility detected<br>Adaptive changes in genes identified |
| P12<br>Wu et al, 2016[22]<br>-<br>2.c<br>(7/9) | Laboratory-based, experimental | Scenario: 14 clinical isolates; serial passages of sub-MIC concentration of antibiotics, germicides, and antimicrobial Chinese herbs (ACHs)<br>Aim: "to examine whether concentrations of antibiotics, biocides, and ACHs below the minimum inhibitory concentration could lead to mutual cross-resistance or decreased susceptibility in bacteria" | CHG | *S aureus* | Exposure of strains to antibiotics, CHG, and *Rhizoma coptidis* extract at sub-MICs<br>MIC using geometric microdilution<br>ATCC 25923 as control | Most strains showed change in susceptibility to CHG <4-fold MIC increase, except for 6 isolates<br>CHG exposure: cross-resistance to at least 1 antibiotic; 7 strains became less susceptible to *Rhizoma coptidis* extract (≥ 4-fold MIC increase) |
| P13<br>Hijazi et al, 2016[23]<br>-<br>1.d<br>(8/12) | Longitudinal | Scenario: followup study of previous report showing efficacy of MRSA infection control measures in intensive care unit; CHG baths used routinely over 6 years; 81 isolates, including MRSA strains, from clinical specimens (blood and screening samples)<br>Aim: "*qac*A/B genes were screened in *Staphylococcus* isolates collected over another 6- year period in the same intensive care unit" | CHG | MRSA, MSSA, *S epidermidis* | MIC by agar dilution<br>Ethidium bromide used as positive control for *qac*A pump activity<br>Detection of *qac*A/B by PCR<br>Whole genome sequencing<br>MLST typing<br>Antibiotic susceptibility by disk diffusion | Presence of *qac*A/B in *S aureus*<br>Presence of *qac*A/B in *S epidermidis* associated with reduced susceptibility to CHG; 65% of *S epidermidis* belonged to MDR clone ST2 |

*ATCC*, American Type Culture Collection; *CCCP*, carbonyl cyanide m-chlorophenyl hydrazone; *CHG*, chlorhexidine gluconate; *ECOFF*, epidemiological cut-off value (upper limit of normal MIC distribution for a given antimicrobial agent and species); *HH*, hand hygiene; *MDR*, multidrug-resistant; *MIC*, minimum inhibitory concentration; *MLST*, multilocus sequence typing; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-susceptible *Staphylococcus aureus*; *PCR*, polymerase chain reaction; *PFGE*, pulsed-field gel electrophoresis; *Q*, question; *RT-qPCR*, real-time quantitative polymerase chain reaction; *S aureus*, *Staphylococcus aureus*; *SCCmec*, staphylococcal cassette chromosome; *S epidermidis*, *Staphylococcus epidermidis*.

*Levels of evidence classified according to the Joanna Briggs Institute Levels of Evidence.

†The MAStARI tool was applied specifically for each type of study design. The numerator indicates the number of affirmative answers and the denominator the total number of checklist questions.

a significant correlation between the exposure index and susceptibility (MIC or zone of inhibition). The highest MICs tended to concentrate in patients in surgical intensive care and hematology-oncology units.

P08[9] characterized a collection of MRSA and methicillin-susceptible *Staphylococcus aureus* (MSSA) strains. The *qac* gene was more frequently identified in MRSA (12.3%) than MSSA (5.4%) strains. However, the authors observed a reduced susceptibility to CHG in MSSA isolates that did not harbor *qac* genes and pointed out that other mechanisms may be involved in tolerance to CHG.

P09[5] was performed in a children's hospital with a high use of CHG since 2002. A high proportion of *S aureus* strains having at least 1 gene related to CHG tolerance (*smr* or *qacA/B*) was identified. Of note, the proportion of these genes varied with time, although the reasons for these temporal changes were unclear. The study showed *smr*-positive strains were more likely to be associated with resistance to methicillin, ciprofloxacin, and clindamycin. There was no difference in mortality rates in patients with and without antiseptic tolerance genes. Because $MIC_{90}$ strains harbored both genes, the authors suggested they may have had a synergistic effect on antiseptic efflux.

P10[6] demonstrated the characteristics of MRSA and MSSA regarding CHG and triclosan in a collection of clinical sample isolates. Higher MICs were observed for CHG, with lower levels observed for triclosan. However, at least 1 strain exhibited higher MICs for both antiseptics. ST22 SCCmec IV MRSA was associated with higher MICs for CHG.

In P11,[21] the authors observed an in vitro evolution of *Enterococcus faecium* resistance to vancomycin. After serial passaging using CHG 4% for 21 days, they detected a reduced MIC for CHG. This reduction showed a 4-fold increase compared with strains undergoing serial passaging in media without CHG. They also observed adaptive changes in genes, such as global nutritional response, nucleotide metabolism, phosphate acquisition, and glycolipid biosynthesis. Reduced daptomycin susceptibility emerged in a subpopulation of strains undergoing serial CHG passaging.

P12[22] also tested serial passage of bacterial cells at concentrations below the MIC for selected antibiotics, CHG, and antimicrobial Chinese herbs, predominantly *Rhizoma coptidis.* This study demonstrated that among strains exposed to subconcentrations of CHG, many of them exhibited less susceptibility to at least 1 antibiotic and to *Rhizoma coptidis e*xtract.

In P13,[23] the authors searched for *qac*A/B genes in samples of *Staphylococcus* from an intensive care unit in which CHG baths were a routine part of infection measures. Among *S epidermidis* strains, there was a minimal increase in MIC values (1 doubling dilution) of *qac*A/B positive strains compared with *qac*A/B negative strains. However, CHG MIC never exceeded 4 mg/mL. Regarding *S aureus*, *qac* carriage was not associated with an increase in CHG MIC.

In summary, of the 13 studies analyzed, 3 did not associate the use of CHG (P01, P02, and P07) with the selection of resistant microorganisms. Of note, only 1 study addressed the use of CHG specifically for HH (P02). Other studies suggested a potential association between the use of CHG and selection of strains exhibiting tolerance or harboring genes of tolerance to CHG. The 2 in vitro studies (P11 and P12) demonstrated an association between exposure to CHG and selection of tolerant strains, including cross-resistance with antibiotics.

*Q3: Is the use of soap with CHG associated with the occurrence of damage to skin integrity?*

The included articles were published between 1995 and 2005; there has been no publication on this topic since then. Of the 7 included studies—all involving care professionals—6 were carried out in intensive care units and wards and 1 was performed in a laboratory. The findings that answer the third question are shown in Table 4.

P01,[24] P02,[15] P03,[25] and P07[26] adopted the same validated instruments to assess skin conditions: the Visual Scoring of Skin Condition and the Hand Skin Assessment form, which is a self-rating scale. All of them compared the use of GCH 2.0% with the use of ethanol containing emollients or nonantimicrobial soap. Although the duration of the interventions varied (P01: 4 weeks; P02: 2 years; P03: 4 weeks), P01, P02, and P03 demonstrated improvement in skin condition in the group that used the nonantimicrobial soap and alcohol-based product when compared to CHG. P07 was the only study that identified similar rates of skin reactions in both groups.

P04[13] was the only study that compared the use of CHG 4.0% with a nonantimicrobial soap using a personal questionnaire to assess the perception of soaps. The results indicated that skin irritation and hand dryness resulted from the use of CHG.

P05[27] was the only study that compared the use of CHG 4.0% with another antimicrobial soap (triclosan 1.0%). The results showed that skin health was worse in the group that used CHG.

P06[28] was a descriptive study that used a self-administered questionnaire to identify subjects with dermatitis. It revealed that people with skin lesions on their hands had had contact with disinfectants, especially CHG and glutaraldehyde.

The analysis of the 7 studies suggests that the use of CHG is associated with a higher number of skin reaction events when compared with other products, such as alcohol-based products, triclosan, and quaternary ammonium.

## DISCUSSION

Regarding Q1, despite a full review of 36 articles, only 4 met the criteria for answering the research question. However, these were not recent studies, having been conducted between 1991 and 2005, and it was not possible to establish a definite benefit of CHG use in relation to decreasing HAI rates. This can be explained by the difficulty of isolating the effects of HH from other interventions addressing HAI prevention. The only study that compared the use of 4.0% CHG with nonantimicrobial soap was P01, and no differences were found in the rates of HAI.[13] The authors of the P02 study concluded that the improvement could be explained, at least in part, by better compliance with HH instructions for soap and water when CHG was used.[14] Assessing the impact on infection rates through a single intervention is complex owing to multiple contributory factors, such as patient risk, unit characteristics, and team behavior. Other practices, such as frequency and quality of HH, are important measures for reducing the risk of cross-transmission.[15] To date, the results of the studies presented in this review suggest that the use of CHG-based products, when compared with nonantimicrobial soap, triclosan, and alcohol-based products, does not bring a higher reduction in HAI rates. However, we found few studies performing such comparisons, and those that did were heterogeneous in terms of methodologic design. For this reason, it was not possible to carry out a meta-analysis to evaluate this outcome.

When measuring the impact of an antimicrobial product on HH, several factors need to be carefully considered. CHG has good antimicrobial activity and residual effect, which could be compensated for by an improvement in the adhesion rate of HH using a nonantimicrobial soap.[29] Overall, we observed a number of studies that assessed (in logarithms) reduction in the contamination of the hands of care professionals, but they did not make associations regarding the impact of this reduction on incidence rates of HAI. We identified a scarcity of well-designed and controlled research addressing this subject. The careful choice of strategies, interventions, tools, and design is essential for achieving better quality studies that do not include multiple interferences.

Regarding question 2, the results of the present review showed that 10 out of 13 studies suggested that the prolonged use of CHG

**Table 4**
Synthesis of review study characteristics that answer Q3: Is the use of soap with CHG associated with the occurrence of damage to the integrity of the hands skin? (Brazil, 2017-2018)

| Publication/level of evidence* (MAStARI†) | Study design | Scenario and aim | Product/exposure time | Comparison | Assessment of skin conditions | Results |
|---|---|---|---|---|---|---|
| P01<br>Larson et al, 2001[24]<br>-<br>1.d<br>(8/13) | Prospective randomized clinical trial | Scenario: 50 professionals from 2 adult critical care units in the United States<br>Aim: "to compare skin condition and skin microbiology among intensive care unit personnel using one of two HH regimens (2% CHG and a waterless handrub containing 61% ethanol with emollients)" | CHG 2%/4 wk | Nonantimicrobial soap and alcohol 61% with emollients | Two validated instruments: the VSS form, which uses stereomicroscopy, and the HSA form, which is a self-rating scale | Participants in the alcohol group had improvements in hand skin evaluation score |
| P02<br>Larson et al, 2005[15]<br>-<br>1.d<br>(8/13) | Experimental, crossover | Scenario: nursing staff from 2 neonatal ICUs from a North American hospital (43- and 50-bed units)<br>Aim: "to compare the effect of 2 hand hygiene regimens on infection rates and skin condition and microbial counts of nurses' hands in neonatal intensive care units" | CHG 2%/2 y | Nonantimicrobial soap with isopropyl alcohol 60% and emollients | Measured by 2 tools monthly: HSA form and VSS form | Nurses' skin condition improved using alcohol-based product compared to CHG |
| P03<br>Larson et al, 2000[25]<br>-<br>1.d<br>(7/9) | Quasi-experimental, prospective, randomized | Scenario: 16 nurses with no dermatologic conditions from a 47-bed neonatal ICU in New York<br>Aim: "to compare 2 hand care regimens in a neonatal intensive care unit" | CHG 4% and 2%/4 wk | Nonantimicrobial soap wash with subsequent alcohol-based rinse for degerming as necessary | Two validated instruments: VSS form and HAS form | Significant improvement in skin condition ($P = .005$) in group that used nonantimicrobial soap and alcohol-based product compared to CHG |
| P04<br>Marena et al, 2002[13]<br>-<br>1.d<br>(6/9) | Prospective, randomized, crossover | Scenario: 74 professionals from 2 surgical (vascular and neurologic) wards of a 1,200-bed Italian hospital<br>Aim: "to improve the motivation and awareness of the importance of HH practices, to assess the effectiveness of a new chemical system in checking HH compliance, and to evaluate the efficacy and tolerability of 2 soap solutions used during regular working hours" | CHG 4%/4 mo | Nonantimicrobial soap | Questionnaire to assess personal perception of hand soaps used and to report untoward effects | CHG caused skin irritation and dryness in the hands of 5 health workers during the study; 2 presented clear signs of acute dermatitis after use for 2 and 4 d, respectively |
| P05<br>Webster, 1992[27]<br>-<br>1.d<br>(6/9) | Experimental, nonrandomized | Scenario: 109 professionals from 2 neonatal ICUs<br>Aim: to evaluate the effectiveness of triclosan 1% against MRSA and its effect on skin were compared with chlorhexidine gluconate 4% (Hibiclens) | CHG 4%/7 wk | Triclosan 1% | Daily responses to structured questionnaire | Sixty-five (60.7%) professionals reported 1 or more skin problems, such as dryness, redness, peeling, cracking, and bleeding, while using triclosan when CHG reached 95.3% |
| P06<br>Stingeni et al, 1995[28]<br>-<br>4.c<br>(7/8) | Descriptive | Scenario: 1,301 professionals of an Italian hospital<br>Aim: to investigate the epidemiology of contact dermatitis in health care personnel | CHG 4%, 1.5%, and 0.5%<br>Sectional study | Alcohol: benzethonium (quaternary) glutaraldehyde hydrogen peroxide<br>PVPI | Self-administered questionnaire to identify subjects with dermatitis; all persons who reported skin diseases were examined | Hand dermatitis was the most frequent and occurred in 21.2% of examined subjects ($P < .001$); 94% of lesions were related to contact with disinfectants, especially CHG and glutaraldehyde |
| P07<br>Cimiotti et al, 2003[26]<br>-<br>2.c<br>(7/9) | Quasi-experimental, prospectively controlled study | Scenario: 50-bed neonatal intensive care unit in the United States<br>Aim: to describe skin reactions and compare typical reactions associated with HH with an antimicrobial soap and use of alcohol-based hand-hygiene products | 2.0% CHG/1 y | 61% ethanol containing emollients and nonantimicrobial soap | Two methods used: an instrument to collect data on skin condition and hand hygiene habits and a postcard-size diary card plus patch testing for nurses with dermatologic reactions | Seven of 58 nurses (1.1%) had skin reactions associated with the alcohol-based product compared with 4 of 58 nurses (1.0%) that had reactions associated with antiseptic soap containing CHG; patch test was positive in 3 of 4 nurses |

*CHG*, chlorhexidine gluconate; *HAS*, Hand Skin Assessment; *HH*, hand hygiene; *ICU*, intensive care unit; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *PVPI*, povidone-iodine; *VSS*, Visual Scoring of Skin.
*Levels of evidence classified according to the Joanna Briggs Institute Levels of Evidence.
†The MAStARI tool is applied specifically for each type of study design. The numerator indicates the number of affirmative answers and the denominator the total number of checklist questions.

might select tolerant strains. These studies involved different types of species and strains, including MRSA, *P aeruginosa, Klebsiella pneumoniae*, and *Acinetobacter baumannii*. Some of these studies associate the use of CHG with the presence of resistance genes (*qacA*, *qacB*) showing an increased MIC or MBC. These genes encode efflux pumps, which seem to be important resistance mechanisms.[4] It is relevant to highlight that, so far, there is no standardized method available for defining CHG resistance, and even the concept of tolerance or reduced susceptibility is not consensual.[9,20] Lack of a clearly defined susceptibility breakpoint means that an increase in MIC may not be easily understood as resistance.[4] However, the simple presence of gene encoding tolerance to biocides such as *qac* may not be a good marker for resistance since there have been studies showing reduced susceptibility to CHG in strains not harboring these genes.[7,9] Strains containing these genes may have an ecologic advantage in environments with frequent use of germicides or other fitness advantages, regardless of the use of CHG.[6] Even so, these findings should be interpreted with caution, taking into consideration that the use of CHG occurs mainly in areas with critical patients, where the use of antibiotics and invasive procedures is most frequent. Thus, antibiotic use, cross-infection, and immunosuppression are confounding variables.

In an intensive care unit, a greater exposure to CHG occurs if the antimicrobial soaps for HH contains CHG in their formulas. Although the theory of cross-resistance to antibiotics remains controversial, hypothetically, massive exposure to CHG may increase the risk of resistance to some antibiotics.[30] The major concern involves the possibility of cross-resistance between germicides and antibiotics related to *qac* genes. These genes are often present in integrons carried by plasmids, which, in turn, are widely disseminated in gram-negative bacteria. These integrons have been associated with the occurrence of efflux pumps—efficient mechanisms of resistance to antibiotics—in gram-negative bacteria.[31,32]

The tolerance of microorganisms to biocides has been reported by different mechanisms, the acquisition of plasmids being 1 of the most frequent.[33] The mechanism of action of germicides is different from that of antibiotics, particularly because the latter have very specific target sites, whereas germicides have more generic mechanisms that reach cellular structures more broadly.[33,34] However, the transfer of resistance genes between species is a possible phenomenon. For this reason, some authors express concern about the widespread use of germicides[31,33] and instead propose a "stewardship of biocides" initiative. Nevertheless, other authors believe this risk is still low—if germicides are used in appropriate concentrations.[34]

The findings from the reviewed studies demonstrated that detection of tolerance genes is frequent.[5] The clinical impact of this is not yet evident. So far, the majority of articles presenting strains with higher MIC or MBC to CHG have reflected concentrations below those commercially available. The clinical relevance of such findings is still unlikely.[6] Despite this, the identification in some studies of simultaneous carriage of these strains of antibiotic resistance is a matter of concern.[5] The concomitant carriage of resistance to antiseptics other than CHG is also possible.[6]

The concern about the large scale use of CHG should be regarded globally because of the rapid evolution in the dynamics of development and selection of resistance genes. In addition to the use of CHG for routine HH, the continuous use of CHG for many other procedures may lead to positive pressure in the selection of resistant microorganisms. From this point of view, the indiscriminate use of this antiseptic should also be reconsidered for other practices, such as skin preparation (eg, surgical skin antisepsis and preoperative baths). The rational use of germicides for skin preparation is addressed by the World Health Organization in its surgical site infection prevention guidelines, in which there is a recommendation to maintain preoperative baths with CHG only in patients undergoing cardiac or orthopedic surgery.[35] The studies using serial passage experiments were able to demonstrate the potential of exposure to CHG to select mutants with not only reduced MIC to CHG but also reduced susceptibility to other antimicrobials and pointed out that antibiotics and biocides may share mechanisms of actions that can be overcome by resistant mutants.[21,22]

Finally, with regard to the association of CHG use with the occurrence of damage to skin integrity (Q3), reactions were associated with extensive use, appearing after days or weeks of continuous use.[26] The main skin reactions reported were dryness, redness, cracking, and sometimes bleeding.[26] It is unclear if skin irritation was owing to the use of CHG itself or to the lack of emollients, such as those included in alcohol handrub products. It is important to point out, however, that the choice of CHG may have a potential detrimental impact on the skin health of professionals' hands, and that lesions may act as a gateway for microorganisms.

Our study, although comprehensive, has limitations, mainly owing to the low number of high-quality articles offering evidence regarding the risks and benefits of CHG use in routine HH. Using a search time frame beginning in 1985 could be a limitation since CHG appeared in the literature years before. However, we took into consideration that its scaled use potentially occurred after the first HH guideline, and that in many countries CHG was only available on the market in the 1980s.

## CONCLUSIONS

This study did not identify evidence in the literature regarding the benefits of routine use of CHG in HH for reducing HAI rates. The direct relationship of CHG use and the emergence of resistance is still inconclusive, although studies have pointed out the potential selection of CHG-resistant microorganisms. The continuous use of antimicrobial soap with CHG for HH may lead to skin damage. Because of the potential risk of selecting mutants that carry genes for cross-resistance to CHG and antibiotics, it is advisable to reserve the use of CHG for purposes other than HH.

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