Objective: The aim of the study was to summarize the latest evidence for patient bathing with a 2% to 4% chlorhexidine gluconate solution to reduce multidrug-resistant organism (MDRO) transmission and infection.

Methods: We searched 3 databases (CINAHL, MEDLINE, and Cochrane) for a combination of the key words “chlorhexidine bathing” and MeSH terms “cross-infection prevention,” “drug resistance, multiple, bacterial,” and “drug resistance, microbial.” Articles from January 1, 2008, to December 31, 2018, were included, as well as any key articles published after December 31.

Results: Our findings focused on health care–associated infections (HAIs) and 3 categories of MDROs: methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and carbapenem-resistant Enterobacteriaceae (CRE). Chlorhexidine bathing reduces MRSA acquisition and carriage, but not all studies found significant reductions in MRSA infections. Several studies found that chlorhexidine bathing reduced VRE acquisition and carriage, and one study showed lower VRE infections in the bathing group. Two studies found that bathing reduced CRE carriage (no studies examined CRE infections). Two very large studies (more than 140,000 total patients) found bathing significantly reduced HAIs, but these reductions may be smaller when HAIs are already well controlled by other means.

Conclusions: There is a high level of evidence supporting chlorhexidine bathing to reduce MDRO acquisition; less evidence is available on reducing infections. Chlorhexidine bathing is low cost to implement, and adverse events are rare and resolve when chlorhexidine use is stopped. There is evidence of chlorhexidine resistance, but not at concentrations in typical use. Further research is needed on chlorhexidine bathing’s impact on outcomes, such as mortality and length of stay.

Key Words: chlorhexidine, multidrug-resistant organisms, drug resistance, infection prevention, infection control

Chlorhexidine Bathing Strategies for Multidrug-Resistant Organisms: A Summary of Recent Evidence

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Multidrug-resistant organisms (MDROs) are microorganisms, mainly bacteria, that are resistant to 1 or more antimicrobial agents. The World Health Organization recognizes MDROs as a growing threat. Multidrug-resistant organisms are of particular concern for vulnerable patients, such as those who have received organ transplantation, those with cancer, preterm infants, and immune-suppressed patients. With limited effective antimicrobials, MDROs are responsible for approximately 23,000 deaths annually in the United States. The Centers for Disease Control and Prevention (2018) states that 11% of individuals screened in healthcare facilities are asymptomatic carriers for a transmissible, “hard-to-treat” microorganism. Chlorhexidine solutions are used as topical disinfectants and as part of recommended strategies for MDRO control. Chlorhexidine solutions are commercially available in concentrations from 0.5% to 4%, with bathing solutions (such as prepacked cloths or liquid soap) generally ranging from 2% to 4%. This review article summarizes the recent evidence for chlorhexidine bathing to reduce MDRO transmission and infection.

METHODS

We searched 3 databases (CINAHL, MEDLINE, and Cochrane) for a combination of the key words “chlorhexidine bathing” and MeSH terms related to “cross-infection prevention,” “drug resistance, multiple, bacterial,” and “drug resistance, microbial.” Articles from 2008 through December 31, 2018, were included. Any relevant articles published after the original search are included in Figure 1, the search methods flow chart, as additional sources.

The initial search yielded 317 results; after duplicates were removed, 300 (including 6 articles from other sources) were screened for inclusion and 124 full-text articles were retrieved. Of those, 42 were selected for inclusion. Articles were excluded if they did not mention skin or oropharyngeal application of chlorhexidine or use of chlorhexidine outside of health care environments. Chlorhexidine oral care was included in this review, as were in vitro studies of chlorhexidine resistance. For systematic reviews or meta-analyses, the project team accepted the authors’ assessments of study quality and overall strength of evidence.

In this review, we define “chlorhexidine bathing” as no-rinse application of chlorhexidine to the skin or oropharyngeal surfaces, for the purposes of decolonization and infection prevention. Oropharyngeal surfaces are a reservoir for MDROs in mechanically ventilated patients, and thus, we include oral care as part of a chlorhexidine bathing routine.

RESULTS

With a wide variety of outcomes across all studies, we chose to focus on results for methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), carbapenem-resistant Enterobacteriaceae (CRE), and health care–associated infections (HAIs). Methicillin-resistant S. aureus (MRSA) continues to make up half of S. aureus–related health care–associated infections. Similarly, 50% of health care–associated Enterococcus infections are vancomycin-resistant and are increasingly resistant to alternative antibiotic treatments. Carbapenem-resistant Enterobacteriaceae is considered an urgent public health threat by the Centers for Disease Control and Prevention because of its difficulty to treat. In addition, CRE and carbapenem-resistant genes are increasingly widespread: some subsets are endemic in healthcare facilities in parts of the United States, and there is evidence of carbapenem resistance in the community. The results of the review are summarized hereinafter, with additional detail on each study in Tables 1–5. Where possible, we specify whether all infections or MDRO-only infections are reported.
Methicillin-Resistant *Staphylococcus aureus*

Evidence suggests that chlorhexidine bathing in the hospital setting reduces MRSA acquisition and carriage, but this may not always result in fewer MRSA-related infections. Three systematic reviews and 3 studies (2 experimental, 1 quasi-experimental) found evidence that chlorhexidine bathing reduces MRSA acquisition and carriage, although one review did include studies where no reduction was found.7,11,12,14,15,17 A prospective cohort study by Ruiz et al16 (2017) found no reduction in MRSA colonization rates but did find a significant reduction in total MDRO colonization.

Interpreting the impact of chlorhexidine bathing on infection rates is complicated by its use in multicomponent decolonization protocols (including nasal mupirocin and oral antibiotics). For MRSA, it may be more appropriate to study how chlorhexidine bathing can reduce resource-intensive practices, such as patient isolation.6,30 Peterson et al’s15 cluster-randomized study in long-term care facilities demonstrated that a thorough decolonization protocol

**TABLE 1.** Summary of MRSA Results

| Study                        | Type of Study                                      | Setting                        | MRSA Results                                                                 |
|------------------------------|----------------------------------------------------|--------------------------------|------------------------------------------------------------------------------|
| Climo et al,11 2013          | Multicenter, nonblinded cross-over trial           | Hospital (ICU)                 | Reduced MRSA acquisition: total MDRO acquisition (MRSA or VRE) reduced from 6.6/1000 patient-days to 5.1/1000 patient-days (P = 0.03). |
| Denny and Munroe,7 2017      | Systematic review                                  | Hospital                       | Reduced MRSA acquisition, colonization, transmission and infection rates (statistical findings not reported for all studies). |
| Derde et al,12 2012          | Systematic review                                  | Hospital                       | Reduced MRSA acquisition and carriage but not consistently reduced MRSA infections (statistical findings not reported for all studies). |
| Huang et al,13 2019          | Cluster-randomized trial                           | Hospital, noncritical care units | No statistically significant reduction in MRSA-positive cultures, except for a subgroup of patients with invasive medical devices. The HR for the decolonization group of those patients was 0.8 (95% CI = 0.69–0.96) compared with the routine care group’s HR of 1.17 (95% CI = 1.00–1.37) for MRSA- or VRE-positive culture (P = 0.0004). |
| Musuuza et al,14 2017        | Quasi-experimental, pretest/posttest study         | Hospital (ICU)                 | Reduced MRSA colonization, but not statistically significant (9.2%–5.6%, P = 0.119). |
| Peterson et al,15 2016       | Prospective, cluster-randomized trial              | Long-term care facility         | Reduced MRSA colonization.                                                   |
| Ruiz et al,16 2017           | Prospective cohort study                           | Hospital (ICU)                 | No reduction in MRSA colonization.                                           |
| Silder et al,17 2014         | Systematic review                                  | Hospital (ICU)                 | Reduced MRSA acquisition and carriage but not consistently reduced MRSA infections. |

CI, confidence interval; HR, hazard ratio.
including chlorhexidine bathing can reduce MRSA colonization without patient isolation.

**Vancomycin-Resistant Enterococcus**

Similar to MRSA, studies reported on various VRE prevention outcomes: acquisition, colonization, carriage, and infection. Three systematic reviews found that chlorhexidine can reduce VRE carriage in hospital patients.\(^7,12,17\) One rigorous multicenter study and 2 quasi-experimental studies found that chlorhexidine bathing reduces VRE acquisition.\(^11,14,18\) One of the quasi-experimental studies also found a reduction in VRE-related infections when daily bathing was combined with skin antisepsis for central venous catheter insertion and before surgery or biopsies.\(^18\)

**Carbapenem-Resistant Enterobacteriaceae**

Few studies directly addressed chlorhexidine bathing for CRE. Of those that did, 2 observational cohort studies found that chlorhexidine bathing can reduce CRE colonization and potentially CRE infection.\(^16,19\)

**Other Pathogens**

No systematic reviews recommended or discouraged chlorhexidine bathing for preventing/reducing general multidrug-resistant gram-negative bacteria (MDR-GNB) colonization.\(^12,17,29\) One review found only temporary decolonization of MDR-GNB using chlorhexidine, and 1 randomized, open-label controlled trial found no reduction or delay in MDR-GNB acquisition.\(^20,29\) Kengen et al’s\(^24\) retrospective time study (2018) found no difference in MDRO acquisition with chlorhexidine bathing as compared with soap and water, whereas Ruiz et al\(^16\) (2017) saw a reduction in MDRO acquisition, including MDR-GNB.\(^16,24\) Musuuza et al’s\(^14\) pre-post study (2017) found reduced MDR-GNB colonization with chlorhexidine bathing as compared with soap and water, whereas Ruiz et al\(^16\) (2017) saw a reduction in MDRO acquisition with chlorhexidine as compared with soap and water, whereas Ruiz et al\(^16\) (2017) saw a reduction in MDRO acquisition, including MDR-GNB.

**Health Care–Associated Infections**

Many studies examined the effect of chlorhexidine bathing on catheter-associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP), and central line–associated bloodstream infection (CLABSI). One review and several studies, including 2 large studies with more than 400,000 patients, found evidence that chlorhexidine bathing can reduce device-associated HAIs.\(^7,13,23\) Specifically, Abboud et al’s\(^19\) observational cohort study found chlorhexidine bathing reduced HAI in CRE-colonized patients. Among ICU patients, 2 studies\(^11,12\) found significant reductions in CLABSI, although the reduction in MRSA-related BSIs in Huang et al’s\(^13\) (2013) study was not statistically significant. However, in Huang et al’s\(^13\) later (2019) study of noncritical care patients, the authors found significant reductions in all-cause BSIs for the subgroup of patients with medical devices.

Although some studies did not show an effect on HAIs, these were considerably smaller than the 2 studies by Huang et al’s\(^13,23\). A 2015 rigorous cluster-randomized trial by Noto et al\(^25\) found no impact on CLABSI, CAUTI, VAP, or *Clostridioides difficile* infection rates among the 9340 patients in the study. Ruiz et al\(^16\)

### TABLE 3. Summary of CRE Results

| Study          | Type of Study          | Setting               | CRE Results                                                                 |
|----------------|------------------------|-----------------------|----------------------------------------------------------------------------|
| Abboud et al\(^19\) 2016 | Observational pre-post cohort study | Hospital (surgery ICU) | Significant reduction in CRE colonization (26.8% preintervention, 9.3% postintervention, \(P < 0.001\)). |
| Ruiz et al\(^16\) 2017   | Prospective cohort study | Hospital (ICU)        | Reduction in MDRO colonization, including Enterobacteriaceae (22.0% versus 18.4%, \(P = 0.01\)). |
observed reduced MDRO colonization in their single-site study, but this did not lead to a reduction in HAIs. In addition, they noted that longer ICU stays were associated with higher overall incidence of HAIs, regardless of chlorhexidine bathing.16

Two studies compared chlorhexidine bathing to bathing with soap and water and found no improvement in HAI rates, especially when the HAIs are caused by MDR-GNB.20,24 Camus et al21 (2014) were able to reduce HAIs from MDR-GNB by adding mupirocin application to chlorhexidine bathing (for all patients) and polymyxin/trimethoprim/amphotericin B in the oropharynx and gastric tubes of intubated patients. However, this study was not designed to control for the impact of these additional steps, and more research is needed on whether these may be sufficient (in settings where HAIs are already well controlled by other means). This also suggests that chlorhexidine bathing has limited benefit for HAI reduction in settings where HAIs are already well controlled by other means.

Two studies found chlorhexidine bathing only effective for some HAIs. Dusznyska et al22 (2017) also found no conclusive evidence that chlorhexidine bathing reduces SSIs despite observing a reduction in SSIs among CRE-colonized patients in their study. Another re-view found mixed evidence on the efficacy of chlorhexidine bathing in reducing SSIs among CRE-colonized patients. Reduced SSIs in only 189,081 patients in the baseline period and 339,902 patients in the intervention period)

Chlorhexidine Resistance

Resistance to chlorhexidine is detected by observing higher minimum inhibitory concentrations (MICs) and higher minimum bactericidal concentrations. Two in vitro studies found chlorhexidine resistance more common in settings with routine chlorhexidine bathing.34,35 One retrospective cohort study found no conclusive trends in the prevalence of chlorhexidine-resistant MDROs after
implementing bathing, but the authors hypothesize that some increases may be due to readmitted patients with persistent colonization.\textsuperscript{16}

McNeil et al\textsuperscript{15}' study of \textit{S. aureus} in a pediatric hospital (2014) showed that organisms with chlorhexidine resistance genes had MICs twice as high and minimum bactericidal concentrations 8 to 16 times as high as more susceptible organisms ($P < 0.005$). However, one in vitro study of ICU isolates collected after a chlorhexidine bathing initiative found that resistance genes were linked to higher MICs in 1 MRSA strain but not another.\textsuperscript{38} Similarly, Musuuza et al\textsuperscript{14}'s study of hospital MRSA isolates found that although not genetically resistant, oral MRSA biofilms studied in vitro show considerable resistance to chlorhexidine mouthwashes, which may account for failure of oral washing to prevent VAP and for frequent oral MRSA recolonization.\textsuperscript{39}

The clinical impact of chlorhexidine resistance genes is unclear. One in vitro study of hospital MRSA isolates found that resistant strains showed more resistance to chlorhexidine than methicillin-susceptible strains.\textsuperscript{40} Similarly, Alotaibi et al's (2017) found more chlorhexidine resistance in VRE than in vancomycin-susceptible Enterococci. Hayashi et al\textsuperscript{42} (2016) found that \textit{Acinetobacter baumannii} epidemic strains from hospital isolates showed increased resistance to chlorhexidine in vitro, but not at concentrations generally used for disinfection.

Two studies found evidence that chlorhexidine bathing can favor general resistance. Abboud et al\textsuperscript{19} found that an increase in colonization with \textit{Pseudomonas aeruginosa} and \textit{A. baumannii} after chlorhexidine bathing was implemented in an ICU. However, Ca	extsuperscript{43}mus et al (2016) found no increase in MDR-GNB rates after implementation of oral chlorhexidine bathing for ventilated patients, but it is unclear what affect the additional components of that intervention (mupirocin ointment and antibiotics) had on MDR-GNB rates. Finally, 2 studies found that chlorhexidine-resistant genes were also associated mupirocin resistance in isolates.\textsuperscript{37,44}

### DISCUSSION

This review found evidence that chlorhexidine bathing can reduce MDR-GNB acquisition and carriage, but not necessarily infection. A recent (2019) Cochrane review concluded that more evidence is needed on whether this reduces infections, mortality, and length of stay in ICUs.\textsuperscript{45} At the concentrations typically used for bathing (2\%–4\%), chlorhexidine is still effectively microbicidal; however, overdiluted solutions may fail to kill organisms, especially when biofilms develop.\textsuperscript{46–48}

In addition to efficacy against CRE and emerging chlorhexidine resistance, additional research on chlorhexidine bathing could include:

- studies on frequency and duration of bathing;
- studies that examine the efficacy chlorhexidine in reducing infections due to existing colonization (“self-infection”) as well as infections caused by MDR-GNB shedding;
- evaluations of chlorhexidine bathing’s role in multicomponent programs (also suggested in commentary by Horner et al,\textsuperscript{49} 2013); and
- continued research on chlorhexidine resistance and related clinical outcomes, especially for biofilms (suggested by Gruscha,\textsuperscript{50} 2014) and Gram-negative bacteria (suggested by Strich and Palmore,\textsuperscript{51} 2017).

### LIMITATIONS

This study only included publications for which English-language versions were available. Few studies specifically examined CRE; instead, many more studies examined MDR-GNB (including Enterobacteriaceae species). Although the use of the key word “chlorhexidine bathing” was consistent with the key words used in the included articles, this may have excluded studies that meet our operational definition of “chlorhexidine bathing” without using that term.

### CONCLUSIONS

Chlorhexidine bathing is effective at reducing acquisition and decolonization, particularly by MDR gram-positive bacteria; more

### TABLE 5. Summary of Other Results

| Study                      | Type of Study                          | Other Results                                                                 |
|----------------------------|----------------------------------------|-------------------------------------------------------------------------------|
| Boonyasiri et al\textsuperscript{20}, 2016 | Randomized, open-label controlled trial | Hospital (ICU) No reduction/delay in MDR-GNB acquisition                     |
| Derde et al\textsuperscript{12}, 2012    | Systematic review                       | Hospital                                                                       | Little evidence supporting chlorhexidine bathing for MDR-GNB. |
| Kengen et al\textsuperscript{24}, 2018  | Single-site retrospective, open-label, sequential period, interrupted time series study | Hospital (ICU) No reduction in ICU-associated, clinically significant blood cultures or in MDR-GNB acquisition. |
| Maxwell et al\textsuperscript{27}, 2017 | Prospective, randomized control trial   | Hospital                                                                       | No difference between soap and chlorhexidine at reducing infections from GNB or GPB. |
| Mendes et al\textsuperscript{18}, 2016  | Quasi-experimental observational study  | Hospital (transplant ward)                                                    | Not effective in reducing colonization from MDR-GNB. |
| Musuuza et al\textsuperscript{14}, 2017 | Quasi-experimental, pretest/posttest study | Hospital (ICU) Reduced prevalence of colonization with fluoroquinolone-resistant GNB. |
| Pedreira et al\textsuperscript{28}, 2009 | Randomized control study                | Hospital (PICU) No reduction in MDRO colonization rates (compared with standard care) when chlorhexidine was added to oral care (toothbrushing) in PICU patients |
| Ruiz et al\textsuperscript{16}, 2017    | Prospective cohort study                | Hospital (ICU) Reduction in overall MDRO colonization, including MDR-GNB.     |
| Silder et al\textsuperscript{17}, 2014  | Systematic review                       | Hospital (ICU) Little evidence supporting chlorhexidine bathing for MDR-GNB.   |
| Taiconelli et al\textsuperscript{27}, 2014 | Systematic review                      | Hospital                                                                       | Only temporary decolonization of MDR-GNB. |

GPB, gram-positive bacteria; PICU, pediatric intensive care unit.
evidence is needed to show whether this ultimately reduces infection, length of stay, and mortality. As an intervention, chlorhexidine bathing is low cost to implement with few adverse events (skin sensitivity, which resolves after stopping bathing), but compliance can wane over time. Low levels of chlorhexidine resistance have been observed in vitro but at concentrations far below those recommended for bathing. Although there are no clinical impacts described in the literature to date, resistance should continue to be monitored.

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