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

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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

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Multidrug-resistant organisms (MDROs) are microorganisms, mainly bacteria, that are resistant to 1 or more antimicrobial agents.[1] The World Health Organization recognizes MDROs as a growing threat.[2] 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.[2] With limited effective antimicrobials,[3] MDROs are responsible for approximately 23,000 deaths annually in the United States.[1] 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.[4]

Chlorhexidine solutions are used as topical disinfectants and as part of recommended strategies for MDRO control.[5,6] 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%.[7] 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.[6]

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.[8] Similarly, 30% of health care–associated *Enterococcus* infections are vancomycin-resistant and are increasingly resistant to alternative antibiotic treatments.[9] Carbapenem-resistant Enterobacteriaceae is considered an urgent public health threat by the Centers for Disease Control and Prevention because of its difficulty to treat.[8] 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.[10] 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.

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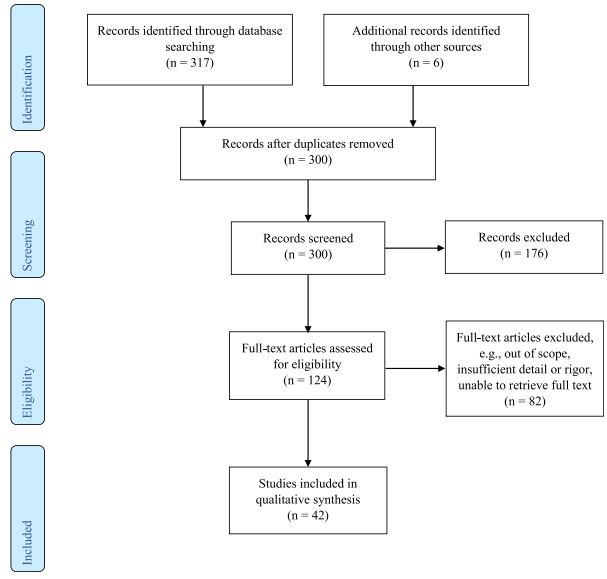

FIGURE 1. Chlorhexidine bathing study selection for review.

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 al[16] (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's[15] 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, cluster-randomized, 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.

TABLE 2. Summary of VRE Results

Study	Type of Study	Setting	VRE Results
Climo et al,[11] 2013	Multicenter, cluster-randomized, nonblinded cross-over trial	Hospital (ICU)	Reduced VRE 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 VRE carriage (statistical findings not reported for all studies).
Derde et al,[12] 2012	Systematic review	Hospital	Reduced VRE carriage (statistical findings not reported for all studies).
Huang et al,[13] 2019	Cluster-randomized trial	Hospital, noncritical care units	No statistically significant reduction in VRE-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 ($P = 0.0004$).
Mendes et al,[18] 2016	Quasi-experimental observational and in vitro resistance study	Hospital (Transplant ward)	Reduced VRE colonization and infection rates (colonization change in trend: β-3 = −0.040, $P = 0.001$; infection change in trend: β-3 = −0.086, $P = 0.001$).
Musuuza et al,[14] 2017	Quasi-experimental, pretest/posttest study	Hospital (ICU)	Reduced VRE colonization (14.5%–8.4%, $P = 0.030$).
Silder et al,[17] 2014	Systematic review	Hospital (ICU)	Reduced VRE carriage in 1 meta-analysis reviewed (incidence rate ratio = 0.51; 95% CI = 0.36–0.73 and 0.57; 95% CI = 0.33–0.97; for VRE colonization and VRE infection, respectively).

CI, confidence interval.

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, but Mendes et al's[18] quasi-experimental observational study did not. Maxwell et al[27] (2017) found no difference between chlorhexidine and soap bathing for lowering all-MDRO infection rates.

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 blood stream 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 HAIs in CRE-colonized patients. Among ICU patients, 2 studies[11,23] found significant reductions in CLABSIs, although the reduction in MRSA-related BSIs in Huang et al[23] (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.[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%, $P = 0.01$).

TABLE 4. Summary of HAI Results

Authors	Type of Study	Setting	HAI Results
Abboud et al,[19] 2016	Observational pre-post cohort study	Hospital (surgery ICU)	Significant reduction in CLABSIs (2.07/1000 line days to 0.23/1000 line days, $P < 0.002$), VAP, and UTI rates in CRE-colonized patients. Reduced SSIs in only in noncolonized, bathed patients (2.4%–0.8%, $P < 0.003$).
Boonyasiri et al,[20] 2016	Randomized, open-label controlled trial	Hospital (ICU)	No impact on HAI rates, in settings where >60% of HAIs were caused by MDR-GNB.
Camus et al,[21] 2014	Multicenter, placebo-controlled, randomized, double-blind trial	Hospital (ICU)	When combined with mupirocin and administration oral antibiotics, reduction in HAIs caused by MDR-GNB (5.45%–1.59%, $P < 0.0001$).
Climo et al,[11] 2013	Multicenter, cluster-randomized, nonblinded cross-over trial	Hospital (ICU)	Reduction in CLABSIs (6.60/1000 patient-days to 4.78/1000 patient-days, $P = 0.007$).
Denny and Munro,[7] 2017	Systematic review	Hospital	Reduced CAUTI, VAP, and CLABSI rates, across all studies reviewed (statistical findings not reported for all studies).
Dusznyska et al,[22] 2017	Observational study	Hospital (ICU)	Reduction in catheter-related infections ($P = 0.005$); nonsignificant reductions in UTIs and intubation-associated pneumonia.
Huang et al,[13] 2019	Cluster-randomized trial	Hospital, noncritical care units	No statistically significant reduction in all-cause BSIs among total population (189,081 patients in the baseline period and 339,902 patients in the intervention period). However, a subgroup of high risk patients (those with medical devices) did have a significantly reduced HR of all-cause BSIs in the decontamination group compared with the routine care group (0.81 [95% CI = 0.70–0.94] versus 1.13 [95% CI = 0.96–1.33], $P = 0.0032$).
Huang et al,[23] 2013	Cluster-randomized trial	Hospital (ICU)	Reduced all-cause BSIs. MRSA-related BSIs reduced, but not significantly.
Kengen et al,[24] 2018	Single-site retrospective, open-label, sequential period, interrupted time series analysis	Hospital (ICU)	No reduction in rates of ICU-associated, clinically significant positive blood cultures, blood culture contamination, newly acquired MDRO isolates, and CDIs.
Noto et al,[25] 2015	Pragmatic cluster-randomized, cross-over study	Hospital (ICU)	No difference was detected between in the rates of CLABSI, CAUTI, VAP, and CDIs
Ruiz et al,[16] 2017	Prospective cohort study	Hospital (ICU)	No reduction in CLABSI, VAP, or UTI rates.
Wittekamp et al,[26] 2018	Randomized trial of oropharyngeal decontamination	Hospital (ICU)	No reduction in BSIs caused by MDR-GNB.

CDIs, *Clostridioides difficile* infections; CI, confidence interval; SSIs, surgical site infections.

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 al[21] (2014) were able to reduce HAIs from MDR-GNB by adding mupirocin application to chlorhexidine bathing (for all patients) and polymyxin/tobramycin/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 the presence or absence of chlorhexidine bathing).

Two studies found chlorhexidine bathing only effective for some HAIs. Dusznyska et al's[22] observation study (2017) also found no reduction in intubation-related pneumonia, nor in UTIs, although overall infections and catheter-related infections were significantly lower. A randomized trial of oropharyngeal decontamination using chlorhexidine found no effect on reduced BSIs from MDR-GNB in mechanically ventilated patients.[26]

Although chlorhexidine is routinely used as a preoperative antisepsis, Abboud et al[19] (2016) found no supporting literature that chlorhexidine bathing reduces SSIs despite observing a reduction in SSIs among CRE-colonized patients in their study. Another review found mixed evidence on the efficacy of chlorhexidine bathing for preventing SSIs.[7] Two meta-analyses from the Cochrane Database of Systematic Reviews (Dumville et al,[31] 2013; Webster and Osborne,[32] 2015) found no definitive evidence that chlorhexidine antisepsis or patient showering/bathing (including bathing with rinsing) before surgery reduced SSI rates.

Finally, Urbanic et al[33] (2018) raise an important consideration: HAIs can be infrequent events, and the number needed to treat with chlorhexidine bathing to significantly reduce infections may have been, in some cases, larger than the study population. This also suggests that chlorhexidine bathing has limited benefit for HAI reduction in settings where HAIs are already well controlled by other means.

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

TABLE 5. Summary of Other Results

Study	Type of Study		Other Results
Boonyasiri et al,[20] 2016	Randomized, open-label controlled trial	Hospital (ICU)	No reduction/delay in MDR-GNB acquisition
Derde et al,[12] 2012	Systematic review	Hospital	Little evidence supporting chlorhexidine bathing for MDR-GNB.
Kengen et al,[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 MDRO acquisition.
Maxwell et al,[27] 2017	Prospective, randomized control trial	Hospital (ICU)	No difference between soap and chlorhexidine at reducing infections from GNB or GPB.
Mendes et al,[18] 2016	Quasi-experimental observational study	Hospital (transplant ward)	Not effective in reducing colonization from MDR-GNB.
Musuuza et al,[14] 2017	Quasi-experimental, pretest/posttest study	Hospital (ICU)	Reduced prevalence of colonization with fluoroquinolone-resistant GNB.
Pedreira et al,[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,[16] 2017	Prospective cohort study	Hospital (ICU)	Reduction in overall MDRO colonization, including MDR-GNB
Silder et al,[17] 2014	Systematic review	Hospital (ICU)	Little evidence supporting chlorhexidine bathing for MDR-GNB.
Tacconelli et al,[29] 2014	Systematic review	Hospital	Only temporary decolonization of MDR-GNB.

GPB, gram-positive bacteria; PICU, pediatric intensive care unit.

implementing bathing, but the authors hypothesize that some increases may be due to readmitted patients with persistent colonization.[36]

McNeil et al's[37] study of *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.[38] Similarly, Musuuza et al's[14] pre-post study did not show increased MICs in MRSA and fluoroquinolone-resistant GNB after a daily bathing intervention in their hospital. 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.[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.[40] Similarly, Alotaibi et al[41] (2017) found more chlorhexidine resistance in VRE than in vancomycin-susceptible Enteroccoci. Hayashi et al[42] (2016) found that *Acinetobacter baumanii* 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[19] found that an increase in colonization with *Pseudomonas aeruginosa* and *A. baumanii* after chlorhexidine bathing was implemented in an ICU. However, Camus et al[43] (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.[37,44]

DISCUSSION

This review found evidence that chlorhexidine bathing can reduce MDRO 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.[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.[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 MDRO shedding;
- evaluations of chlorhexidine bathing's role in multicomponent programs (also suggested in commentary by Horner et al,[49] 2013); and
- continued research on chlorhexidine resistance and related clinical outcomes, especially for biofilms (suggested by Grascha,[50] 2014) and Gram-negative bacteria (suggested by Strich and Palmore,[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

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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